Table 16. Summary of Adverse Events by Body System (continued)

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
GASTRO-INTESTINAL DISORDERS	11 (26.8)	19 (40.4)	18 (72.0)	48 (42.5)	0.260
NAUSEA	7 (17.1)	11 (23.4)	18 (72.0)	36 (31.9)	0.598
VOMITING	5 (12.2)	8 (17.0)	12 (48.0)	25 (22.1)	0.563
DIARRHEA	1 (2.4)	3 (6.4)	-	4 (3.5)	0.620
MELAENA	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000
FLATULENCE	2 (4.9)	0 (0.0)	-	2 (1.8)	0.214
ERUCTATION	0 (0.0)	2 (4.3)	-	2 (1.8)	0.497
RECTAL DISORDER	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
MOUTH DRY	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
DYSPEPSIA	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
CONSTIPATION	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
CENTRAL AND PERIPHERAL NERVOUS SYST.	19 (46.3)	28 (59.6)	-	47 (41.6)	0.285
CRAMPS	16 (39.0)	16 (34.0)	-	32 (28.3)	0.662
DIZZINESS	6 (14.6)	9 (19.1)	-	15 (13.3)	0.777
CRAMPS LEGS	3 (7.3)	5 (10.6)	-	8 (7.1)	0.719
PARAESTHESIA	4 (9.8)	3 (6.4)	-	7 (6.2)	0.700
VERTIGO	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
CONVULSIONS	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
ATAXIA	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
RESPIRATORY DISORDERS	16 (39.0)	13 (27.7)	-	29 (25.7)	0.363
DYSPNEA	3 (7.3)	7 (14.9)	-	10 (8.8)	0.327
UPPER RESP TRACT INFECTION	5 (12.2)	2 (4.3)	-	7 (6.2)	0.244
COUGHING	3 (7.3)	4 (8.5)	-	7 (6.2)	1.000
RHINITIS	4 (9.8)	1 (2.1)	-	5 (4.4)	0.180
PNEUMONIA	2 (4.9)	0 (0.0)	-	2 (1.8)	0.214
SINUSITIS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
PULMONARY EDEMA	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
PHARYNGITIS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
LARYNGITIS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466

(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)

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Table 16. Summary of Adverse Events by Body System (continued)

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
SKIN AND APPENDAGES DISORDERS	12 (29.3)	7 (14.9)	7 (28.0)	26 (23.0)	0.124
PRURITUS	3 (7.3)	4 (8.5)	-	7 (6.2)	1.000
ITCHING	0 (0.0)	0 (0.0)	7 (28.0)	7 (6.2)	
SWEATING INCREASED	3 (7.3)	1 (2.1)	-	4 (3.5)	0.335
RASH	3 (7.3)	1 (2.1)	-	4 (3.5)	0.335
SKIN ULCERATION	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
SKIN NODULES	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
SKIN DRY	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
SKIN DISORDER	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
CYST, SKIN	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
METABOLIC AND NUTRITIONAL DISORDERS	16 (39.0)	10 (21.3)	-	26 (23.0)	0.101
HYPERKALEMIA	5 (12.2)	2 (4.3)	-	7 (6.2)	0.244
EDEMA GENERALIZED	3 (7.3)	3 (6.4)	-	6 (5.3)	1.000
EDEMA LEGS	4 (9.8)	0 (0.0)	-	4 (3.5)	0.043
EDEMA PERIPHERAL	1 (2.4)	2 (4.3)	-	3 (2.7)	1.000
HYPOKALEMIA	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000
HYPOGLYCEMIA	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000
EDEMA	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000
HYPERVOLAEMIA	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
GOUT	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
OBESITY	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
AUTONOMIC NERVOUS	0 (0.0)	0 (0.0)	17 (68.0)	17 (15.0)	
MUSCLE CRAMP	0 (0.0)	0 (0.0)	17 (68.0)	17 (15.0)	
RESTLESSNESS	0 (0.0)	0 (0.0)	6 (24.0)	6 (5.3)	
RED BLOOD CELL DISORDERS	7 (17.1)	7 (14.9)	-	14 (12.4)	1.000
ERYTHROCYES ABNORMAL	4 (9.8)	5 (10.6)	-	9 (8.0)	1.000
ERYTHROCYTES ABNORMAL	4 (9.8)	1 (2.1)	-	5 (4.4)	0.180
ANEMIA	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000

(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)

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Table 16. Summary of Adverse Events by Body System (continued)

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
PSYCHIATRIC DISORDERS	6 (14.6)	4 (8.5)	-	10 (8.8)	0.504
AGITATION	2 (4.9)	2 (4.3)	-	4 (3.5)	1.000
SOMNOLENCE	2 (4.9)	0 (0.0)	-	2 (1.8)	0.214
ANOREXIA	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000
DEPRESSION	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
ANXIETY	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
CARDIOVASCLUAR DISORDERS	4 (9.8)	5 (10.6)	-	9 (8.0)	1.000
SYNCOPE	2 (4.9)	4 (8.5)	-	6 (5.3)	0.681
HOT FLUSHES	2 (4.9)	1 (2.1)	-	3 (2.7)	0.596
HEART RATE AND RHYTHM DISORDERS	3 (7.3)	5 (10.6)	-	8 (7.1)	0.719
TACHYCARDIA	2 (4.9)	4 (8.5)	-	6 (5.3)	0.681
BRADYCARDIA	3 (7.3)	0 (0.0)	-	3 (2.7)	0.097
PALPITATION	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
VISION DISORDERS	4 (9.8)	1 (2.1)	-	5 (4.4)	0.180
CONJUNCTIVITIS	3 (7.3)	1 (2.1)	-	4 (3.5)	0.335
VISION AB	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
MUSCULO-SKELETAL DISORDERS	2 (4.9)	3 (6.4)	-	5 (4.4)	1.000
MYALGIA	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000
STIFFNESS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
MUSCLE CONTRACTIONS INVOLUNTARY	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
BONE FRACTURE	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
WHITE CELL AND RES DISORDERS	3 (7.3)	1 (2.1)	-	4 (3.5)	0.335
LYMPHADENOPATHY	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000
LYMPHOMA-LIKE DISEASE	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
LEUKOCYTOSIS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
LEUCOCYTOSIS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466

(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)

Table 16. Summary of Adverse Events by Body System (continued)

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
URINARY DISORDERS	1 (2.4)	3 (6.4)	-	4 (3.5)	0.620
URINARY TRACT INFECTION	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000
URINARY INCONTINENCE	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
RENAL CALCULUS	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
HAEMATURIA	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
REPRODUCTIVE DISORDERS, FEMALE	2 (4.9)	0 (0.0)	-	2 (1.8)	0.214
MENORRHAGIA	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
LEUKORRHEA	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
PLATELET, BLEEDING AND CLOTTING DISOR	2 (4.9)	0 (0.0)	-	2 (1.8)	0.214
PURPURA	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
COAGULATION TIME INCREASED	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
MYO-, ENDO-, PERICARDIAL AND VALVE DI	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000
AORTIC STENOSIS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
ANGINA PECTORIS	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
HEARING AND VESTIBULAR DISORDERS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
DEAFNESS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
ENDOCRINE DISORDER	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
HYPERTHYROIDISM	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
SPECIAL SENSES DISORDER	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
TASTE PERVERSION	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
LIVER AND BILIARY DISORDERS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
HEPATIC FUNCTION ABNORMAL	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466

* 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)

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Table 16a. Summary of Adverse Event (Cramps)

	Treatment Group							
	500 mg (N = 41)		1000 mg (N = 47)		Control* (N = 25)		Total (N = 113)		p-value+
Adverse Event	n	%	n	%	n	%	n	%	500 vs. 1000
CRAMPS	17	(41.5)	18	(38.3)	17	(68.0)	52	(46.0)	0.829

* Historical control data taken from Abuelo et al. (54).
+ p-value is associated with Fisher's Exact Test.

(Cross-reference: Appendix 13.2.3)

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9.2.3 ANALYSIS OF ADVERSE EVENTS

In the comparisons of the incidences of AEs in the high-dose and low-dose groups, the numbers of patients experiencing each type of AE were similar, except for chest pain, which was experienced by significantly more patients in the high-dose group (p=0.033), and leg edema, which was experienced by significantly more patients in the low-dose group (p=0.043). The clinical relevance of these observations is unknown, and the significant results may be due to the low absolute numbers (1 and 8 patients experiencing chest pain in the low- and high-dose groups, respectively, and 4 and 0 patients experiencing leg edema in the low- and high-dose groups, respectively).

9.2.4 LISTING OF ADVERSE EVENTS BY PATIENT

Each patient's AEs are listed in Appendix 13.2.3.

9.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

9.3.1 LISTING OF DEATHS AND OTHER SERIOUS ADVERSE EVENTS

There was 1 death, following hospitalization, of a patient during the study (Patient #109). Seventeen other patients experienced serious AEs, and these are listed in Appendix 13.2.4. A copy of the CRF of each patient who died or experienced a serious AE is in Appendix 13.4.

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reported here are consistent with the summary of the larger group of hemodialysis patients, except for bilirubin. For bilirubin, the value was abnormal for no patients in the historical (oral-dose) control group and for 0.9% of patients in the NIDDK patient summary. For Ferrlecit-treated patients, the percentage of abnormal values for bilirubin varies by whether the upper limit of normal is that used by the site laboratory or that used by the control site and in the NIDDK study. With the site specific upper limit of normal, 27.7% of the patients in the high-dose group and 19.5% of the patients in the low-dose group were abnormal. With the higher NIDDK limit of abnormal, no treated patients had abnormal bilirubin values at baseline.

9.5 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Systolic and diastolic blood pressure readings, pulse, and respiration evaluations are summarized in Table 17. Mean values at baseline and Day 19 for systolic and diastolic blood pressure were slightly lower in the low-dose group than those in the high-dose group. Mean values for pulse and respiration rates were similar between the two groups.

Vital signs measurements for the historical (oral-dose) control group were available only for baseline and only for systolic and diastolic blood pressure and for pulse. Mean values for diastolic and systolic blood pressure were slightly higher and the mean value for pulse was lower for the historical (oral-dose) control group than for either dose group.

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All AEs typically associated with allergic reactions (rash, pruritus, hypotension, syncope, and death) have been separately tabulated in Tables 21 and 22. Table 21 displays the total incidence of these reactions, and Table 22 displays those reactions identified by investigators as bearing a relationship to study drug. These tables indicate that Type I hypersensitivity reactions with Ferrlecit are unlikely to occur at the rate reported for iron dextran. Furthermore, the potential allergic reactions associated with Ferrlecit appear to be limited to the development of pruritus and/or rash.

9.7 IDIOSYNCRATIC IRON REACTIONS

A syndrome of flushing and hypotension, which spontaneously resolves within less than 2 hours of drug administration, has been reported consequent to the administration of all iron compounds, including oral dosages (39, 50, 51, 52). This syndrome has been reported following administration of Ferrlecit (47, 48). In this study, a single patient experienced "syncope" that the investigator associated with drug administration. Investigators did not identify a patient in the study as suffering from flushing, hypotension, or the combination of flushing and hypotension that was associated with drug administration.

9.8 SAFETY CONCLUSIONS

In dose-control comparisons, chest pain occurred more frequently in the high-dose group and leg edema occurred more frequently in the low-dose group. When compared to the historical control, however, both high dose and low dose patients experienced less chest pain. Leg edema was not reported for historical control patients. All other AEs were similar between the groups. No serious AEs or deaths were judged by the investigator to be related to study drug. No Type I hypersensitivity reactions (anaphylaxis) were reported. Two rashes were identified as "possibly" or "probably" related to study drug. Previous reports of transient hypotension with Ferrlecit administration were not confirmed in this study, although the total number of patients may not have been sufficient to reliably detect this reaction if its incidence were less than 1%.

In laboratory comparisons between the dose groups, significant differences were noted from baseline to Day 47 for percentage of basophils, where the category of normal→abnormal occurred more frequently in the low dose group. The significance of this finding, besides the failure to control for repeated measures, is unknown. When compared with the historical (oral-dose) control group, Ferrlecit-treated patients had significantly fewer abnormalities in alkaline phosphatase and greater abnormalities in bilirubin values, although the bilirubin disparity was lost when a uniform upper limit of normal (1.6 mg/dL) was used for all patient values. All other laboratory comparisons were similar between the groups.

The study drug, Ferrlecit at 500-mg and 1000-mg doses, is safe in adult humans (63).

ATTACHMENT 13

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8.4.4 EFFICACY CONCLUSIONS

Treatment with Ferrlecit significantly improved hemoglobin and hematocrit as indicators of anemia in ESRD patients on chronic hemodialysis when compared with oral iron treatment alone.

Age, race, and baseline EPO dose did not significantly impact the efficacy results. Gender, however, did show a significant effect on the outcome of treatment. Females in the Ferrlecit-treatment group had significantly greater increases in hemoglobin and hematocrit than females in the historical (oral-dose) control group, while changes in hemoglobin and hematocrit in males were similar among the 2 groups.

9. SAFETY EVALUATION

Study 5600-03

9.1 EXTENT OF EXPOSURE

Thirty-eight patients were enrolled in the study and received at least 1 dose of Ferrlecit. All 38 patients were included in the safety evaluations, as were the 25 historical (oral-dose) control patients. This was a variable dose study; the maximum amount of Ferrlecit received during the treatment course by any patient was 1125 mg and the minimum amount was 62.5 mg.

9.2 ADVERSE EVENTS

9.2.1 BRIEF SUMMARY OF ADVERSE EVENTS

Four patients were hospitalized while receiving study medication. Only 1 patient had serious AEs thought to be related to the study drug. Patient 552 experienced dizziness, diplopia, malaise, and asthenia thought by the investigator to be probably related to the study drug. Symptoms resolved without sequelae within several hours. The patient was never hypotensive. Ferrlecit administration was discontinued (Appendix 13.2.4).

The majority of patients in each group experienced at least 1 AE, 73.7% (28/38) of the Ferrlecit-treated patients and 92.0% (23/25) of the historical-control patients. In the Ferrlecit-treated patients, the body systems in which the majority of AEs occurred were body as a whole (experienced by 44.7% of patients) and skin and appendages (28.9%). In the historical (oral-dose) control group, the body systems in which the majority of AEs occurred were cardiovascular disorders (92.0%) and gastro-intestinal disorders (72.0%).

The most frequent AE experienced by patients in the Ferrlecit-treatment group was application site reaction (26.3% of patients). None of these reactions were considered

by the investigator to be related to the study drug. Application site reactions were not reported for patients in the historical (oral-dose) control group. Pain and other complaints related to the hemodialysis access site are common among dialysis patients and may not have been recorded at the control center as adverse events.

In the historical (oral-dose) control group, the most frequent AEs reported were hypotension (92.0%), nausea (72.0%), and muscle cramps (68.0%). Hypotension, nausea, and cramps are common symptoms of hemodialysis (54). In the Ferrlecit-treatment group, hypotension was reported in 10.5% of patients and nausea in 5.3% of patients. Muscle cramps were not reported in any of the Ferrlecit-treated patients, but leg cramps were reported in 7.9% of these patients. In order to compare the incidence of cramps between the treatment groups, both categories of cramps were combined (See Table 8a). The percentage of Ferrlecit-treated patients who experienced cramps was lower than the corresponding percentage of control patients (7.9% *vs* 68%).

Adverse events that were possibly or probably related to Ferrlecit were: (1) dizziness, diplopia, malaise, and asthenia in 1 patient and (2) diarrhea, myalgia, and arthralgia in a second patient.

9.2.2 DISPLAY OF ADVERSE EVENTS

Adverse events are summarized by body system in Table 8.

9.2.3 ANALYSIS OF ADVERSE EVENTS

No inferential analyses were performed on the AE data.

9.2.4 LISTING OF ADVERSE EVENTS BY PATIENT

Adverse events are listed by patient in Appendix 13.2.3.

9.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

9.3.1 LISTING OF DEATHS AND OTHER SERIOUS ADVERSE EVENTS

There were no deaths during the study. Four patients experienced serious AEs (Section 9.3.2.1). A copy of the case report form of each patient who experienced a serious AE is in Appendix 13.4.

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Table 8. Summary of Adverse Events by Body System and Preferred Term

BODY SYSTEM Adverse Event	Ferrlecit (N = 38) n	 %	Control* (N = 25) n	 %
ANY BODY SYSTEM	28	73.7	23	92.0
BODY AS A WHOLE				
Chest Pain	17	44.7	9	36.0
Headache	4	10.5	9	36.0
Chills	0	0.0	6	24.0
Fever	3	7.9	2	8.0
Asthenia	2	5.3	2	8.0
Abscess	3	7.9	-	
Pain Back	3	7.9	-	
Abdominal Pain	0	0.0	3	12.0
Carcinoma	3	7.9	-	
Sepsis	2	5.3	-	
Pain	2	5.3	-	
Infection	2	5.3	-	
Flu Syndrome	2	5.3	-	
Malaise	1	2.6	-	
	1	2.6	-	
CARDIOVASCULAR DISORDERS				
Hypotension	4	10.5	23	92.0
	4	10.5	23	92.0
GASTRO-INTESTINAL DISORDERS				
Nausea	8	21.1	18	72.0
Vomiting	2	5.3	18	72.0
Diarrhea	4	10.5	12	48.0
Nausea and Vomiting	3	7.9	-	
Nausea Vomiting and Diarrhea	1	2.6	-	
Dyspepsia	1	2.6	-	
	1	2.6	-	
AUTONOMIC NERVOUS				
Muscle Cramp	0	0.0	17	68.0
Restlessness	0	0.0	17	68.0
	0	0.0	6	24.0
SKIN AND APPENDAGES				
Application Site Reaction	11	28.9	-	
Skin Carcinoma	10	26.3	-	
	1	2.6	-	
DIGESTIVE SYSTEM				
Gastrointestinal Disorder	6	15.8	-	
Rectal Disorder	2	5.3	-	
Large Intestine Perforation	2	5.3	-	
Gastrointestinal Hemorrhage	1	2.6	-	
Gastroenteritis	1	2.6	-	
Anorexia	1	2.6	-	
	1	2.6	-	

* Historical control data taken from Abeuelo et al. (54).
\+ - = No data available.

(continued)

(Cross-reference: Appendix 13.2.3)

NO! This was study 5600-01

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Table 8 (continued). Summary of Adverse Events by Body System and Preferred Term

BODY SYSTEM Adverse Event	Ferrlecit (N = 38) n	 %	Control* (N = 25) n	 %
CARDIOVASCULAR SYSTEM	4	10.5	-	-
Myocardial Infarct	2	5.3	-	-
Syncope	1	2.6	-	-
Atrial Fibrillation	1	2.6	-	-
Angina Pectoris	1	2.6	-	-
SKIN AND APPENDAGES DISORDERS	0	0.0	7	28.0
Itching	0	0.0	7	28.0
MUSCULOSKELETAL SYSTEM	7	18.4	-	-
Leg Cramps	3	7.9	-	-
Arthralgia	2	5.3	-	-
Tenosynovitis	1	2.6	-	-
Myalgia	1	2.6	-	-
Arthritis	1	2.6	-	-
RESPIRATORY SYSTEM	5	13.2	-	-
Dyspnea	4	10.5	-	-
Lung Edema	1	2.6	-	-
Cough Increased	1	2.6	-	-
NERVOUS SYSTEM	5	13.2	-	-
Dizziness	2	5.3	-	-
Insomnia	1	2.6	-	-
Hypesthesia	1	2.6	-	-
Depersonalization	1	2.6	-	-
Agitation	1	2.6	-	-
METABOLIC AND NUTRITIONAL DISORDERS	2	5.3	-	-
Hypoglycemia	1	2.6	-	-
Hypervolemia	1	2.6	-	-
SPECIAL SENSES	2	5.3	-	-
Diplopia	1	2.6	-	-
Abnormal Vision	1	2.6	-	-
HEMIC AND LYMPHATIC SYSTEM	1	2.6	-	-
Hypochromic Anemia	1	2.6	-	-

* Historical control data taken from Abeuelo et al. (54).
\+ - = No data available.

(Cross reference: Appendix 13.2.3)

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Table 8a. Summary of Adverse Event (Cramps)

Adverse Event	Ferrlecit (N = 38) n	%	Control* (N = 25) n	%
Cramps	3	(7.9)	17	(68.0)

* Historical control data taken from Abeuelo et al. (54).

(Cross reference: Appendix 13.2.3)

9.3.2 NARRATIVES OF DEATHS, OTHER SERIOUS ADVERSE EVENTS AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

9.3.2.1 Narratives of Patients with Serious Adverse Events

All of the patients in the following list were hospitalized because of the indicated event(s). In each case, the AE was considered to be serious because hospitalization was required.

Patient Number	Age	Sex	Event	Relation to study drug
536	38	M	Rigors and chills. Blood cultures showed *Staphylococcus aureus* bacteremia. Received 1000 mg Ferrlecit.	None
538	68	M	Myocardial infarction. One dose of Ferrlecit was withheld. Received 1125 mg Ferrlecit.	None
544	35	M	Chills. Four blood cultures showed *Staphylococcus* epidermis bacteremia. Received 375 mg Ferrlecit.	Unlikely
552	65	M	Dizziness, lightheadedness, diplopia, malaise, and weakness. Received 125 mg Ferrlecit.	Probable

9.3.3 ANALYSIS AND DISCUSSION OF DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

All of the study patients requiring hospitalization were male, and all were hospitalized for medical reasons. One of the hospitalized patients completed the full course of Ferrlecit treatment after having 1 dose withheld during the AE. Two of the hospitalized patients received only partial courses of Ferrlecit treatment. In the other hospitalized patient, Patient #536, who received 1000 mg of Ferrlecit, the exact number and timing of Ferrlecit doses were not available.

9.4 CLINICAL LABORATORY EVALUATION

9.4.1 LISTING OF INDIVIDUAL LABORATORY MEASUREMENTS BY PATIENT AND EACH ABNORMAL LABORATORY VALUE

Listing of individual laboratory measurements by patient are in Appendix 13.2.5. Laboratory values are summarized in shift table format (Table 10).

9.4.2 EVALUATION OF EACH LABORATORY VARIABLE

9.4.2.1 Laboratory Values Over Time

Laboratory values at baseline and at the last available observation through Day 50 were categorized for the Ferrlecit-treatment and the historical (oral-dose) control groups. Results are in Table 10.

For the liver enzymes ALT and AST, the majority of the results were in the normal-normal category. There was a significant difference ($p=<0.001$, Appendix 13.3) between the 2 groups in the distribution of alkaline phosphatase values. In the Ferrlecit-treated patients, the majority of the alkaline phosphatase values fell in the normal-normal category, while in the historical (oral-dose) control patients, the majority of the values fell in the abnormal-abnormal category. In order to rule out artificial differences between the treatment groups due to variation in normal ranges, the data for the variable alkaline phosphatase was reanalyzed by applying the normal ranges for the control data to the Ferrlecit-treatment data. Results are in Table 10a and are similar to the results from the original analyses. All bilirubin values in the historical (oral-dose) control group were in the normal-normal category. Bilirubin values were not available for the Ferrlecit-treatment group.

All BUN and creatinine results were in the abnormal-abnormal category in both groups. For glucose results, there was a significant difference ($p=0.015$) between the 2 groups where the Ferrlecit-treatment group had the highest percentage of patients

in the normal-normal category, and the historical-control group had the highest percentage of patients in the abnormal-abnormal group.

The majority of results in both groups were in the normal-normal category for WBC counts and platelets. In the Ferrlecit-treatment group, basophil and monocyte results were in the normal-normal category for 2 patients and in the normal-abnormal category for 1 patient. The eosinophil results were in the normal-normal, abnormal-normal, and abnormal-abnormal categories for 1 patient each in the Ferrlecit-treatment group. All lymphocyte values in the Ferrlecit-treatment group were in the abnormal-abnormal category. Results of the WBC differential counts were not available for the historical (oral-dose) control group.

Baseline laboratory values from a population of approximately 1,100 hemodialysis patients are summarized in Table 11. These data were obtained from the NIDDK Hemodialysis Study's Data Coordinating Center. In patients with renal dysfunction, baseline values for creatinine are essentially always abnormal, results of alkaline phosphatase, and glucose tests are variable, and results of ALT, AST, bilirubin, and WBC count tests are typically normal. Baseline results from patients in the study reported here are consistent with the summary of the larger group of hemodialysis patients, except for alkaline phosphatase. Alkaline phosphatase was normal at baseline for 65.8% of the patients in the Ferrlecit-treatment group, for no patients in the historical (oral-dose) control group and 52.15% of patients in the NIDDK patient summary when the values were analyzed using the normal ranges for the NIDDK Hemodialysis Study data.

9.5 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Systolic and diastolic blood pressure readings, pulse, temperature, and weight evaluations are summarized in Table 9. In the Ferrlecit-treatment group, the mean values for all variables at Day 0 and Day 50 were similar.

Vital sign measurements for the historical (oral-dose) control group were available only for baseline and only for systolic and diastolic blood pressure and for pulse. Mean diastolic blood pressure and pulse was similar between the 2 groups. The mean value for the systolic blood pressure was higher for the historical (oral-dose) control group than for the Ferrlecit-treatment group at Day 0 or Day 50.

9.6 SAFETY CONCLUSIONS

Hypotension, nausea, and cramps occurred more frequently in the historical (oral-dose) control group than in the Ferrlecit-treatment group. Application site reaction was the most frequently reported AE in the Ferrlecit-treatment group, but was not

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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:

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	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.

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Overall Safety Experience with Ferrlecit

The Integrated Summary of Safety for this NDA included safety information from: Studies 5600-01 and -03, published reports, two small "maintanence" studies, and post-marketing data from Italy and Germany.

The primary Ferrlecit-associated adverse events in Study 5600-01, were allergic reactions that occurred in 3 out of a total of 83 (or 3.6% of) Ferrlecit-treated patients, and which resulted in premature study discontinuation. Available information for these cases is summarized 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.

Of the 38 patients exposed to Ferrlecit in Study 5600-03, 1 patient (or 2.6%) 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.

Of the 177 renal dialysis patients exposed to Ferrlecit in the previously-discussed published literature, 3(1.7%) patients experienced serious adverse events, which were: 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.

An additional published report by Zamen et. al., entitled, "Oversaturation of transferrin after intravenous ferric gluconate (Ferrlecit®) in hemodialysis patients," (Nephrol Dial Transplant 1996 11 820), conducted a study of peak serum iron study values following the i.v. administration of Ferrlecit. This study was initiated following development of nausea, facial reddening, and hypotension in 2 chronic hemodialysis patients who were receiving monthly infusions of 62.5 to 125 mg of Ferrlecit, and who were also determined to have TSAT values of > 100% at the time of symptoms. The authors found that longer infusions and lower doses of Ferrlecit resulted in lower peak serum iron, and iron saturation values. The relationship of serum iron study values

and the development of nausea, facial reddening, and flushing however, was not established in this study.

Two "maintenance studies" were submitted to provide further information of the use of Ferrlecit in chronic hemodialysis patients. The first was a compassionate-use, single-center study of 29 chronic hemodialysis patients who were administered 125 mg of i.v. Ferrlecit for 8 consecutive dialysis sessions, followed by a maintenance dose of 62.5 mg once weekly. No patient in this study discontinued study drug due to an adverse event, and there were no serious adverse events. A total of 13 adverse events occurred in 11 patients that the clinical coordinator felt were possibly or probably related to drug therapy. These reactions included flushing (3 patients), nausea and/or vomiting (3 patients), and transient hypotension, abdominal pain, sweating, headache, and flatulence (1 patient each).

The second "maintenance study" was a trial conducted by Dr. Allen Nissenson, who treated a total of 5 chronic hemodialysis patients with a history of anaphylaxis to iron dextran, with up to 1000 mg of i.v. Ferrlecit. No adverse events resulted.

Ferrlecit Injection has been used since 1959 in over 20 countries outside of the United States. Ninety-seven percent of the total sales of Ferrlecit in 1996 were in Germany, Italy, and Spain; over 80% of it's use in Germany is in renal hemodialysis patients, while 90% of it's use in Italy is as an oral dietary supplement.

Postmarketing information from Germany and Italy was obtained from the manufacturer of Ferrlecit (Rhone Polenc Rorer). Most all reported serious adverse events were allergic/anaphylactoid in nature. During the period 1976-96, there were 74 reports of allergic/anaphylactoid reactions for Ferrlecit Injection from Italy and Germany; none resulted in death, although 3 had unknown outcomes.

Notably, an increase in the number of reported anaphylactiod reactions in 1995 (i.e. 8 in 1994, and 25 in 1995) prompted an investigation of batch production records by the manufacturer. High molecular weight polysaccharides, probably α-1,6-glucans, in a new commercial source of sucrose, was identified as the culprit. When production was switched to the original source of sucrose, reports of allergic/anaphylactoid adverse events dropped (from 25 in 1995 to 6 in 1996).

In a sponsor-supported study by Faich and Strobos entitled, "Ferrlecit injection: safer intravenous iron therapy than iron dextrans," information was provided which indicated that the use of Ferrlecit results in a decreased reporting rate of

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6.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Study design. Following consultation with the FDA, data from an historical (oral-dose) control phase were included in the final analyses, in addition to data from the dose-control phase described in the protocol.

Data sets used. Although not described in the study protocol or analysis plan, data sets used were defined prior to performing analyses. The safety data set consisted of all patients who received Ferrlecit (test or study dose) and the historical (oral-dose) control group, and was used for safety evaluations. The intent-to-treat data set consisted of all patients from the dose-control and historical (oral-dose) control groups for which baseline and endpoint data were available and was used for efficacy analyses. Efficacy analyses were also performed on the per-protocol data set, which consisted of the intent-to-treat data set, excluding 29 patients who did not complete the study per protocol. Twenty-two of these patients required changes in rHuEPO dosage during the study, 5 discontinued the study, and 3 did not meet the inclusion criteria (including 1 whose rHuEPO dosage changed). The stable-EPO data set consisted of all patients from the intent-to-treat data set whose rHuEPO dose did not change during the study.

Efficacy evaluations. The efficacy evaluations described in Section 6.5.3 differed slightly from those described in the protocol. Primary and secondary efficacy variables were not defined in the protocol, but were in the analysis plan. Evaluations of mean changes in efficacy variables from baseline to endpoint by using paired t-test and repeated measures ANOVA, and evaluations of the influence of baseline rHuEPO dose on change in efficacy variables were described in the analysis plan, but not in the protocol. Evaluations of the effect of investigator site on efficacy results were discussed if they yielded a p-value of ≤ 0.10, not ≤ 0.15, as stated in the protocol. Red blood cell/reticulocyte ratio was described as an efficacy variable in the analysis plan, but analyses of this variable were not performed because of incomplete data collection.

The effects of gender, race (white or other), and age (less than 51 years, 51 to 65 years or greater than 65 years for females, and less than or equal to 65 or greater than 65 for males) on change in hemoglobin were analyzed for the dose-control phase of the study, and the effects of age on change in hemoglobin were also analyzed for the historical (oral-dose) control phase of the study. Additional efficacy analyses that were not described in the analysis plan were performed in order to evaluate the effects of confounding factors (baseline efficacy value, baseline rHuEPO dose, and change from baseline in rHuEPO). These analyses are described in Section 6.7.1.3.

Patients from the intent-to-treat data set (see Section 8.1) whose hemoglobin increased by 0.5 g/dL or more from baseline to last observation through Day 40 were

Table 3. Summary of Patient Demographic and Baseline Variables (continued)

Variable	Treatment Group			p-value*			
	500 mg (N = 41)	1000 mg (N = 47)	Control (N = 25)	500 vs. 1000	500 vs. Control	1000 vs. Control	Overall
Age Group (n %)							
Female: age<=51	10 (24.4)	6 (13.0)	8 (32.0)	0.143	0.267	0.574	0.060
Female: 51<age<=65	5 (12.2)	8 (17.4)	6 (24.0)	0.445	0.559	0.308	0.543
Female: age>65	8 (19.5)	11 (23.9)	3 (12.0)	0.512	0.796	0.513	0.351
Male: age<=65	13 (31.7)	15 (32.6)	6 (24.0)	0.779	1.000	0.583	0.588
Male: age>65	5 (12.2)	6 (13.0)	2 (8.0)	0.866	1.000	0.701	0.704
Gender (n %)							
Female	23 (56.1)	25 (53.2)	17 (68.0)	1.000	0.438	0.318	0.536
Male	18 (43.9)	21 (44.7)	8 (32.0)				
Missing	0 (0.0)	1 (2.1)	0 (0.0)				
Race (n %)							
White	30 (73.2)	36 (76.6)	10 (40.0)	0.813	0.003	<0.001	0.001
Black	8 (19.5)	5 (10.6)	8 (32.0)				
Latin	2 (4.9)	2 (4.3)	0 (0.0)				
Asian	1 (2.4)	1 (2.1)	1 (4.0)				
Hispanic	0 (0.0)	0 (0.0)	5 (20.0)				
Native American	0 (0.0)	1 (2.1)	0 (0.0)				
Persian	0 (0.0)	1 (2.1)	0 (0.0)				
Unknown	0 (0.0)	0 (0.0)	1 (4.0)				
Missing	0 (0.0)	1 (2.1)	0 (0.0)				
Height (in)							
n	41	46	-	0.483	NA#	NA	0.483
Mean (Std)	65.2 (4.1)	64.6 (4.6)					
Min	59.0	53.0					
Max	74.0	73.0					
Weight (lbs)							
n	39	43	25	0.765	0.054	0.088	0.126
Mean (Std)	165.9 (45.3)	163.0 (48.7)	143.6 (35.9)				
Min	92.0	90.0	83.0				
Max	280.0	330.0	222.7				

(continued)

* For a continuous variable, an ANOVA model with effects for treatment group was used to compare the group means, and the p-value was associated with the F test. For a categorical variable, the p-value was associated with the Fisher's Exact Test.
+ - = No data available.
# NA = Not Applicable.

(Cross-reference: Appendix 13.2.1 and 13.2.2)

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For percent iron saturation, serum iron, and MCHC, significant differences in mean changes over time were noted (p=0.008, p=0.015, and p=0.003, respectively). Mean changes for hematocrit and MCH were not significantly different over time.

8. Influence of Baseline rHuEPO Dose on Change in Secondary Efficacy Variables. The possible influence of baseline rHuEPO dose on changes in secondary variables was examined by using an ANCOVA. The baseline dose significantly influenced change in hematocrit from baseline to endpoint (p=0.004). No other secondary efficacy variables were significantly affected by baseline rHuEPO (Appendix 13.3). See results of analyses of confounding factors, Sections 8.4.1.5 and 8.4.1.6.

9. Subgroup Analyses. In the analyses of treatment groups by age, race, and gender, no significant effects were found on change in hemoglobin. The treatment mean did not vary significantly across any of the subgroup categories (Appendix 13.3).

8.4.1.2 Dose-control Phase, Per-protocol Patients

1. Analysis of Variance of Mean Change in Hemoglobin. Changes in hemoglobin from baseline to endpoint (last available observation through Day 40) for patients who completed the study per protocol are summarized by dose group in Table 7. Mean change in hemoglobin from baseline to endpoint for the high-dose group was significantly greater than that for the low-dose group (p=0.013, Appendix 13.3).

Table 7. Primary Analysis of the Change in Hemoglobin from Baseline to the Last Available Observation Through Day 40 (Per-protocol Patients)

Variable	Treatment Group: 500 mg (N = 24)	1000 mg (N = 35)	p-value*
Hemoglobin (g/dL)			
n	24	35	
Mean	0.5	1.2	0.013
Std	1.0	1.1	
Min	-2.4	-1.1	
Max	2.0	3.6	
c.i.	(0.1, 0.8)	(0.9, 1.5)	
Probt+	0.024	<0.001	

* p-value is associated with the ANOVA.
\+ p-value is associated with the paired t-test.

(Cross-reference: Appendix 13.2.2)

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If the response to oral iron is inadequate, the diagnosis must be reconsidered. A full laboratory evaluation should be carried out, and such factors as the presence of a concurrent inflammatory disease or poor compliance by the patient must be assessed. A source of continued bleeding obviously should be sought. If no other explanation can be found, an evaluation of the patient's ability to absorb oral iron should be considered. There is no justification for merely continuing oral iron therapy beyond 3 to 4 weeks if a favorable response has not occurred.

Once a response to oral iron is demonstrated, therapy should be continued until the hemoglobin returns to normal. Treatment may be extended if it is desirable to establish iron stores. This may require a considerable period of time, since the rate of absorption of iron by the intestine will decrease markedly as iron stores are reconstituted. The prophylactic use of oral iron should be reserved for patients at high risk, including pregnant women, women with excessive menstrual blood loss, and infants. Iron supplements also may be of value for rapidly growing infants who are consuming substandard diets and for adults with a recognized cause of chronic blood loss. Except for infants, in whom the use of supplemented formulas is routine, the use of "over-the-counter" mixtures of vitamins and minerals to prevent iron deficiency should be discouraged.

Therapy with Oral Iron. Orally administered ferrous sulfate, the least expensive of iron preparations, is the treatment of choice for iron deficiency (Callender, 1974; Bothwell *et al.*, 1979). Ferrous salts are absorbed about three times as well as ferric salts, and the discrepancy becomes even greater at high dosage (Brise and Hallberg, 1962). Variations in the particular ferrous salt have relatively little effect on bioavailability, and the sulfate, fumarate, succinate, gluconate, and other ferrous salts are absorbed to approximately the same extent.

Ferrous sulfate (*iron sulfate;* FEOSOL, others) is the hydrated salt, $FeSO_4 \cdot 7H_2O$, which contains 20% iron. *Dried ferrous sulfate* (30% elemental iron) also is available. *Ferrous fumarate* (FEOSTAT, others) contains 33% iron and is moderately soluble in water, stable, and almost tasteless. *Ferrous gluconate* (FERGON, others) has also been successfully used in the therapy of iron-deficiency anemia. The gluconate contains 12% iron. *Polysaccharide–iron complex* (NIFEREX, others), a compound of ferrihydrite and carbohydrate, is another preparation with comparable absorption. The effective dose of all of these preparations is based on iron content.

Other iron compounds have utility in fortification of foods. Reduced iron (metallic iron, elemental iron) is as effective as ferrous sulfate, provided the material employed has a small particle size. Large-particle *ferrous reductum* and iron phosphate salts have a much lower bioavailability (Cook *et al.*, 1973), and their use for the fortification of foods is undoubtedly responsible for some of the confusion concerning effectiveness. Ferric edetate has been shown to have good bioavailability and to have advantages for maintenance of the normal appearance and taste of food (Viteri *et al.*, 1978).

The amount of iron, rather than the mass of the total salt in iron tablets, is important. It is also essential that the coating of the tablet dissolve rapidly in the stomach. Surprisingly, since iron usually is absorbed in the upper small intestine, certain delayed-release preparations have been reported to be effective and have been said to be even more effective than ferrous sulfate when taken with meals. However, reports of absorption from such preparations vary. Because a number of different forms of delayed-release preparations are on the market and information on their bioavailability is limited, the effectiveness of most such preparations must be considered questionable.

A variety of substances designed to enhance the absorption of iron have been marketed, including surface-acting agents, carbohydrates, inorganic salts, amino acids, and vitamins. One of the more popular of these is ascorbic acid. When present in an amount of 200 mg or more, ascorbic acid increases the absorption of medicinal iron by at least 30%. However, the increased uptake is associated with a significant increase in the incidence of side effects (Hallberg *et al.*, 1966); therefore, the addition of ascorbic acid seems to have little advantage over increasing the amount of iron administered. It is inadvisable to use preparations that contain other compounds with therapeutic actions of their own, such as vitamin B_{12}, folate, or cobalt, since the patient's response to the combination cannot be easily interpreted.

The average dose for the treatment of iron-deficiency anemia is about 200 mg of iron per day (2 to 3 mg/kg), given in three equal doses of 65 mg. Children weighing 15 to 30 kg can take half the average adult dose, while small children and infants can tolerate relatively large doses of iron—for example, 5 mg/kg. The dose used is a practical compromise between the therapeutic action desired and the toxic effects. Prophylaxis and mild nutritional iron deficiency may be managed with modest doses. When the object is the prevention of iron deficiency in pregnant women, for example, doses of 15 to 30 mg of iron per day are adequate to meet the 3- to 6-mg daily requirement of the last two trimesters. When the purpose is to treat iron-deficiency anemia, but the circumstances do not demand haste, a total dose of about 100 mg (35 mg three times daily) may be used.

The responses expected for different dosage regimens of oral iron are given in Table 53–5. However, these effects are modified by the severity of the iron-deficiency anemia and by the time of ingestion of iron relative to meals. Bioavailability of iron ingested with food is probably one-half or one-third of that seen in the fasting subject (Grebe *et al.*, 1975). Antacids also reduce the absorption of iron if given concurrently. It is always preferable to administer iron in the fasting state, even if the dose must be reduced because of gastrointestinal side effects. For patients who require maximal therapy to encourage a rapid response or to counteract continued bleeding, as much as 120 mg of iron may be administered four times a day. The timing of the dose is important. Sustained high rates of red cell production require an uninterrupted supply of iron. Oral doses should be spaced equally to maintain a continuous high concentration of iron in plasma.

Table 53–5
Average Response to Oral Iron

TOTAL DOSE, mg of iron per day	ESTIMATED ABSORPTION		INCREASE IN HEMOGLOBIN, g/liter of blood per day
	%	*mg*	
35	40	14	0.7
105	24	25	1.4
195	18	35	1.9
390	12	45	2.2

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The duration of treatment is governed by the rate of recovery of hemoglobin and the desire to create iron stores. The former depends on the severity of the anemia. With a daily rate of repair of 2 g of hemoglobin per liter of whole blood, the red cell mass is usually reconstituted within 1 to 2 months. Thus, an individual with a hemoglobin of 50 g per liter may achieve a normal complement of 150 g per liter in about 50 days, whereas an individual with a hemoglobin of 100 g per liter may take only half that time. The creation of stores of iron is a different matter, requiring many months of oral iron administration. The rate of absorption decreases rapidly after recovery from anemia and, after 3 to 4 months of treatment, stores may increase at a rate of not much more than 100 mg per month. Much of the strategy of continued therapy depends on the estimated future iron balance of the individual. The person with an inadequate diet may require continued therapy with low doses of iron. The individual whose bleeding has stopped will require no further therapy after the hemoglobin has returned to normal. For the individual with continued bleeding, long-term, high-dose therapy is clearly indicated.

Untoward Effects of Oral Preparations of Iron. Intolerance to oral preparations of iron is primarily a function of the amount of soluble iron in the upper gastrointestinal tract and of psychological factors. Side effects include heartburn, nausea, upper gastric discomfort, constipation, and diarrhea. A good policy, particularly if there has been previous intolerance to iron, is to initiate therapy at a small dosage, to demonstrate freedom from symptoms at that level, and then gradually to increase the dosage to that desired. With a dose of 200 mg of iron per day divided into three equal portions, symptoms occur in approximately 25% of individuals, compared with an incidence of 13% among those receiving placebos; this increases to approximately 40% when the dosage of iron is doubled. Nausea and upper abdominal pain are increasingly common manifestations at high dosage. Constipation and diarrhea, perhaps related to iron-induced changes in the intestinal bacterial flora, are not more prevalent at higher dosage, nor is heartburn. If a liquid is given, one can place the iron solution on the back of the tongue with a dropper to prevent transient staining of teeth.

Toxicity caused by the long-continued administration of iron with the resultant production of iron overload (hemochromatosis) has been the subject of a number of case reports (for example, *see* Bothwell *et al.*, 1979). Available evidence suggests that the normal individual is able to control absorption of iron despite high intake, and it is only individuals with underlying disorders that augment the absorption of iron who run the hazard of developing hemochromatosis. However, recent data indicate that hemochromatosis may be a relatively common genetic disorder, present in 0.5% of the population.

Iron Poisoning. Large amounts of ferrous salts of iron are toxic but, in adults, fatalities are rare. Most deaths occur in childhood, particularly between the ages of 12 and 24 months (Bothwell *et al.*, 1979). As little as 1 to 2 g of iron may cause death, but 2 to 10 g is usually ingested in fatal cases. The frequency of iron poisoning relates to its availability in the household, particularly the supply that remains after a pregnancy. The colored sugar coating of many of the commercially available tablets gives them the appearance of candy. All iron preparations should be kept in childproof bottles.

Signs and symptoms of severe poisoning may occur within 30 minutes or may be delayed for several hours after ingestion. They consist largely of abdominal pain, diarrhea, or vomiting brown or bloody stomach contents containing pills. Of particular concern are pallor or cyanosis, lassitude, drowsiness, hyperventilation due to acidosis, and cardiovascular collapse. If death does not occur within 6 hours, there may be a transient period of apparent recovery, followed by death in 12 to 24 hours. The corrosive injury to the stomach may result in pyloric stenosis or gastric scarring. Hemorrhagic gastroenteritis and hepatic damage are prominent findings at autopsy. In the evaluation of the child who is thought to have ingested iron, a color test for iron in the gastric contents and an emergency determination of the concentration of iron in plasma can be performed. If the latter is less than 63 μM (3.5 mg per liter), the child is not in immediate danger. However, vomiting should be induced when there is iron in the stomach, and an x-ray should be taken to evaluate the number of pills remaining in the small bowel (iron tablets are radioopaque). Iron in the upper gastrointestinal tract can be precipitated by lavage with sodium bicarbonate or phosphate solution, although the clinical benefit is questionable. When the plasma concentration of iron is greater than the total iron binding capacity (63 μM; 3.5 mg per liter), deferoxamine should be administered; dosage and routes of administration are detailed in Chapter 66. Shock, dehydration, and acid–base abnormalities should be treated in the conventional manner. Most important is the speed of diagnosis and therapy. With early effective treatment, the mortality from iron poisoning can be reduced from as high as 45% to about 1%.

Therapy with Parenteral Iron. Parenteral administration of iron is an alternative to the use of oral preparations (Bothwell *et al.*, 1979). The rate of response to parenteral therapy is similar to that which follows usual oral doses (Pritchard, 1966). One advantage is that iron stores may be created rapidly, something that would take months to achieve by the oral route. The most important indications for use of parenteral iron are in patients with a disease such as sprue, which prevents absorption of iron from the gastrointestinal tract, and in patients who are receiving parenteral nutrition. Parenteral iron also may be indicated when oral administration has an adverse effect on inflammatory disease of the bowel and, on rare occasions, when intolerance to oral iron prevents effective therapy. In chronic disease states, such as rheumatoid arthritis, the utilization of parenteral iron can be suboptimal because of the inflammatory block in reticuloendothelial iron transport. Other indications have been suggested for parenteral iron that do not seem to be based on sufficient objective criteria, including the unsubstantiated beliefs that the response to parenteral iron is faster than that to oral iron and

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that patients undergoing dialysis (who absorb oral iron perfectly well) are better managed by the parenteral route. An exception to this may well be the need to use parenteral iron initially in patients with renal disease who are receiving erythropoietin. Otherwise, the supply of iron may become the rate-limiting factor in the response of the marrow (Eschbach *et al.*, 1987).

Iron dextran injection (INFED) is the parenteral preparation currently in general use in the United States. It is a complex of ferric oxyhydroxide with dextrans of 5000 to 7000 daltons in a viscous solution containing 50 mg/ml of iron. When given intramuscularly, a variable portion (10% to 50%) may become fixed locally for many months. The remainder enters the blood, mostly through the lymphatic circulation, and elevates the concentration of iron in plasma for days or 1 or 2 weeks due to the presence of the iron–dextran complex. During this time determination of plasma iron does not indicate the amount of iron present on transferrin. The iron dextran must first be phagocytized by reticuloendothelial cells and the iron released from the sugar molecule of the dextran before it becomes available to the body. A portion of the processed iron is rapidly returned to the plasma and made available to the erythroid marrow; however, an even greater portion remains temporarily trapped within reticuloendothelial cells (Henderson and Hillman, 1969). These iron dextran deposits are converted gradually into a usable form of iron. While all iron is eventually used (Kernoff *et al.*, 1975), many months are required before this is complete, and, in the interim, iron dextran within reticuloendothelial cells can confuse the physician who attempts to evaluate the iron status of the patient.

Intramuscular injection of iron dextran can be carried out with an initial test dose of 0.5 ml. If no adverse reactions are observed, the injection 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 4.5 kg (10 lb), 1.0 ml (50 mg of iron) for children under 9.0 kg (20 lb), and 2.0 ml (100 mg of iron) for other patients. Iron dextran should be injected only into the muscle mass of the upper outer quadrant of the buttock using a z-track technique (displacement of the skin laterally prior to injection). However, local reactions, including long-continued discomfort at the site of injection and local discoloration of the skin, and the concern about malignant change at the site of injection (Weinbren *et al.*, 1978) make intramuscular administration inappropriate except when the intravenous route is inaccessible.

The technique of intravenous administration involves first the injection of 0.5 ml of iron dextran over a period of 5 minutes; the patient then is observed for 1 hour for signs or symptoms of anaphylaxis. Daily doses of 2.0 ml then are administered until the total calculated dose is reached. It is essential to administer the drug slowly and to stop the infusion immediately if the patient complains of perioral numbness, tingling, back pain, or chest pain. Alternatively, after a test dose to rule out possible anaphylaxis as described above, the total dose needed to reconstitute red cell mass and tissue stores may be diluted in 250 to 1000 ml of 0.9% sodium chloride solution and administered in one infusion over several hours. Such a dose (in mg) may be calculated from the following formula:

$$\begin{bmatrix}\text{Total}\\ \text{Iron}\\ \text{(mg)}\end{bmatrix} = \left[0.66 \begin{pmatrix}\text{Body}\\ \text{Weight}\\ \text{(kg)}\end{pmatrix}\right] \times \left[100 - \frac{\begin{bmatrix}\text{Hgb}\\ \text{(g/dl)}\end{bmatrix} \times 100}{14.8}\right]$$

Where Hgb refers to hemoglobin levels determined in clinical assays. The weight factor (0.66[Body Weight (*kg*)]) *can be replaced by* (0.3[Body Weight (*lb*)]) *if the patient's weight is measured in pounds.*

Such calculations do not take into consideration the delay in the utilization of the material injected or the possibility of continued loss of iron.

Reactions to intravenous iron include headache, malaise, fever, generalized lymphadenopathy, arthralgias, urticaria, and, in some patients with rheumatoid arthritis, exacerbation of the disease. Phlebitis may occur with prolonged infusions of a concentrated solution or when an intramuscular preparation containing 0.5% phenol is used in error. Of greatest concern, however, is the rare anaphylactic reaction, which may be fatal in spite of treatment. While only a few such deaths have been reported, it remains a deterrent to the use of iron dextran. Thus, there must be specific indications for the parenteral administration of iron.

COPPER

Copper deficiency is extremely rare in human beings (Evans, 1973). The amount present in food is more than adequate to provide the needed body complement of slightly over 100 mg. There is no evidence that copper ever needs to be added to a normal diet, either prophylactically or therapeutically. Even in clinical states associated with hypocupremia (sprue, celiac disease, nephrotic syndrome), effects of copper deficiency usually are not demonstrable. However, anemia due to copper deficiency has been described in individuals who have undergone intestinal bypass surgery (Zidar *et al.*, 1977), in those who are receiving parenteral nutrition (Dunlap *et al.*, 1974), in malnourished infants (Holtzman *et al.*, 1970; Graham and Cordano, 1976), and in patients ingesting excessive amounts of zinc (Hoffman *et al.*, 1988). While an inherited disorder affecting the transport of copper in human beings (Menkes' disease; steely hair syndrome) is associated with reduced activity of several copper-dependent enzymes, this disease is not associated with hematological abnormalities.

Copper deficiency in experimental animals interferes with the absorption of iron and its release from reticuloendothelial cells (Lee *et al.*, 1976). The associated microcytic anemia is related both to a decrease in the availability of iron to the normoblasts and, perhaps even more importantly, to a decreased mitochondrial production of heme. It may be that the specific defect in the latter case is a decrease in the activity of cytochrome oxidase. Other pathological effects involving the skeletal, cardiovascular, and nervous systems have been observed in deficient experimental animals (O'Dell, 1976). In human beings, the outstanding findings have been leukopenia, particularly granulocytopenia, and anemia. Concentrations of iron in plasma are variable, and the anemia is not always microcytic. When a low plasma copper concentration is deter-

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Maintenance Studies Included in the ISS (from Lindsay and Nissenson)

Lindsay Study

As per vol. 22, pg. 45:

Beginning in July, 1996, Dr. Robert Lindsay at London Health Services, Ontario, Canada, had administered Ferrlecit Injection to dialysis patients on a compassionate-use and maintenance basis. The following protocol was adopted: 1) test dose administration of 25 mg in 50 mL of normal saline over one hour; 2) therapeutic administration of 125 mg in 100 ml of normal saline over one hour for eight consecutive dialysis sessions; and 3) maintenance administration of 62.5 mg in 50 mL of normal saline over 30 minutes, once weekly following iron repletion.

Twenty-nine patients were treated between 7/28/96 thorough 11/22/97. Data entry captured the first 10 dosage administrations, i.e. through the first maintenance dose. Eleven patients completed the first 10 doses according to the protocol. Seven patients were switched to maintenance dosing early. Six patients ended the protocol before completion of 10 doses, or the protocol was not complete by 11/22/97. Patient specific modifications were made on 5 patients. There were a total of 278 separate drug administrations in these 29 patients.

No patient discontinued study drug due to an adverse event. No patient experienced a serious adverse event. There were 13 adverse events that the clinical coordinator felt were possibly or probably related to drug therapy, or where the relationship was unknown. These adverse events occurred in 11/29 (or 38%) patients, and are summarized below (vol. 22, pp. 47-9).

Adverse Events that Occurred in the Compassionate-Use, Maintenance Study of Lindsay et. al.

Patient	Adverse Event	Total Dose
100 64 M	Flushing	1087.5 mg
101 62 M	Transient tachycardia Nausea and vomiting	962.5 mg
107 56 M	Nausea Itching	1087.5 mg
108 48 F	Flushing	1087.5 mg
109 64 M	Headache	900 mg
112 85 M	Transient hypotension	837.5 mg

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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

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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

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Overall Safety Experience with Ferrlecit

The Integrated Summary of Safety for this NDA included safety information from: Studies 5600-01 and -03, published reports, two small "maintanence" studies, and post-marketing data from Italy and Germany.

The primary Ferrlecit-associated adverse events in Study 5600-01, were allergic reactions that occurred in 3 out of a total of 83 (or 3.6% of) Ferrlecit-treated patients, and which resulted in premature study discontinuation. Available information for these cases is summarized below:

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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.

Of the 38 patients exposed to Ferrlecit in Study 5600-03, 1 patient (or 2.6%) 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.

Of the 177 renal dialysis patients exposed to Ferrlecit in the previously-discussed published literature, 3(1.7%) patients experienced serious adverse events, which were: 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.

An additional published report by Zamen et. al., entitled, "Oversaturation of transferrin after intravenous ferric gluconate (Ferrlecit®) in hemodialysis patients," (Nephrol Dial Transplant 1996 11 820), conducted a study of peak serum iron study values following the i.v. administration of Ferrlecit. This study was initiated following development of nausea, facial reddening, and hypotension in 2 chronic hemodialysis patients who were receiving monthly infusions of 62.5 to 125 mg of Ferrlecit, and who were also determined to have TSAT values of > 100% at the time of symptoms. The authors found that longer infusions and lower doses of Ferrlecit resulted in lower peak serum iron, and iron saturation values. The relationship of serum iron study values

and the development of nausea, facial reddening, and flushing however, was not established in this study.

Two "maintenance studies" were submitted to provide further information of the use of Ferrlecit in chronic hemodialysis patients. The first was a compassionate-use, single-center study of 29 chronic hemodialysis patients who were administered 125 mg of i.v. Ferrlecit for 8 consecutive dialysis sessions, followed by a maintenance dose of 62.5 mg once weekly. No patient in this study discontinued study drug due to an adverse event, and there were no serious adverse events. A total of 13 adverse events occurred in 11 patients that the clinical coordinator felt were possibly or probably related to drug therapy. These reactions included flushing (3 patients), nausea and/or vomiting (3 patients), and transient hypotension, abdominal pain, sweating, headache, and flatulence (1 patient each).

The second "maintenance study" was a trial conducted by Dr. Allen Nissenson, who treated a total of 5 chronic hemodialysis patients with a history of anaphylaxis to iron dextran, with up to 1000 mg of i.v. Ferrlecit. No adverse events resulted.

Ferrlecit Injection has been used since 1959 in over 20 countries outside of the United States. Ninety-seven percent of the total sales of Ferrlecit in 1996 were in Germany, Italy, and Spain; over 80% of it's use in Germany is in renal hemodialysis patients, while 90% of it's use in Italy is as an oral dietary supplement.

Postmarketing information from Germany and Italy was obtained from the manufacturer of Ferrlecit (Rhone Polenc Rorer). Most all reported serious adverse events were allergic/anaphylactoid in nature. During the period 1976-96, there were 74 reports of allergic/anaphylactoid reactions for Ferrlecit Injection from Italy and Germany; none resulted in death, although 3 had unknown outcomes.

Notably, an increase in the number of reported anaphylactiod reactions in 1995 (i.e. 8 in 1994, and 25 in 1995) prompted an investigation of batch production records by the manufacturer. High molecular weight polysaccharides, probably α-1,6-glucans, in a new commercial source of sucrose, was identified as the culprit. When production was switched to the original source of sucrose, reports of allergic/anaphylactoid adverse events dropped (from 25 in 1995 to 6 in 1996).

In a sponsor-supported study by Faich and Strobos entitled, "Ferrlecit injection: safer intravenous iron therapy than iron dextrans," information was provided which indicated that the use of Ferrlecit results in a decreased reporting rate of

allergic/anaphylactoid reactions, and decreased case fatality rate. However, significant underreporting, and differences in the reporting patterns of different countries, complicate the interpretation of these results.

OVERALL CONCLUSIONS

The efficacy of Ferrlecit for the treatment of anemia in iron-deficient renal hemodialysis patients was primarily supported by the results of the dose-comparison concurrent control study 5600-01. Additional supportive information included the compassionate-use study 5600-03, as well as several reports from the literature.

Eligibility criteria for Study 5600-01 included a hemoglobin of < 10 g/dL or hematocrit of < 32%; and a serum ferritin of < 100 ng/mL or iron saturation of < 18%, in chronic renal dialysis patients who were receiving erythropoietin. Pre- and post-therapy results for intent-to-treat patients who received the high-dose Ferrlecit regimen (i.e. 1000 mg divided over 8 consecutive dialysis sessions) are summarized below.

Mean Pre- and Post-Therapy Results for High-Dose Ferrlecit Patients in Study 5600-01 (Intent-to-Treat Population)

	PRE-THERAPY	POST-THERAPY
Hemoglobin (g/dL)	9.6	10.7
Hematocrit (%)	29	33
Iron saturation (%)	16	25
Serum Ferritin (ng/mL)	88	287

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Note that the above post-therapy results approach the target values that are recommended by the National Kidney Foundation (Amer J Kid Dis 1997 30 S194); viz., a hemoglobin of 11-12 g/dL, hematocrit of 33-36%, iron saturation ≥20% (and <50%), and serum ferritin ≥100 ng/mL (and <800 ng/mL).

Note also that the results of patients who received the low-dose Ferrlecit regimen (i.e. 500 mg divided over 8 dialysis sessions), were equivalent to those of historical control patients, who received oral iron therapy only.

The primary safety concern with the use of Ferrlecit is the incidence of allergic/anaphylactoid reactions. These reactions occurred at a rate of 3.6% in Study 5600-01, 2.6% in Study 5600-03, 1.7% in the available published literature, and there have been 74 reports to the manufacturer of allergic/anaphylactoid reactions in the past 20 years from Italy and Germany. There

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Study 5600-01

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Safety Analysis

Extent of Exposure

A total of 88 patients received Ferrlecit in study 5600-01. Five patients discontined prematurely: one of these patients received a total of 375 mg, one patient received 125 mg, and one patient received 62.5 mg. Two patients received only the 25 mg test dose before discontinuing. Forty-four patients received a total of 1000 mg of Ferrlecit, and thirty-nine patients received a total of 500 mg.

Deaths

One patient (#109) died during the study. A narrative of this death is reproduced below (vol. 16, p. 143).

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Patient #109 was a 49-year-old male with multiple illnesses and abnormalities. The patient was severely anemic (hematocrit 26%, red blood cell count 2.6 mil/cmm, hemoglobin 8.6 g/dL, ferritin 118 ng/mL, and iron saturation 12%).

Prior to starting Ferrlecit therapy (Day 10), the patient had complained of pain at the graft site used for hemodialysis access. The pre-treatment WBC count was 9000 with a shift to 75% neutrophils. The patient received Ferrlecit (62.5 mg, IV) on each of 8 consecutive hemodialysis days. He tolerated the treatment well except for occasional complaints of graft-site pain. On the day of the 7th Ferrlecit treatment, the patient reported edema of the lower extremities and a weight gain of 19 lbs from baseline (156 lbs at baseline, 175 lbs at Treatment 7).

Two days after completion of the Ferrlecit treatment (Day 19), the patient's rHuEPO was increased from 4,000 to 10,000 units because his hematocrit was still low. Liver function test values had increased, and the patient's WBC was 12,800 with 84.9% neutrophils.

Two days later, the patient was hospitalized with cellulitis of the lower extremities, left lower lobe pneumonia, volume overload, cardiomegaly, hyperkalemia, and congestive heart failure. Antibiotic therapy and supportive measures were initiated. Over the course of the following 2 weeks, the patient's condition worsened, and signs of systemic involvement were observed. Tentative diagnoses of septic phlebitis and biliary tract sepsis were considered and treated. Liver function deteriorated further, and the patient died 17 days after completion of the Ferrlecit treatment.

The chronology of events as described above is consistent with a progressive and overwhelming infectious process in a patient whose health was compromised with numerous pre-existing medical problems. The infection may have pre-dated the start of Ferrlecit therapy (75% neutrophils at baseline) and seems, in any case, to have developed independently of the Ferrlecit treatment. Systemic involvement ensued with liver function deterioration, as well as other complications. Although blood cultures were negative, the final diagnosis was sepsis.

The investigator concluded that "there does not appear to be any relation between this patient's death and his receiving Ferrlecit".

Premature Withdrawals

Five patients were prematurely withdrawn from the study, for the reasons cited below (vol. 8.1, p. 2). No further information beyond what is presented below was available from the sponsor.

Reasons for Premature Withdrawals from Study 5600-01

Patient	Reasons for Study Discontinuation
004	"Blood diarrhea"; Evaluation revealed A-V malformations that were surgically corrected. Patient discontinued following the test dose of Ferrlecit
120	"Change in mental status"; No further details provided. Patient was in the low-dsoe group, and discontinued following the 6th dose of Ferrlecit.
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.

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Serious Adverse Events

A total of 17 patients experienced a serious adverse event; none were attributed by the study investigator to study drug. All of these events resulted in hospitalization (and hence were designated as "serious"). Information provided for these cases is reproduced below (vol. 16, pp. 144-145). Note that no further information beyond what is provided below, was available from the sponsor (information amendment dated 4/6/98, vol. 10.1).

Patients who Experienced a Serious Adverse Event

Patient	Adverse Event
004 72 F	"Bloody diarrhea." Patient evaluation revealed: hemorrhoids, diverticulosis, arterio-venous malformations/corrected surgically. Patient received only a test dose of Ferrlecit.
110 77 F	Abdominal/flank pain, and shortness of breath in a patient with a pre-existing nephrolithiasis. Patient received 1000 mg of Ferrlecit.
113 61 F	Fever and cervical lymphadenopathy. Tentative diagnosis was tuberculosis. Patient received 1000 mg of Ferrlecit.
120 74 F	"Changed mental status." Patient had a history of diabetes and peripheral neuropathy, and had a R BKA. Patient received 375 mg of Ferrlecit.
121 77 M	Shortness of breath, fluid overload. Patient received 1000 mg of Ferrlecit.
122 32 M	Fever, premature ventricular contractions, fatigued for 3 weeks before event. Tentative diagnosis was viral enteritis. CMV antibodies were positive. Patient received 1000 mg of Ferrlecit.
126 81 F	Right leg pain, tingling, and discomfort, for 2 weeks. History of peripheral vascular disease and R femoral arterio-venous graft. Patient received 500 mg of Ferrlecit.
129 82 M	"Changed mental status," fever, cough. History of multi-infarct dementia and dehydration. Patient received 1000 mg of Ferrlecit.
137 78 F	Abdominal pain, melena, and diverticulosis. Patient received 1000 mg of Ferrlecit.
316 32 F	"Generalized pain." Pre-existing lupus, fibromyalgia, left leg dystrophy, and Raynaud's disease. Patient received 500 mg of Ferrlecit.
324 80 F	Right upper lobe pneumonia, weakness, dizziness, and vomiting. Patient received 500 mg of Ferrlecit.
327 87 F	Patient hospitalized for creation of arterio-venous fistula. Patient received 1000 mg of Ferrlecit.
331 45 F	Patient hospitalized for R Forearm thrombectomy. Patient received 500 mg of Ferrlecit.
332 64 M	Patient hospitalized for a ventral hernia repair and arterio-venous fistula creation. Patient received 1000 mg of Ferrlecit.
333 80 F	"Decreased level of consciousness" with tonic-clonic seizure. History of confusion for 24 hours following dialysis. EEG showed evidence of metabolic encephalopathy. Patient received 1000 mg of Ferrlecit.
338 72 M	Patient hospitalized for arterio-venous fistula creation. Patient received 1000 mg of Ferrlecit.

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315 78 F	Gortex graft insertion. Collapsed vein. Patient received 1000 mg of Ferrlecit.

None of the above serious adverse events were felt by the on-site investigator to be related to study drug.

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All Adverse Events

Note that safety data was not collected for historical control patients. Thus safety data was extracted from literature review articles of adverse events that have been reported in chronic hemodialysis patients. These adverse events were then proportionally distributed among the 25 historical control patients. The study report states that the review chapter to be used for this purpose was by Levin NW et. al ("Complications During Hemodialysis," in Clinical Dialysis, 2nd edition, Norwalk, Appleton, and Lange, 1990), while the table of adverse events in the "Results" section of the NDA study report states that the review article by Abuelo JG et. al., entitled, "Acute Symptoms Produced by Hemodialysis: a Review of Their Causes and Associations," (Semin Dial 1993 6 59) was used.

The incidences of adverse events were 93% in the low-dose group, 96% in the high-dose group, and 92% in the historical/literature control patients.

Individual adverse events that occurred with a frequency of ≥ 5.0% in Ferrlecit-treated patients are shown below (Tables 16 and 16a, vol. 16, pp. 137-42).

Adverse Events that Occurred with a Frequency of ≥5.0%

ADVERSE EVENT	TREATMENT GROUP		
	500 mg (N=41)	1000 mg (N=47)	Historical/Literature Control (N=25)
Body As a Whole			
Injection site reaction	15(37%)	17(36%)	-
Chest pain	1(2%)	8(17%)	9(36%)
Headache	2(5%)	7(15%)	6(24%)
Pain	5(12%)	6(13%)	-
Fatigue	3(7%)	4(9%)	-
Fever	2(5%)	2(4%)	2(8%)
Asthenia	1(2%)	5(11%)	-
Back pain	0(0%)	3(6%)	3(12%)
Abdominal pain	1(2%)	4(9%)	-
Malaise	3(7%)	1(2%)	-
Cardiovascular Disorders			
Hypotension	14(34%)	18(38%)	23(92%)
Hypertension	7(17%)	10(21%)	-
Syncope	2(5%)	4(9%)	-
Gastrointestinal Disorders			
Nausea	7(17%)	11(23%)	18(72%)
Vomiting	5(12%)	8(17%)	12(48%)
Diarrhea	1(2%)	3(6%)	-
Central and Peripheral Nervous System Disorders			
Cramps	17(42%)	18(38%)	17(68%)
Dizziness	6(15%)	9(19%)	-
Paraesthesia	4(10%)	3(6%)	-

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Respiratory Disorders			
Dyspnea	3(7%)	7(15%)	-
Upper respiratory tract infection	5(12%)	2(4%)	-
Skin and Appendages Disorders			
Pruritis	3(7%)	4(9%)	-
Itching	0(0%)	0(0%)	7(28%)
Rash	3(7%)	1(2%)	-
Metabolic and Nutritional Disorders			
Hyperkalemia	5(12%)	2(4%)	-
Edema, generalized	3(7%)	3(6%)	-
Edema, legs	4(10%)	0(0%)	-
Heart Rate and Rhythm Disorders			
Tachycardia	2(5%)	4(9%)	-
Bradycardia	3(7%)	0(0%)	-

Those adverse events that occurred more often in high-dose patients, by a difference of ≥ 5%, are tabulated below (Table 16 and 16a, vol. 16, pp. 137-42).

Adverse Events that Occurred More Often in High-Dose Ferrlecit Patients, By a Difference of ≥ 5%

ADVERSE EVENT	TREATMENT GROUP	
	500 mg (N=41)	1000 mg (N=47)
Body As a Whole		
Chest pain	1(2%)	8(17%)
Headache	2(5%)	7(15%)
Asthenia	1(2%)	5(11%)
Back pain	0(0%)	3(6%)
Abdominal pain	1(2%)	4(9%)
Gastrointestinal Disorders		
Nausea	7(17%)	11(23%)
Vomiting	5(12%)	8(17%)
Respiratory Disorders		
Dyspnea	3(7%)	7(15%)

When the incidences of adverse events were statistically compared between high- and low-dose patients, only chest pain was found to occur more often in high-dose patients (p=0.033, Fisher's Exact Test); and leg edema occurred more often in low-dose patients (p=0.043, Fisher's Exact Test).

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Those adverse events that were considered by the on-site Investigator to be "possibly" or "probably" related to study drug are summarized below (Appendix 13.2.3, vol. 17, pp. 31ff.).

Adverse Events Reported to be "Possibly" or "Probably" Related to Study Drug

Patient	Dose Group	Adverse Event	Severity	Relation to Study Drug
335	500mg	Rash	Severe	Possible
302	1000mg	Cramps	Mild	Possible
311	1000mg	Nausea, abdominal pain, back pain, and fatigue Rash	Moderate Mild	Probable Possible
333	1000mg	Agitation	Moderate	Possible
102	1000mg	Nausea, vomiting Syncope	Mild Moderate	Possible Possible
116	1000mg	Pruritis, Chest Pain	Moderate	Probable
117	1000mg	Parasthesia	Mild	Probable
121	1000mg	Erythrocytes Abnormal	Mild	Possible

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Study 5600-03

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Safety Analysis

Extent of Exposure

As per vol. 20, p. 40: "This was a variable dose study; the maximum amount of Ferrlecit received during the treatment course by any patient was 1125 mg, and the minimum amount was 62.5 mg."

Deaths

There were no deaths in Study 5600-03.

Premature Discontinuations

One patient (#552) discontinued due to dizziness, lightheadedness, diplopia, malaise, and weakness, considered by the investigator to be "probably" related to study drug. This patient had received a total of 125 mg of Ferrlecit. No further information was provided.

Serious Adverse Events

A total of 4 patients were hospitalized for the following (serious) adverse events. Available information on these cases is reproduced below (vol. 20, p. 44).

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Serious Adverse Events

Patient Number	Age	Sex	Event	Relation to study drug
536	38	M	Rigors and chills. Blood cultures showed *Staphylococcus aureus* bacteremia. Received 1000 mg Ferrlecit.	None
538	68	M	Myocardial infarction. One dose of Ferrlecit was withheld. Received 1125 mg Ferrlecit.	None
544	35	M	Chills. Four blood cultures showed *Staphylococcus* epidermis bacteremia. Received 375 mg Ferrlecit.	Unlikely
552	65	M	Dizziness, lightheadedness, diplopia, malaise, and weakness. Received 125 mg Ferrlecit.	Probable

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All Adverse Events

Note that safety data was not collected for historical control patients. Instead, safety data was extracted from a literature review article by Abuelo et. al. (Semin Dial 1993 6 59). These adverse events were then proportionally distributed among the 25 historical control patients.

A total of 74% of Ferrlecit-treated patients experienced an adverse event, and these are summarized below (Table 8, vol. 20, pp. 42-3).

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All Adverse Events

BODY SYSTEM Adverse Event	Ferrlecit (N = 38) n	%	Control* (N = 25) n	%
ANY BODY SYSTEM	28	73.7	23	92.0
BODY AS A WHOLE	17	44.7	9	36.0
Chest Pain	4	10.5	9	36.0
Headache	0	0.0	6	24.0
Chills	3	7.9	2	8.0
Fever	2	5.3	2	8.0
Asthenia	3	7.9	-	
Abscess	3	7.9	-	
Pain Back	0	0.0	3	12.0
Abdominal Pain	3	7.9	-	
Carcinoma	2	5.3	-	
Sepsis	2	5.3	-	
Pain	2	5.3	-	
Infection	2	5.3	-	
Flu Syndrome	1	2.6	-	
Malaise	1	2.6	-	
CARDIOVASCULAR DISORDERS	4	10.5	23	92.0
Hypotension	4	10.5	23	92.0
GASTRO-INTESTINAL DISORDERS	8	21.1	18	72.0
Nausea	2	5.3	18	72.0
Vomiting	4	10.5	12	48.0
Diarrhea	3	7.9	-	
Nausea and Vomiting	1	2.6	-	
Nausea Vomiting and Diarrhea	1	2.6	-	
Dyspepsia	1	2.6	-	
AUTONOMIC NERVOUS	0	0.0	17	68.0
Muscle Cramp	0	0.0	17	68.0
Restlessness	0	0.0	6	24.0
SKIN AND APPENDAGES	11	28.9	-	
Application Site Reaction	10	26.3	-	
Skin Carcinoma	1	2.6	-	
DIGESTIVE SYSTEM	6	15.8	-	
Gastrointestinal Disorder	2	5.3	-	
Rectal Disorder	2	5.3	-	
Large Intestine Perforation	1	2.6	-	
Gastrointestinal Hemorrhage	1	2.6	-	
Gastroenteritis	1	2.6	-	
Anorexia	1	2.6	-	

CARDIOVASCULAR SYSTEM		
Myocardial Infarct	4 (10.5)	-
Syncope	2 (5.3)	-
Atrial Fibrillation	1 (2.6)	-
Angina Pectoris	1 (2.6)	-
	1 (2.6)	-
SKIN AND APPENDAGES DISORDERS		
Itching	0 (0.0)	7 (28.0)
	0 (0.0)	7 (28.0)
MUSCULOSKELETAL SYSTEM		
Leg Cramps	7 (18.4)	-
Arthralgia	3 (7.9)	-
Tenosynovitis	2 (5.3)	-
Myalgia	1 (2.6)	-
Arthritis	1 (2.6)	-
	1 (2.6)	-
RESPIRATORY SYSTEM		
Dyspnea	5 (13.2)	-
Lung Edema	4 (10.5)	-
Cough Increased	1 (2.6)	-
	1 (2.6)	-
NERVOUS SYSTEM		
Dizziness	5 (13.2)	-
Insomnia	2 (5.3)	-
Hypesthesia	1 (2.6)	-
Depersonalization	1 (2.6)	-
Agitation	1 (2.6)	-
	1 (2.6)	-
METABOLIC AND NUTRITIONAL DISORDERS		
Hypoglycemia	2 (5.3)	-
Hypervolemia	1 (2.6)	-
	1 (2.6)	-
SPECIAL SENSES		
Diplopia	2 (5.3)	-
Abnormal Vision	1 (2.6)	-
	1 (2.6)	-
HEMIC AND LYMPHATIC SYSTEM		
Hypochromic Anemia	1 (2.6)	-
	1 (2.6)	-

* Historical control data taken from Abeuelo et al. (54).
\+ - = No data available.

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Adverse events that were reported by the on-site Investigator to be "possibly" or "probably" related to Ferrlecit were: dizziness, diplopia, malaise, and asthenia in one patient; and diarrhea, myalgia, and arthralgia in a second patient.

Clinical Laboratory Evaluation

Shift table analyses of clinical laboratory parameters (which included liver function tests, complete blood count, and BUN, creatinine, and glucose values) during the study were performed (Table 10, vol. 20, pp. 50-1). Those laboratory values for which ≥ 5% of patients were in the "normal→abnormal" category at Day 50 compared to baseline, were: glucose (5/38 patients or 13%), and WBC (2/38 patients or 5%). No information was recorded for bilirubin or neutrophil values.

For comparison, baseline laboratory values from a population of approximately 1100 hemodialysis patients were obtained from the NIDDK Hemodialysis Study, Data Coordinating Center, (Cleveland Clinic Foundation). These values are summarized below (Table 20, vol. 16, p. 163).

ATTACHMENT 21

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Blood: Principles and Practice of Hematology
Bridges and Seligman

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who have had significant allergic reactions including anaphylaxis and local urticaria. Such a procedure should be performed in a setting where life support systems, including an anesthesiologist, are available.

Other side effects of desferrioxamine are less threatening, but troublesome nonetheless. The most common of these is inflammation at the site of the infusion. This is a chemical irritation and not an allergic phenomenon and is much more common in adults than in children. Erythema, swelling, tenderness, and occasionally blistering and ulceration can occur. Hydrocortisone greatly reduces this local reaction. Two or three mg of hydrocortisone in solution are mixed with the desferrioxamine and included in the infusion, or 1% hydrocortisone ointment is applied to the site of the infusion.

Cataracts have developed in some experimental animals treated with desferrioxamine and have been reported on rare occasions in patients receiving the drug.[404] This appears to be a dose-dependent phenomenon. Before beginning treatment, patients should be checked for cataracts by an ophthalmologist. Thereafter, they should have yearly ophthalmologic examinations. Cessation of desferrioxamine therapy halts and may even reverse the progression of cataracts. One group of children treated with doses of desferrioxamine ranging from 34 to 150 mg/kg over 12 hours developed optic and vestibular neurotoxicity, resulting in impaired vision and balance.[405] These toxic effects were also reversed with the cessation of treatment.

A major factor limiting the usefulness of desferrioxamine therapy is its expense. The infusion pump alone costs about $1000. The drug is expensive, and with the associated needles, infusion tubing, and other supplies, the annual total may exceed $12,000 to $15,000. Third-party payers generally cover only 80% of this cost at most, leaving a very large bill for the patient and family. In addition, the socioeconomic profiles of the patients tend to magnify the problem. Because thalassemia is a hereditary disorder, more than one child may be affected in a given family, creating a tremendous financial burden. Moreover, some of the countries in which thalassemia is prevalent lack the financial resources to provide such an expensive form of treatment. The myelodysplastic anemias of adulthood, on the other hand, present in older patients who often are near the age of retirement. The expense of desferrioxamine treatment can be devastating to families on fixed incomes.

Compliance with desferrioxamine therapy is often poor. Consequently, a search is continuing for orally active iron chelators that are less expensive to administer than desferrioxamine. Some of the newer lipophilic chelators appear poised to fill this role.

Lipophilic Iron Chelators

The mechanism by which lipophilic chelators mobilize iron from cells is complex. The relative lipid solubility of the free and iron-complexed forms of the chelators greatly influences iron mobilization, as do the iron-binding constants of the molecules.[406] With the hydroxypyridin-4-one class of chelators, iron mobilization from primary hepatocyte cultures is most effective when the components are about equally soluble in lipid or aqueous phases. Highly hydrophilic compounds may fail to mobilize enough iron, whereas the highly lipophilic compounds tend to be toxic. Comparison of chelators with similar lipid partition coefficients and different iron-binding constants reveals that the affinity of the chelator for Fe^{3+} is especially important at concentrations of less than 10 μmol/L. At concentrations exceeding 500 μmol/L, the size of the chelatable iron pool in the cells determines the degree of iron mobilization. The ability of iron chelators to cross the barrier presented by the cell membrane greatly influences their ability to mobilize iron. The fact that the most active hydroxypyridin-4-one type chelators release more iron than equimolar concentrations of desferrioxamine reflects this point.

Pyridoxal isonicotinylhydrase (PIH) is a potent and clinically promising lipophilic chelator. In reticulocytes, the primary site from which the drug mobilizes iron appears to be the mitochondria.[407] The agent mobilizes little iron in reticulocytes in which heme biosynthesis is not blocked either by isoniazid or by succinylacetone, an inhibitor of δ-aminolevulinic acid dehydrase, which is the second enzyme in the heme biosynthetic pathway. The uptake of PIH into reticulocytes is rapid, attaining a plateau after 10 to 15 minutes.[407] The compound crosses the membrane by passive diffusion, reflecting its lipophilic character. One characteristic of PIH that makes it particularly effective in iron mobilization from cells is that the agent retains a relatively high lipid partition coefficient even after it binds iron. Some lipophilic chelators, such as α,α'-bipyridyl, assume a much lower lipid partition coefficient after binding iron. As a result, the agents may enter cells readily, but become entrapped after iron chelation.[408]

When tested for their ability to inhibit the uptake of labeled iron into primary cultures of rat hepatocytes, PIH and the related chelator, pyridoxal benzoylhydrazone, are at least as efficient as desferrioxamine in this regard.[409] The chelators reduce both the net uptake of ^{59}Fe into the cells and the incorporation of the iron into ferritin. Pyridoxal benzoylhydrazone, a more lipophilic compound, in fact exceeds both PIH and desferrioxamine in this capacity, bolstering the conclusion that lipophilicity plays an important role in iron mobilization by these chelators.

Oral Iron Chelation

Despite its impressive clinical record of safety and efficacy in the treatment of transfusional iron overload, the requirement for parenteral administration has been a severe stumbling block in the use of desferrioxamine. The drug is not completely inactive when given orally and when administered in this fashion in doses ranging from 3 to 9 g/d, desferrioxamine mesylate substantially increases iron excretion in patients with transfusional hemochromatosis.[410] In no instance does the level of iron excretion in response to orally administered desferrioxamine approach that achieved when the drug is given parenterally.

The search for alternative, orally active chelating agents had a number of false starts and disappointing leads.[411] Some promising leads have developed, but no agent has received endorsement for general clinical use.[412] The prospect has improved for an effective and safe orally active chelator to be available in the near future.

ACUTE IRON TOXICITY

Iron poisoning is rare except in children who have accidentally ingested iron preparations. The clinical sequelae to the ingestion of 2 g of ferrous sulfate occurs in two stages, with the first developing in about 30 minutes.[413-415] The iron salt produces irritation of the stomach and duodenum manifested by nausea, vomiting, and abdominal pain. Necrosis of the epithelial cells of the gastrointestinal tract leads to hemorrhage and hematemesis, which may be followed by shock. Diarrhea, drowsiness, and coma can develop, and death can occur in 5 to 6 hours after ingestion of the iron.

Often, the patient with acute iron toxicity survives the initial phase and appears to enter a period of recovery. Rapid influx of iron into the plasma overwhelms the binding capacity of transferrin, leaving much of the mineral in

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loose association with other proteins such as albumin.[414,415] This excess free iron can cause cardiovascular collapse and death. In other cases, the excess iron is deposited in the liver, producing hepatic necrosis and fibrosis. Other long-term complications in survivors of iron overdose include pyloric stenosis and severe gastric scarring from the initial necrotizing mucosal injury.

Treatment of acute iron overdose includes gastric lavage to remove as much iron as possible, followed by administration of desferrioxamine, both orally and intravenously. The orally administered chelator binds the free iron that remains in the gastrointestinal tract. The chelator given parenterally binds and inactivates excess iron in the plasma and tissues.[414,415] Intravenous desferrioxamine should be continued until the transferrin saturation is consistently maintained below about 80%. The patient should be supported with fluid and electrolytes as needed to correct any imbalances that could occur. Iron overdose, particularly in children, requires consultation with an experienced clinical toxicologist, who should individualize the therapeutic plan.

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Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

MAY 18 1998

Application Number: NDA 20-955

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

Sponsor: R & D Laboratories, Inc.

Material Reviewed

Submission Date(s): BL April 6, 1998 (Color mock carton and immediate container labels)

Receipt Date(s): April 7, 1998

Background and Summary Description: NDA 20-955 for Ferrlecit® was submitted December 30, 1997 for first line treatment for iron deficiency anemia in renal hemodialysis patients on supplemental recombinant human erythropoetin. A draft package insert was included in Volume 1.1, pages 2.1-2.10(c) and Volume 1.5, pages 4.140-4.189 of the original submission. In response to the Division's January 27, 1998 request, the firm submitted color mock carton and immediate container labels April 6, 1998. Three column labeling including the firm's draft labeling, the Division's revisions and comments, and annotations will be prepared for the package insert when all reviewer's comments have been received. The firm proposes to market Ferrlecit® in 5ml ampules packaged in foil-covered trays of five ampules with two trays per carton of ten ampules. The April 6, 1998 submission included color mock carton, foil-on-tray, and immediate container labels.

Review

Carton Label

1. The bottom panel includes the statement, "Store at controlled room temperature 15°-30° C (59°- 86°F).".

   The storage statement is acceptable per CMC reviewer Ray Frankewich, May 18, 1998.

2. Per 21 CFR 201.100(b)(7) the label should include, "A statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its identity, strength, quality, and purity.". No such statement is included.

   Per Ray Frankewich, a special container, (i.e., light resistant, glass) is not

required, so no additional statement is necessary.

Foil-on-Tray Label

1. Per 21 CFR 201.1, the name and place of business of the manufacturer, packer, or distributor is required on the label. This information is lacking.

2. Per the FDA Modernization Act of 1997 the statement, "Rx only" is required on the label of prescription drugs. This statement is lacking.

3. Per 21 CFR 201.100(b)(2) and 201.55, the label of a prescription drug must bear a statement of the usual or recommended dosage or a statement such as, "See package insert for dosage information". This information is lacking.

4. Per 21 CFR 201.100(b)(5)(iii) the label of a prescription drug must bear the established names and quantities of the inactive ingredients. This information is lacking.

5. Per 21 CFR 201.100(b)(6) the label of a prescription drug must bear an identifying lot or control number. This information is lacking.

6. Per 21 CFR 211.137(a) the label of a prescription drug must, "... bear an expiration date determined by appropriate stability testing...". There is no provision for an expiration date.

7. Per 21 CFR 211.137(b) the expiration date, "... shall be related to any storage conditions stated on the labeling as determined by stability studies...". Storage conditions are not stated.

Ampule Label

1. Per the FDA Modernization Act of 1997 the statement, "Rx only" is required on the label of prescription drugs. This statement is lacking.

2. Per 21 CFR 201.100(b)(5)(iii) the label of a prescription drug must bear the established names and quantities of the inactive ingredients. This information is lacking.

3. Per 21 CFR 201.100(b)(6) the label of a prescription drug must bear an identifying lot or control number. This information is lacking.

4. Per 21 CFR 211.137(a) the label of a prescription drug must, "... bear an expiration date determined by appropriate stability testing...". There is no provision for an expiration date.

5. Per 21 CFR 211.137(b) the expiration date, "... shall be related to any storage conditions stated on the labeling as determined by stability studies...". Storage conditions are not stated.

Conclusions

Foil-on-Tray Label

The firm should be requested to 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. an identifying lot or control number;
6. an expiration date determined by appropriate stability testing;
7. and appropriate storage conditions.

Ampule Label

The firm should be requested to add the following information to the ampule label:

1. the statement "Rx only";
2. the established names and quantities of inactive ingredients;
3. an identifying lot or control number;
4. an expiration date determined by appropriate stability testing;
5. and appropriate storage conditions.

/S/ [redacted]
Consumer Safety Officer 5/18/98

CSO/Strangin

Division of Gastrointestinal and Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-955

SEP 14 1998

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

Sponsor: R & D Laboratories, Inc.

Material Reviewed

Submission Date(s): AZ, August 19, 1998 (complete response to the June 30, 1998 approvable letter including revised draft labeling)

BL, August 19, 1998 (revised foil-on-tray label)

Background and Summary Description: NDA 20-955 for Ferrlecit was submitted December 30, 1997 for first line treatment of iron deficiency anemia in renal hemodialysis patients on supplemental recombinant human erythropoetin. The application was approvable June 30, 1998 pending a complete response to CMC questions and final printed labeling identical in content to the marked-up draft labeling attached to the approvable letter. The firm submitted a complete response to the approvable letter August 19, 1998 including a revised draft package insert and a revised foil-on-tray label. The revised package insert is compared to the marked-up draft labeling attached to the approvable letter. The foil-on-tray label is compared to the information requested in the approvable letter. The differences are noted below.

Review

Package Insert

1. Black Box Warning

   The Black Box Warning is removed and replaced with bolded [redacted] subsections to the WARNINGS section.

2. DESCRIPTION section

   A. The word "[redacted]" is deleted from the tradename.

   This is acceptable since "injection" is included in the established name.

   B. The phrase at the end of the first sentence in the first paragraph beginning with the words, "[redacted]" is deleted.

C. A new sentence beginning with, [redacted] is added after the first paragraph.

The firm was directed, in the marked-up draft labeling, to delete the proposed structural formula.

D. Active and inactive ingredients are listed in the third paragraph as requested in the approvable letter.

With the exception of item A, the review chemist will review the proposed changes.

3. CLINICAL PHARMACOLOGY section

Two paragraphs discussing iron metabolism, absolute iron deficiency, and functional iron deficiency are added at the beginning of this section.

The medical officer will review the proposed change.

4. INDICATIONS AND USAGE section

A. The phrase [redacted] is added.

The medical officer will review the proposed change.

B. Minor editorial changes are made.

The minor editorial changes are acceptable.

5. CLINICAL STUDIES section

A. A tabular presentation and summary of the results of Study 5600-01 are added as requested in the marked-up draft labeling attached to the approvable letter.

B. A tabular presentation and summary of the results of Study 5600-03 are added as requested in the marked-up draft labeling attached to the approvable letter.

C. A tabular presentation of the number of Ferrlecit doses received by patients in Study 5600-03 is added as requested in the marked-up draft labeling attached to the approvable letter.

D. Minor editorial changes are made.

The medical officer will review the proposed changes.

6. WARNINGS section

A. The "Transient flushing and hypotension" subsection is revised including bolding, a recommended infusion rate, and a statement that these reactions are not associated with hypersensitivity.

B. A bolded subsection entitled, [redacted]s" is added in place of the boxed warning.

The medical officer will review the proposed changes.

7. PRECAUTIONS subsection

The phrase, [redacted] is added to the "Geriatric Use" subsection.

The medical officer will review the proposed change.

8. ADVERSE REACTIONS section

A. "Transient flushing and hypotension" subsection

1. The first paragraph of the "Transient flushing and hypotension" subsection is revised identically to the corresponding subsection of the WARNINGS section.

2. The sentence beginning, [redacted] is added to the second paragraph.

3. The sentence beginning, [redacted] is added at the end of this subsection.

B. "Hypersensitivity reactions" subsection

1. A new first sentence regarding fatal hypersensitivity reactions is added.

2. The words, [redacted] are added to the second sentence, first paragraph and the number of Ferrlecit exposed patients in Study 5600-01 is changed from 83 to 88.

3. Most of the second paragraph is deleted and replaced with, [redacted]

4. The phrase, [redacted] is added to the third paragraph.

5. The number of Ferrlecit treated patients reported in the literature is increased from 177 to 226 in the fourth paragraph.

6. In the fourth paragraph, the number of Ferrlecit treated patients reported in the literature that experienced adverse reactions which recurred on drug rechallenge was changed from three to two. A patient reported to have experienced an anaphytactoid reaction is deleted.

7. The sentence beginning, [redacted] is added at the end of this subsection

C. "Laboratory Changes" subsection

The text regarding the lack of abnormal laboratory findings associated with Ferrlecit is revised.

D. "Other Adverse Events Observed During Clinical Trials" subsection

The requested list of adverse events by body system in descending order by frequency and severity is included.

The medical officer will review the proposed changes.

9. OVERDOSAGE section

A. Text regarding acute iron poisoning following rapid infusions of Ferrlecit is deleted in the first sentence of the third paragraph.

B. The words, [redacted] are deleted from the last sentence in the third paragraph.

C. Minor editorial changes are made.

The medical officer will review item A. The pharmacology team leader will review item B.

10. DOSAGE AND ADMINISTRATION section

A. The words, [redacted] are added to the first sentence in the second paragraph and the words "[redacted]" are added to the last sentence in that paragraph.

The medical officer will review the proposed change.

C. The sentence, '[redacted]' is added at the end of this section.

The CMC reviewer will review the proposed change.

Foil-on-Tray Label

The following items are added as requested in the approvable letter dated June 30, 1998:

A. the names and places of business of the manufacturer and distributor;

B. the statement "Rx only";

C. a reference to the package insert for complete prescribing information;

D. the established names and quantities of the inactive ingredients;

E. space for an identifying lot number;

F. space for an expiration date;

G. and a storage statement.

The CMC reviewer will review the list of active and inactive ingredients. The remainder of the foil-on-tray label is acceptable.

Ampule Label

The following items are added as requested in the approvable letter dated June 30, 1998:

A. the statement "Rx only";

B. the established names and quantities of the inactive ingredients;

C. space for an identifying lot number;

D. space for an expiration date;

E. and a storage statement.

The CMC reviewer will review the list of active and inactive ingredients. The remainder of the ampule label is acceptable.

Conclusions

Package Insert

The medical officer, CMC reviewer, and pharm/tox team leader will review the appropriate sections of the package insert as described above.

Foil-on-Tray Label

The CMC reviewer will review the foil-on-tray label as described above.

Ampule Label

The CMC reviewer will review the ampule label as described above.

BEST POSSIBLE

/S/

Regulatory Health Project Manager

9-14-98

cc:
Original NDA 20,955
HFD-180/Div.Files
HFD-180/B.Strongin
HFD-180/Reviewers

APPEARS THIS WAY ON ORIGINAL

Drafted: BKS/September 10, 1998
R/d Init:
Final:

CSO Review

GREENBERG TRAURIG
ATTORNEYS AT LAW

ORIGINAL

ORG. AZ 09/03/98 NC-T

Jur Strobos
202/331-3150

ORIG AMENDMENT

August 19, 1998

Dr. Murray M. Lumpkin
Deputy Director
Center for Drug Evaluation and Research
HFD-3; Room 6027
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

Dr. Paula Botstein, Director
Office of Drug Evaluation I
HFD-103; Pkln. Bldg. 13B45
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

In re NDA 20-955
R&D Laboratories, Inc.
Amendment # 20

Dear Drs. Botstein and Lumpkin:

On behalf of R&D Laboratories, Inc., please find enclosed an amendment to the above-captioned NDA. This is a complete response to the June 30, 1998, "approvable" letter. The amendment consists of: (1) this letter; (2) attachments to the letter [Package Insert Appendix (Tabs A-Z)]; (3) an annotated spread sheet (8½" x 14") with the sponsor's underlined, strikeout revision of agency's proposed package insert (PI); (4) a response to Chemistry, Manufacturing and Controls questions with attachments designated with Roman numerals (including Tab II which is the 9-month ICH stability report; (5) 20 copies of the proposed final printed PI; and, (6) 20 copies of the ampule and immediate container labeling (10 are on heavy-weight material).

This cover letter and the Package Insert Appendix are also the background materials for the September 29th meeting.

/S/ 8-19-98

GREENBERG TRAURIG HOFFMAN LIPOFF ROSEN & QUENTEL
A PARTNERSHIP OF PROFESSIONAL CORPORATIONS
1300 CONNECTICUT AVENUE, N.W.
WASHINGTON, D.C. 20036
202-331-3100 FAX 202-331-3101
MIAMI NEW YORK WASHINGTON, D.C. PHILADELPHIA SAO PAULO
FORT LAUDERDALE WEST PALM BEACH ORLANDO TALLAHASSEE BOCA RATON

For convenience, the agency's proposed black box statement and the firm's proposed response are at Tab A. The agency's comments on "rate of administration" and acute iron toxicity along with the firm's proposed response are provided at Tab B. This cover letter also requests expiration dating of 24 months.

Summary

There are compelling reasons to differentiate iron dextrans from Ferrlecit® in labeling, including the black box warning. First, clinical data do not support identical warnings. Second, Ferrlecit® has a different indication and is a new chemical entity. Third, the sponsor believes that the proposed black box may lead to iatrogenic injury from unwarranted pressor administration. Fourth, FDA's existing policies on black box labeling do not support a black box for Ferrlecit®. Fifth, in light of the differences in indication, the proposed black box represents a recommendation on off-label usage. Sixth, the language is inaccurate. Seventh, the black box warning is premature and may prejudice proposed phase IV data collection. Eighth, the sponsor believes that a better alternative is careful monitoring of post-launch use given the indicated patient population.

Discussion

1. Agency's Proposed Black Box Labeling

a. The rate and severity of immunologic reactions to Ferrlecit®.

Hypersensitivity reactions are immunologically-mediated adverse events. Type I hypersensitivity reactions include: IgE-mediated mast cell activation (anaphylaxis); and, direct drug action on mast cells (anaphylactoid). Agents classically responsible for anaphylaxis include hymenoptera venom, penicillin (as a protein bound hapten), and dextran. Agents responsible for direct release of some or all mast cell mediators of anaphylaxis include such drugs as ciprofloxacin, vancomycin and radiocontrast media (RCM). While the clinical syndromes can be identical, two distinguishing features are: (1) anaphylaxis can result from exposure to even minute amounts of allergen in immunologically-sensitized individuals; and, (2) the incidence and severity of anaphylactoid reactions is generally dependent on the rate of drug administration and dosage. Anaphylactoid reactions on average, therefore, have a shorter time course and are less severe than anaphylaxis that is IgE-mediated. Fatal Type I hypersensitivity reactions represent a fractional subset of "serious or life-threatening" events which, in turn, are a fractional subset of all, including less severe, immunologic reactions. The measure of relative intrinsic allergenicity should be assessed by examination of each subset of reactions: (1) fatal reactions; (2) serious or life-threatening; and, (3) all allergic reactions.

The pathognomic signs of Type I hypersensitivity reactions are the combination of cutaneous (rash, angioedema, pruritus, and/or urticaria) and pulmonary signs (wheezing, bronchospasm, and/or oral-pharyngeal edema). There is progression in severe cases to airway obstruction and/or hypotension. Isolated airway obstruction or isolated cardiovascular collapse are

3 pages

DRAFT

LABELING

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ATTORNEYS AT LAW
TRAURIG

09/03/98 BL
NG-T

Jur Strobos
202/331-3150

ORIG AMENDMENT

August 19, 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

By Federal Express

In re NDA 20-955
R&D Laboratories, Inc.
Amendment # 21

Dear Dr. Talarico:

On behalf of R&D Laboratories, Inc., and after discussion with the Consumer Safety Officer, Brian Strongin, please find enclosed an amendment to the above-captioned NDA relating to the labeling of the [redacted] foil which covers each of two molded [redacted] trays.

Each tray is intended to contain five ampules of Ferrlecit® and two trays are packaged in each box which represents the unit of sale and commercial distribution. The labeling for each ampule and for the unit of sale and commercial distribution was provided in Amendment No. 20 which also included samples of the [redacted] foil and the [redacted] tray.

Our initial request was that the [redacted] foil contain no labeling whatsoever based on the view that: (1) the trays do not represent a unit of sale; and, (2) the trays do not represent a unit of pharmacy storage. To that end, once removed from the immediate package, the silver foil is sufficiently flimsy and thin that tearing may occur which would expose the fully labeled ampules. Additionally, satellite and other pharmacies, such as nursing stations, are familiar with the storage of ampules or boxes, but not [redacted] trays which do not have a regular or flat surface below and are only thinly covered, on top, with [redacted] foil. Storage of such an item would lead to accidental dropping and breakage. Individual ampules are commonly stored. Finally, of course, each contained ampule is distinctively labeled and the opening of an ampule requires careful attention by nursing staff.

ORIGINAL

59-14-1

As a small company, we will be ordering supplies from [redacted] which is in current significant volume production of Ferrlecit® for the European market. The lead time for changes to the foil, if it were labeled, would be in excess of six months. Our concern was that, both for launch and if any changes in the label might later be appropriate, a labeled foil with such a lengthy lead time could lead to shortages which could be a public health concern. This is true especially given the nature of the product as an alternative life-saving product for patients who may be allergic to iron dextran. And, of course, there does not seem to be any countervailing legal or public health need for labeling of the foil.

Notwithstanding the foregoing, and given the need for a long lead time before launch, the firm is hereby submitting 20 copies of proposed labeling for the [redacted] foil printed on hard paper (printed foil cannot be readily made, stored, or submitted). The firm suggests that, if labeling is required for the foil, the submitted labeling can be used for launch of the product. The firm would like to preserve the question in the alternative, however, for the agency as to whether foil labeling could be eliminated completely. Under this proposal, if labeling of the foil is required, the submitted labeling could be ready and available for launch following final approval without delay. The CSO has indicated that this is the likely outcome. In the alternative, if no labeling of the foil is permissible, which the firm would prefer, this can also be accomplished.

We appreciate your assistance in this matter.

Sincerely,

[redacted] APPEARS THIS WAY ON ORIGINAL

Jur Strobos

Enclosure—20 copies of sample alternative foil-on-tray labeling.

5 pages

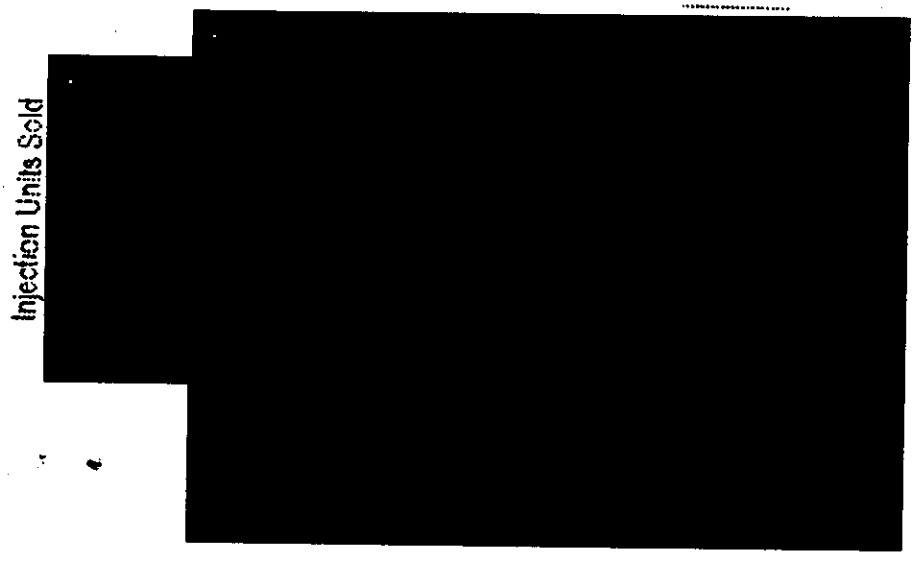
DRAFT

LABELING

C. Foreign Marketing History

Ferrlecit® Injection has been used since 1959 in over twenty countries outside the United States for the intravenous administration of iron to patients with iron deficiency anemia. Currently, the principal intravenous usage is among the 48,000 hemodialysis patients in Germany (41). Foreign countries with recent (1990-1995) sales or marketing shipments include: Germany, Italy, Spain, Saudi Arabia, Austria, the Netherlands, Belgium, Luxembourg, Poland, the Czech Republic, Slovakia, Hungary, Israel, Lithuania, Estonia, Russian Federation, Byelorussia, Ukraine, Croatia, Uzbekistan, Myanmar, Dubai, South Africa, Uruguay. The majority of current usage, however, can be found in Germany, Italy, and Spain. (See Figure 1, below.) Sales records before 1990 were not made available to R&D Laboratories, Inc. In the locations of recent sales, the drug is primarily used (80-85%) in the renal hemodialysis community as a maintenance therapy for iron deficiency at an average weekly dose of 62.5 mg, administered over 30 minutes diluted in 50 mL of normal saline. The drug was introduced in most countries before marketing approvals were formally required.

There have been no withdrawals of marketing approval in any country. Sales in the Netherlands did not justify the fee required for re-registration, so the formal Netherlands registration for Ferrlecit Injection lapsed in 1986. Ferrlecit Injection is still used in the Netherlands under programs in which hospitals may administer drugs available in other European Union countries on a physician's order.



Division of Gastrointestinal and Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-955

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

Sponsor: R & D Laboratories, Inc.

Comparison of the Proposed U.S. and the Approved Italian and German Labeling

	U.S. LABELING	ITALIAN LABELING	GERMAN LABELING
INDICATIONS	Iron deficiency anemia in renal hemodialysis patients on human recombinant erythropoetin	Iron deficiency anemia, manifestations of iron deficiency and "all of the conditions attributable to absolute and relative iron deficiency..."	Iron deficiency anemia, iron defieiency conditions, impaired iron absorption or intolerance to orally administed iron
DOSAGE	500mg - 1000mg in divided doses over 8 dialysis sessions	62.5 mg - 125 mg/day. Total dose to be based on the extent of iron deficiency as calculated by the hemoglobin level.	None Given
ADVERSE EFFECTS	Transient flushing and hypotension, nausea/vomiting, abdominal/chest and/or back pain, allergic reactions	Headaches, discomfort, anaphylactic reactions	Dizziness, palpitations, hypotension, anaphylactoid reactions, anaphylactic reactions
PRECAUTIONS & WARNINGS	Transient flushing and hypotension, Pregnancy Category "C", use caution when administering to a nursing mother, contains benzyl alcohol so avoid in neonates	Parenteral use only "when strictly necessary", contains benzyl alcohol so avoid in less than 2 years of age, inject slowly and do not mix with other preparations	Administer slowly to a recumbent patient to avoid hypotension, dizziness, palpitations, etc.,
CONTRA - INDICATIONS	Anemias not associated with iron deficiency, hypersensitivity	Hypersensitivity, iron storage disease, chronic hemolytic states, lead anemia	Neonates, hypersensitivity, impaired iron utilization

BEST POSSIBLE

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 12, 1999

FROM: Lilia Talarico, M.D., Director, HFD-180 /S/ 2-16-99

SUBJECT: NDA 20-955, Ferrlecit: Safety Update and Proposed Pediatric Study Request

TO: NDA 20-955, Ferrlecit (ferric sodium gluconate complex in sucrose injection)

NDA 20-955 for Ferrlecit (sodium ferric gluconate complex in sucrose injection) was submitted December 30, 1997 for treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoetin therapy. An approvable action was taken June 30, 1998 pending an acceptable response to CMC questions, FPL identical to marked-up draft labeling attached to the action letter, and the submission of a safety update.

The submission dated February 4, 1999 was sent in response to the request, stated in our June 30, 1998 approvable letter, for a safety update. In this submission the firm reported that no clinical trials are ongoing or were ongoing at the time of NDA submission, and that no additional safety information is available from worldwide experience of Ferrlecit. This response is acceptable.

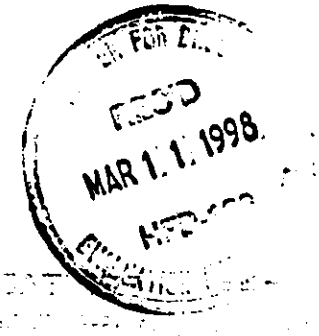
Our letter dated November 2, 1998 included a request to conduct a Phase IV study to determine a safe and effective dosing regimen in the pediatric population. The firm's submission dated December 30, 1998 included a request for a waiver for the neonatal (birth to 1 month) and infant (1 month to 2 years) subpopulations, a commitment to conduct a clinical study in children (2 to 12 years) and a pharmacokinetic study in adolescents (12 to < 16 years), and outlines for the proposed studies. The firm's submission dated January 4, 1999 included draft protocols for both studies. These submissions are currently under review and will be addressed separately. Upon completion of the reviews, a Written Request for pediatric studies will be issued if warranted.

cc:
NDA 20-955
HFD-180/Div.File
HFD-180/L.Talarico
HFD-180/B.Strongin

APPEARS THIS WAY ON ORIGINAL

Drafted: BKS/February 12, 1999
R/D Init: LT/February 16, 1999
Final: BKS/February 16, 1999

Pharmaceutical Research Associates, Inc.



January 16, 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

RE: **NDA # 20955**
Ferriecit® (sodium ferric gluconate in sucrose) Injection
R&D Laboratories, Inc.

Dear Dr. Talarico:

This letter is to confirm that the drug referenced above is not under patent in the United States or any other country. For this reason, no patent information was supplied in the recently submitted NDA.

Sincerely yours,

Howard M. Smith
Director, Regulatory Services

HMS/tlu

APPEARS THIS WAY ON ORIGINAL

cc: Rhoda Makoff, Ph.D.
Jur Strobos, M.D.

2400 Old Ivy Road ■ Charlottesville, Virginia 22903-4826 USA
Tel: 804 977-2772 ■ Fax: 804 293-7084

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Jur Strobos
202/331-3150

March 9, 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 No. 004

Dear Dr. Talarico:

This amendment requests five year marketing exclusivity under the provisions of § 505(c)(3)(D)(ii) for Ferrlecit® Injection or, in the alternative, three year marketing exclusivity under the provisions of § 505(c)(3)(D)(iii) for Ferrlecit® Injection.

Ferrlecit® Injection represents an active ingredient which has not been approved in any other application under subsection (b). Further, new clinical investigations essential to approval were conducted and/or sponsored by the applicant, R&D Laboratories, Inc., of NDA 20-955 for Ferrlecit® Injection. *See* 21 C.F.R. 314.108

1. **Sodium ferric gluconate complex in sucrose (Ferrlecit® Injection) represents a new active ingredient.**

Ferrlecit® Injection represents [redacted]. The ferric oxyhydride-saccharate is also complexed by the carboxylic function of gluconate. There are currently two other intravenous iron products available in the US: INFeD® and Dexferrum®. Both are iron dextrans. In the iron dextrans, there is no covalent bonding to saccharate and there is no carboxylate-mediated complexation of the ferric saccharate by gluconate. As stated in Goodman and Gilman's Pharmacological Basis of Therapeutics,

> Iron dextran . . . is a complex of ferric oxyhydride with dextrans of 5000 to 7000 daltons. [When administered, iron dextran] elevates the concentration of iron in plasma for days or 1 or 2 weeks due to the presence of iron dextran complex. During this time, determination of plasma iron does not indicate the amount of iron present on transferrin. The iron dextran must first be phagocytized by reticuloendothelial cells and the iron released from the sugar molecule of the dextran before it becomes available to the body. A portion of the processed iron is rapidly returned to the plasma and made available to the erythroid marrow; however, an even greater portion remains temporarily trapped within the reticuloendothelial cell. These iron dextran deposits are very gradually converted into a usable form of iron.

See Tab A at 1292.

In the iron dextrans, the dextran component is largely present as a macromolecular polysaccharide shell around an inert—and not covalently bonded—ferric oxide core. In contrast, Ferrlecit® Injection complex consists of mono- and di-nuclear iron (III) oxide hydrates which are directly and covalently bonded to saccharate through the alcohol linkage in a ratio of 2 iron centers to five saccharates. Additionally, there is a cross-linking gluconate which complexes the basic mononuclear ferric saccharate structure. Unlike the dextran, the Ferrlecit® Injection complex is negatively charged. Finally, since there are no saccharide to saccharide linkages, Ferrlecit® Injection complex is not a polysaccharide.

Four sets of investigations establish that Ferrlecit® (sodium ferric gluconate complex in sucrose) Injection contains a new active moiety.

1. Ferrlecit® was assayed using column chromatography against INFeD®. Tab B ([redacted] data originally submitted as part of Amendment [redacted] IND [redacted] The Ferrlecit® Injection complex is separable and distinguishable from iron dextran.

2. Ferrlecit® is a charged complex due to the nature of the linkage between the monomeric covalently bonded ferric saccharate function and the carboxylate function of the gluconate. Iron dextrans are not charged since there is no direct and consistent covalent bonding of the dextran entities to mononuclear units in the ferric oxide core. Ferrlecit® was compared to commercially-obtained INFeD® and Dexferrum® by a standard thin layer cellulose acetate electrophoresis which is used in the Ferrlecit® manufacturing process as an identity test for the Ferrlecit® Injection complex. The negatively charged Ferrlecit® complex moves to the anode. The non-ionic INFeD® and Dexferrum® remain at the baseline. The experimental technique, protocol and results are provided at Tab C. This study demonstrates the differing covalent linkages in the respective complexes.

3. Professor Dr. Bernhard Keppler, now Chairman of the Inorganic Chemistry Institute at the University of Vienna, was commissioned by Rhône-Poulenc Rorer, GmBH, Köln, Federal Republic of Germany, in 1995, to investigate the chemistry of Ferrlecit® Injection. Additional investigations on chemical content were carried out by RPR itself. R&D

Laboratories, Inc. commissioned a summary of these investigation to provide information about the chemical structure of Ferrlecit® Injection. Professor Dr. Keppler's report can be found at Tab D. This analysis and report demonstrate that iron oxyhydride in Ferrlecit® Injection is not an ester, salt, or other non-covalent derivative but represents an entity in which the ferric ion is covalently bonded to the saccharate. This covalent bonding is not found in the iron dextrans. Dr. Gerald Meyer has provided a similar report which can be found at Appendix A.2.3 of the Chemistry, Manufacturing and Controls Section.

4. Dr. Paul Seligman has developed a preliminary assay for serum Ferrlecit® Injection complex in serum. Sequential serum samples from a single patient (#104 at page 8.6.50 of NDA 20-955 [Integrated Safety Summary at page 49]) were obtained after administration of Ferrlecit® Injection. These data demonstrate that: (a) iron bound to Ferrlecit® Injection translocates directly, in small quantities, to transferrin;, and (b) the dissolution of the Ferrlecit® Injection complex in serum after administration occurs completely differently from that of iron dextrans. Dr. Seligman's review of this preliminary data can be found at Tab E. This study provides preliminary evidence that the direct and consistent covalent linkage of each individual ferric ion centers to saccharates produces pharmacology that is distinguishable from the iron dextrans.

2. In any event, Ferrlecit® Injection is clinically superior to the iron dextrans based on the absence of reported fatalities from intravenous administration.

In a clinical epidemiologic study, reported in NDA 20-955 at pages 8.6.50 through 8.6.51, the severity of allergic reactions to Ferrlecit® Injection were compared to those found with iron dextrans between 1976 and 1996. Whereas iron dextrans produce fatal anaphylaxis, there have been no reported fatalities from Ferrlecit® Injection despite similar widespread intravenous use.

Iron dextrans, based on their vastly differing molecular configuration, contain immunogenic polysaccharide dextrans. Dextrans are known to cause fatal anaphylaxis. There have been no reports of fatal anaphylaxis from Ferrlecit® during this entire time period despite similar usage. In contrast, there have been reports of at least 31 deaths from iron dextran use during the same time period.

3. New clinical investigations essential to approval were conducted and/or sponsored by the applicant, R&D Laboratories, Inc.

R&D Laboratories, Inc., sponsored and/or conducted two adequate and well-controlled clinical investigations of the safety and effectiveness of Ferrlecit® Injection. These investigations are reported in NDA 20-955 at pages 8.61 through 8.168 (5600-01) and pages 8.4.2 through 8.4.55 (5600-03). These clinical investigations were identified by the Division of Gastrointestinal & Coagulation Drug Products as essential to approval at a meeting held on June 6, 1994, before commencement of the studies. Throughout the minutes of that meeting, the agency indicated the need for at least two well-controlled clinical trials of the safety and effectiveness of the proposed recommended dose of Ferrlecit® Injection as eventually performed by the applicant. *See* Tab F.

Any doubt about the necessity of these clinical trials to approval of the NDA can be found in the agency's minutes of the meeting held on September 21, 1995, at which:

> Dr. Fredd reminded them [R&D Laboratories, Inc.] of the regulatory requirement for evidence of safety and efficacy from at least two adequate and well controlled clinical trials. The firm was reminded of the June 6, 1994 pre-IND meeting at which the Agency suggested that the firm conduct a dose response study followed by a randomized comparison of Ferrlecit to INFeD (iron dextran) Injection (NDA 17-441, Approved 4/29/74). . . . While reiterating his preference for a randomized study comparing Ferrlecit to INFeD, Dr. Fredd stated that the latter studies may provide pivotal support if compared to an historical control from the literature and then compare the effect of Ferrlecit to that in the literature.

See Tab G.

The clinical studies in NDA 20-955, in which 83 and 38 patients, respectively, received Ferrlecit® Injection were conducted and sponsored by the applicant, R&D Laboratories, Inc. To that end, with regard to the 5600-01 study, the applicant is named as the sponsor of the investigation in the Form FDA-1571 filed under IND [redacted] The other clinical investigation, 5600-03, was conducted by the sponsor under Canadian NDS036325 which was opened by the sponsor's through its clinical research organization. *See* Tab I.

Thank you for your assistance.

Sincerely,

Jur Strobos

[redacted] APPEARS THIS WAY ON ORIGINAL

Attachments as in text.

R&D LABORATORIES

COPY

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: mdlabs@cci.com • INTERNET: http://www.mdlabs.com/mdlabs

DEBARMENT and CONVICTIONS CERTIFICATIONS AS REQUIRED UNDER SECTION 306 (k) of the FEDERAL FOOD AND DRUG COSMETIC ACT

R&D Laboratories, Inc. certifies that it did not use and it will not use, in any capacity, the services of any person debarred under Section 306 (a) or (b) of the Federal Food Drug and Cosmetic Act in connection with this Abbreviated New Drug Application for Ferrlecit (62.5 mg elemental iron per 5 ml).

R&D Laboratories, Inc. also certifies that is has no convictions to report for which a person could be debarred under Section 306 (a) or (b) of the Act for R&D Laboratories, Inc. and for any affiliated persons responsible for the development or submission of this New Drug Application for Ferrlecit (62.5 mg elemental iron per 5 ml).

7/28/97
Date

(signature of responsible individual)

APPEARS THIS WAY ON ORIGINAL

[redacted]

[redacted]

DEBARMENT and CONVICTIONS CERTIFICATIONS AS REQUIRED UNDER SECTION 306(k) of the FEDERAL FOOD DRUG and COSMETIC ACT

[redacted] certifies that it did not use and it will not use, in any capacity, the services of any person debarred under Section 306 (a) or (b) of the Federal Food Drug and Cosmetic Act in connection with this abbreviated New Drug Drug Application for FERRLECIT.

[redacted] also certifies that it has no convictions to report for which a person could be debarred under Section 306 (a) or (b) of the Act for Rhone Poulenc Rorer and for any affiliated persons responsible for the development or submission of this New Drug Application for FERRLECIT.

/S/ [redacted]

2.27.97
Date

(signature of responsible individual)

APPEARS THIS WAY ON ORIGINAL

MEMORANDUM OF TELECON

DATE: January 19, 1999

APPLICATION NUMBER: NDA 20-955; Ferrlecit (sodium ferric gluconate complex in sucrose injection)

BETWEEN:

Name: Jur Strobos, MD, JD
Phone: (310) 305-8053, Extension 295
Representing: R & D Laboratories

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Expiry for Ferrlecit Drug Product

Background

NDA 20-955 for Ferrlecit was submitted December 30, 1997 for first-line treatment for iron-deficiency anemia in renal hemodialysis patients on supplemental recombinate human erythropoetin. An approvable action was taken June 30, 1998 pending FPL and a complete response to CMC questions included in the action letter. The firm's complete response, dated August 19, 1998, is under review. In a letter dated December 31, 1998, Dr. Strobos explained the sponsor's intention to have their contract manufacturer, Rhone-Poulenc-Rorer, begin production of Ferrlecit in January, 1999 with the understanding that the product would be quarantined until NDA approval. In the aforementioned letter, Dr. Strobos requested identification of the expiry for the drug product prior to initiation of production.

Today's Call

At the request of CMC Team Leader, Eric Duffy, Ph.D., I explained that Ferrlecit would be given a 12-month expiry. The call was then concluded.

/S/ [redacted] 1/19/99

Brian Strongin
Regulatory Health Project Manager

CSO|Strongin

NDA 20-955

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

JAN 11 1999

Dear Dr. Makoff:

Please refer to your pending December 30, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit (sodium ferric gluconate complex in sucrose injection) .

We also refer to Dr. Strobos' letter dated December 31, 1998 which included his inquiry as to whether Ferrlecit may be shipped into a warehouse in the United States and quarantined until distribution is lawfully permitted. In response, we have the following recommendations:

1. Contact the importation division of the Food and Drug Administration District Office at the proposed point of entry for your product and jointly work to get your product through customs.

2. Establish a written agreement with the District Office stating that your product will be quarantined until NDA approval and the completion of whatever validation agreement is required by the District Office. The agreement should include a contingency plan in the event your application is not approved imminently.

3. The bulk shipping containers for your drug product should be labeled, "Not to be Sold. Keep Under Quarantine".

4. If you have further questions concerning this matter, please contact John Deitrick, Team Leader, Center for Drug Evaluation and Research, Office of Compliance, Foreign Inspections Team at (301) 594-0095.

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

Sincerely,

/S/ [redacted] 1/11/99

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

APPEARS THIS WAY ON ORIGINAL

Strongin

MEMORANDUM OF TELECON

DATE: June 5, 1998

APPLICATION NUMBER: NDA 20-955; Ferrlecit (sodium ferric gluconate complex in sucrose injection)

BETWEEN:

Name: [redacted]
Phone: [redacted]
Representing: [redacted]

AND

Name: Brian Strongin
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Inability of the Division of Scientific Investigation (DSI) Inspector to Verify Patient Records for Study 5600-03

Background

NDA 20-955 for Ferrlecit (sodium ferric gluconate complex in sucrose injection) was submitted December 30, 1997 for the treatment of iron deficiency anemia in chronic hemodialysis patients. The efficacy and safety of Ferrlecit are supported in this application by Study 5600-01; a multicenter, randomized, open-label study conducted in the United States and Canada, and Study 5600-03; a single-center, variable-dose, open-label, compassionate-use study performed in Canada. Study 5600-03 was audited by DSI between May 11 - May 14, 1998. The inspector was unable to locate the source documentation necessary to verify data for a sample of five patients.

Today's Call

At Dr. Talarico's request I informed the firm of the difficulties encountered by the DSI auditor and informed them that it may be necessary to reinspect this study in the future. I asked for their assistance in locating source documentation for Study 5600-03. Mr. [redacted] explained that, although some of the original source documentation had been lost, the sponsor had been able to replace the lost documentation with photocopies of the originals. He stated that Dr. Kadar of DSI had confirmed the acceptability of the photocopies. The call was then concluded.

/S/ [redacted]
Brian Strongin
Regulatory Health Project Manager

/S/ [redacted] 6-8-98

Strongin

NDA 20-955

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

APR - 1 1998

Dear Dr. Makoff:

Please refer to your pending December 30, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit (sodium ferric gluconate complex in sucrose injection) Injection.

Since sodium ferric gluconate complex in sucrose injection is not an established name as described under section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, you should apply to the USAN Council for adoption of a name that will comply with that section of the act. They can be reached at the following address:

United States Adopted Names (USAN) Council
American Medical Association
535 North Dearborn Street
Chicago, Illinois 60610

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

Sincerely yours,

/S/ [redacted] 3-31-98

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

APPEARS THIS WAY ON ORIGINAL

Strongin

NDA 20-955

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

MAR 16 1998

Dear Dr. Makoff:

Please refer to your pending December 30, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit (sodium ferric gluconate complex in sucrose injection) Injection.

To complete our review of the microbiology section of your submission, we request the following concerning the bacterial endotoxin test for Ferrlecit Injection:

1. Provide data for inhibition/enhancement testing, determination of non-inhibitory concentration and maximum valid dilution of Ferrlecit Injection.

2. Provide data on the endotoxin level on three lots of Ferrlecit Injection.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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

Sincerely yours,

/S/ [redacted] 3-16-98

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

Strongin

NDA 20-955

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

MAR - 2 1998

Dear Dr. Makoff:

Please refer to your pending December 30, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit (sodium ferric gluconate complex in sucrose injection) Injection.

We also refer to your amendments dated December 30, 1997 and January 7, January 23, and January 26, 1998.

To complete our review of the Statistical section of your submission, we request the following:

Concerning Study 5600-03:

1. Provide the following SAS efficacy data sets using the same variables as those included in the data file DER_EFF submitted January 23, 1998:

   A. the original data set with the missing data not being replaced;

   B. the data set with missing data replaced by the worst observed value for that efficacy variable;

   C. and the data set with missing data replaced by the best observed value for that efficacy variable.

2. For each of the three data sets requested in item #1, please perform the following statistical analyses (as specified in the analysis plan of Volume 1.20):

   A. a paired t-test to analyze mean changes in efficacy variables (primary and secondary) from baseline to endpoint;

   B. and an analysis of covariance (ANCOVA) method to compare the mean changes in efficacy variables (primary and secondary) from baseline to endpoint between the two treatment groups with/without baseline EPO as a covariate variable.

3. Submit the SAS (6.11) data sets defined in item #1 and the analysis programs and results from item #2 on a diskette.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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

Sincerely yours,

/S/ [redacted] 2-28-98

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

APPEARS THIS WAY ON ORIGINAL

020.
Strength

NDA 20-955

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

FEB 18 1998

Dear Dr. Makoff:

Please refer to your pending December 30, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit (sodium ferric gluconate complex in sucrose injection) Injection.

We also refer to your amendments dated December 30, 1997 and January 7, January 23, and January 26, 1998.

To complete our review of the Clinical, Statistical, and Chemistry, Manufacturing, and Controls sections of your submission, we request the following:

Clinical

1. Concerning Study 5600-01, provide:

   A. a list of patients excluded from intention-to-treat and per protocol analyses, including the reason(s) for the exclusions;

   B. a list of patients discontinued from the study, including the reason(s) for discontinuation, and the date of discontinuation from the study;

   C. and a list of patients who received increased or decreased rHuEPO doses at or before day 19 and between day 19 and day 47 including the amount and date of the increase or decrease.

2. Concerning Study 5600-03, provide:

   A. a list of patients given eight Ferrlecit doses including the total Ferrlecit dose received and a list of patients given less than eight doses including the total Ferrlecit dose received;

   B. and a list of patients administered rHuEPO during dosing with Ferrlecit including the rHuEPO dosage and the amount and date of any dosage change.

3. Provide analyses of the published efficacy and safety data on Ferrlecit that you submitted in support of study 5600-01.

4. Provide any available clinical data that may support the efficacy and safety of Ferrlecit, i.e., European data.

Statistical

Concerning Study 5600-01:

1. Provide the following SAS efficacy data sets using the same variables as those included in the data file DER_EFF submitted January 23, 1998:

   A. the original data set with the missing data not being replaced;

   B. the data set with missing data replaced by the worst observed value for that efficacy variable;

   C. and the data set with missing data replaced by the best observed value for that efficacy variable.

2. For each of the three data sets requested in item #1, please perform the following statistical analyses:

   A. For dose-control phase, perform the following analyses to compare the differences between the two dose groups (as specified in the analysis plan of Volume 1.16):

      1. Perform an analysis of variance (ANOVA) to analyze the primary efficacy variables. The model should include the following factors: dose group, study center, and the interaction of dose group and study center. The significance of the mean change from baseline to endpoint (last available observation through day 40) for each dose group should be determined by using a paired t-test.

      2. Perform a repeated measures ANOVA to analyze the changes in hemoglobin from baseline to each of the regularly scheduled laboratory easements. The model should include the following factors: dose group, subject within dose group, visit, and the interaction of dose group and visit.

      3. Perform an analysis of covariance (ANCOVA) to examine the possible influence of rHuEPO dose on the primary efficacy outcome. The model should include the following factors: dose group, baseline rHuEPO dose, and the interaction of dose group and baseline rHuPEO dose.

4. The secondary efficacy variables should be analyzed in a manner similar to that of the primary efficacy variable.

B. For the historical control Phase, perform the following analyses to compare the differences between each dose group and the control group (as specified in the analysis plan of Volume 1.16):

1. Perform an analysis of variance (ANOVA) to analyze the primary efficacy variable. The model should include the following factors: treatment group (low-dose, high-dose, and control), baseline hemoglobin level, and the interaction of treatment and baseline hemoglobin level.

2. Perform an analysis of covariance (ANCOVA) to examine the possible influence of rHuEPO dose on the primary efficacy outcome. The model should include the following factors: treatment group, baseline rHuEPO dose, and the interaction of dose group and baseline rHuPEO dose.

3. The secondary efficacy variables should be analyzed in a manner similar to that of primary variable.

3. Submit the SAS (6.11) data sets defined in item #1 and the analysis programs and results from item #2 on a diskette.

4. Indicate where in the protocol the primary endpoint, secondary endpoints, and their statistical analysis methods were specified. If they were not specified in the protocol, explain the rationale for selecting the primary endpoint, secondary endpoints, and the statistical analysis methods used.

Chemistry, Manufacturing, and Controls

1. The characterization/proof of structure of the sodium ferric gluconate complex is [redacted]

2. The methods listed for [redacted] respectively. The only information given to describe these procedures are statements that the procedures are done "in accordance with the details of the RPR

SOP". Provide SOPs [redacted]

3. In Appendix B.6.5 (page 3.289, Volume 1.2) SOPs are not provided for the [redacted] listed and described on page 3.34, Volume 1.2. Provide the SOPs for the [redacted]

4. Four In-Process tests are done during the filling and final inspection procedures [redacted] Inspection); these are listed on page 3.35, Volume 1.2, and references are provided to either "established SOP procedures" (for [redacted] or to specific SOPs (SOP [redacted] Inspection, SOP [redacted] Inspection). Provide these procedures.

5. Procedures to sample the finished drug product for analysis do not appeared to be covered in this submission. How samples are taken for analysis (how large each batch is, how many samples are taken for analysis, and what procedure(s) are used to select the samples) do not appear to be discussed. Provide a complete description of the sampling plan for the finished drug product.

6. There does not appear to be any discussion of a final [redacted] step (a [redacted] step done after the vials have been filled). If a final [redacted] step is omitted, provide justification for its' omission.

7. It is noted on page 3.32, Volume 1.2 that in Appendix B.6.4 other details of the labeling and secondary packaging process is discussed. Provide the location of Appendix B.6.4.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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

Sincerely yours,

/S/ [redacted] 2-17-98

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

APPEARS THIS WAY ON ORIGINAL

Strongin

NDA 20-955

FEB

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

Dear Dr. Makoff:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

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

Therapeutic Classification: Priority

Date of Application: December 30, 1997

Date of Receipt: December 30, 1997

Our Reference Number: 20-955

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 28, 1998 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102[e] of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-0483.

Strongin

NDA 20-955

FEB

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

Dear Dr. Makoff:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

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

Therapeutic Classification: Priority

Date of Application: December 30, 1997

Date of Receipt: December 30, 1997

Our Reference Number: 20-955

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 28, 1998 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102© of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-0483.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/ [redacted]

Brian Strongin
Project Manager
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMORANDUM OF A TELECON

DATE OF THE CALL: January 22, 1998

APPLICATION NUMBER: NDA 20-955; Ferrlecit (sodium ferric gluconate complex in sucrose injection) Injection

FROM: Division of GI and Coagulation Drug Products

Lilia Talarico, M.D.	Director
Jose Canchola, M.D.	Medical Officer
Brian Strongin	Regulatory Health Project Manager

TO: R & D Laboratories

Rhoda Makoff, Ph.D.	CEO
Jur Strobos, M.D., J.D.	Regulatory Consultant
Allen Nissenson, M.D.	Principal Investigator, Study 5600-01
Roland Schaefer, M.D.	Consultant
Gerald Faich, Ph.D.	Consultant Epidemiologist

SUBJECT: Priority Designation for NDA 20-955, Ferrlecit Injection

Background

NDA 20-955 for Ferrlecit (sodium ferric gluconate complex in sucrose injection) Injection was submitted December 30, 1997 for the treatment of iron deficiency anemia in chronic hemodialysis patients. In a letter to the Division dated January 20, 1998 (attached), the sponsor, R & D Laboratories, requested priority designation, arguing that Ferrlecit is a safe alternative treatment for iron deficient dialysis-dependent patients allergic to iron dextran. Currently, such patients have no approved alternative treatment.

Today's Call

Dr. Talarico stated that the request for priority designation was under consideration and that the Division had not, as yet, looked at the submission in detail. She added that the INFed (iron dextran injection USP) package insert includes a boxed warning describing the possibility of fatal anaphylactic-type reactions. If a decision is made to include the boxed warning in the Ferrlecit labeling, priority designation cannot be given. Conversely, if the boxed warning does not appear to be relevant to Ferrlecit, priority designation is a possibility. Dr. Schaefer commented that he has treated approximately 400 hemodialysis patients with Ferrlecit in Germany since 1991 and has never seen an anaphylactic reaction or a severe, life-threatening reaction. The firm stated that they may submit a written description of Dr. Schaefer's experience with Ferrlecit. Dr. Strobos added that the experiences of five dextran allergic patients treated with Ferrlecit are described on page 22 of the Report for Study 5600-01 in NDA 20-955. In

response to Dr. Canchola's question, Dr. Nissenson explained that, in his experience, cross-reactivity between iron dextran and Ferrlecit had not occurred. Dr. Talarico concluded by adding that a decision about the priority designation would be made by the filing date, February 28, 1998. (Note: Dr. Talarico announced at the February 6, 1998 [redacted] that Ferrlecit had been granted priority designation.)

/S/ [redacted] 3/20/98
Brian Strongin

ATTACHMENT

cc:
NDA 20-955
HFD-180
HFD-180/B.Strongin

APPEARS THIS WAY ON ORIGINAL

[redacted]

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Jur Strobos
202/331-3150

January 20, 1998

Dr. Lilia Talarico, Acting Director
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 # _____ (IND [redacted]
Date of Filing: December 30, 1997
Ferrlecit® (sodium ferric gluconate complex in sucrose) Injection
R&D Laboratories, Inc.

ATTN: Brian Strongin; re Priority Teleconference

Dear Dr. Talarico:

This letter confirms a scheduled teleconference on the appropriate management of dextran allergic iron deficient hemodialysis patients and the public health importance of alternative iron therapies scheduled for 2 PM Eastern time on January 22, 1998. We are in the process of arranging for the participation of: (1) Professor Allen Nissenson from UCLA (confirmed); (2) Professor Roland Schaefer from Muenster, Germany (pending); and, (3) Dr Gerald Faich, the author of the clinical epidemiologic study on spontaneously reported allergic events for Ferrlecit as compared to iron dextrans filed in the NDA (pending).

Fundamentally, there are four lines of evidence that support the public health importance of early availability of an alternative to iron dextrans given the significant patient population which is seriously at risk from dextran allergy.

First, small numbers of patients with severe dextran allergy have not reacted to Ferrlecit® Injection. Dr. Allen Nissenson has himself treated four patients with severe anaphylactic reactions to iron dextrans safely with Ferrlecit® Injection. This experience is reported in the NDA as part of the Integrated Safety Summary. Further, neither he nor Dr. Swan—the investigator at the other US site—excluded patients from the study with known dextran allergy so long as that allergic reaction had not been life-threatening. While Dr. Swan was unable to

identify any specific patient among the ten that she treated with dextran allergy. Dr. Nissenson's study coordinator was able to identify up to five such patients. One of these patients (#141) was re-treated with Ferrlecit® Injection as part of the aforementioned four patients (#103). Dr. Lindsay could not possibly exclude "dextran-allergic" patients since the unavailability of dextrans in Canada made the dextran status of his patients unknown. Dr. Nissenson will speak to this experience.

Second, despite the large number of patients treated over the years with Ferrlecit® Injection, the appearance of a true anaphylactic reaction or a life-threatening reaction from Ferrlecit® Injection that required intensive treatment has not been reported either in the medical literature, spontaneous adverse events databases, or by physicians with extensive experience with Ferrlecit® Injection. While this could be characterized as "negative" evidence, it is powerful in light of a number of facts: (1) dextran anaphylactic reactions and deaths are readily reported and widely known throughout the world; (2) there have been at least two reports in the medical literature of acute but short duration hypotensive reactions to Ferrlecit® Injection; (3) administration of Ferrlecit® Injection in Germany occurs largely (>90%) in dialysis units and a slight increase in mild allergic reactions to Ferrlecit® Injection as a result of a manufacturing issue in 1994 was quickly detected by the German spontaneous adverse events reporting system; (4) no anaphylactic reactions were seen in 126 prospectively treated patients in North American clinical trials; and, (5) German physicians do not use a test dose. Drs. Schaefer and Faich will speak to these issues.

Third, the mechanism of the anaphylactic reaction to iron dextran is understood to relate to the high molecular weight dextran content. Dextran is a known allergen on its own. Increasing molecular weight of the dextran component correlates to increased iron dextran reaction. In contrast, Ferrlecit® Injection contains no dextran.

Fourth, the rate of cross-reaction between one allergic condition and another is never 100% anyway. In short, the availability of an alternative chemical entity must, therefore, itself provide a life-saving alternative for at least some patients with dextran allergy. Patients with penicillin anaphylaxis may cross-react to other different substances but not all will. Any alternative to penicillin is thus life-saving regardless of the product's own rate of allergic reaction. The absence of any alternative means that those patients must either be withdrawn from treatment or exposed in a high risk setting with appropriate pre-treatment. When the therapy is life-saving, as iron supplementation is, the approval of any alternative chemical formulation will, therefore, save the lives of a certain portion of highly dextran allergic patients.

As a final note, the agency has specifically requested additional information on patients with known dextran allergies who have been subsequently treated with Ferrlecit® Injection. Unfortunately, the state of medical understanding and the long history of use of Ferrlecit® Injection means that such an experiment can only be conducted spontaneously in a country that has only iron dextran when an alternative becomes newly available. Dextran allergic patients are identified only in countries where dextran is the only available product, such as the United Kingdom and the United States. All other countries which have alternative products do not use iron dextrans. Ferrlecit® Injection is not currently available in the US or UK. While the number

of highly dextran allergic patients is on the order of 5% of the hemodialysis patient population, they are spread thinly throughout the country. Logistics alone preclude a pre-approval study. Thus, there can be no large set of such patients treated with Ferrlecit® Injection until the product is approved. Notwithstanding this impediment, the collected data provide substantial evidence of the safety of Ferrlecit® Injection in dextran allergic patients.

We appreciate the opportunity to discuss these issues with you and hope the teleconference will further elucidate the facts to your satisfaction.

Sincerely,

Jur Strobos

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 4, 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 in the approvable letter of June 30, 1998, to provide an update with regard to new safety information. No studies are nor were ongoing during the pendency of the NDA. There have been no new drug exposures under the sponsor's control since the filing date. We have no additional safety data to report. Therefore, the tabulations of safety data and drop-outs in the NDA submission remain unchanged and retabulation is not required.

We have requested all adverse events reports that may have been submitted to [redacted] and have received none. We are in the process of developing, in anticipation of approval, a mechanism to assure complete and proper reporting of all adverse events that may be reported to [redacted] notwithstanding that product distributed by [redacted] is neither manufactured, distributed, nor marketed under the conditions of NDA 20-955 as currently filed since these reports may have relevance to US marketing.

We have requested reports of all adverse events that may have been associated with Ferrlecit® directly from specific physicians who may have used Ferrlecit® during the pendency of the NDA but not under R&D's supervision and control and have been assured that there are none to report.

Finally, with regard to worldwide experience, we have recently been made aware of a new publication from Israel (enclosed) which reports on usage in 26 non-hemodialysis patients without significant adverse events. This study was not conducted by or for R&D Laboratories,

Inc., and we have no further information other than that contained in the publication. The information in the publication does not suggest any difference in rates of occurrence of adverse events and thus the summary in the NDA as filed should remain unchanged.

Sincerely,

Jur Strobos, MD

Enclosure

APPEARS THIS WAY ON ORIGINAL

Supplementing Iron Intravenously in Pregnancy

A Way To Avoid Blood Transfusions

Mordechai Hallak, M.D., Avi-Shalom Sharon, M.D., Rony Diukman, M.D., Ron Auslender, M.D., and Haim Abramovici, M.D.

OBJECTIVE: To determine the safety and efficacy of maternal intravenous iron administration to avoid blood transfusion in patients who cannot use oral preparations.

METHODS: Patients with persistent iron-deficiency anemia who had one of the following indications were included in this study: severe side effects from oral preparations, lack of improvement despite oral iron intake or history of gastrointestinal operations. The total iron amount needed to regenerate iron stores was calculated according to hemoglobin and the patients' weight. Hemoglobin, hematocrit, mean corpuscular volume, serum iron, transferrin and ferritin were evaluated at the start and conclusion of therapy as well as two weeks afterward.

RESULTS: Twenty-six patients were included in the study; four of them delivered during the therapy course. One patient developed mild signs of allergy (urticaria) after the test dose and was excluded from the study. The remaining 21 pregnant patients (mean gestational age 28 weeks) completed the therapy course and received a mean of 1,000 mg of elemental iron. The hemoglobin was increased from 9.4 ± 1.0 to 10.1 ± 0.6 g/dL at the start and end of therapy, respectively (P < .01) and continued to rise to 10.9 ± 0.6 g/dL two weeks later (P < .01). The serum iron was increased from 3.9 ± 2.0 μmol/L at the start of therapy to 15.5 ± 7.2 at the end (P < .01). The transferrin was decreased from 47.0 ± 7.9 to 41.4 ± 5.3 to 37.1 ± 11.8 μmol/L at the start of, end of and two weeks after therapy, respectively (P < .01). Ferritin levels were increased from 2.9 ± 2.7 ng/mL at the start to 122.8 ± 87.1 at the end of therapy (P < .01) and decreased to 109.4 ± 90.7 ng/mL two weeks after treatment (not significant). Only mild and transient side effects were occasionally reported.

CONCLUSION: Intravenous iron administration during pregnancy is an effective method of regenerating hemoglobin and iron stores. It should be considered for patients with severe iron-deficiency anemia who cannot use oral preparations. (J Reprod Med 1997;42:99–103)

Intravenous iron administration during pregnancy is an effective method of regenerating hemoglobin and iron stores.

Keywords: anemia, iron-deficiency; pregnancy.

Introduction

Iron-deficiency anemia affects 5–10% of women of childbearing age (20–44 years).[1] Among pregnant women, the prevalence of anemia is 20–40%.[2] Heavy menstrual flow, type of contraception (intrauterine device associated with increased blood loss), low socioeconomic status, race and high parity are all risk factors for iron deficiency anemia.[1,2]

From the Departments of Obstetrics and Gynecology, Carmel Medical Center, Haifa, Israel, and Wayne State University School of Medicine, Detroit, Michigan.

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The iron requirements of normal pregnancy total about 1 g to replace net losses, which occur mainly in the second and third trimesters and early puerperium.[2] There is no clear evidence in the current literature that routine iron supplementation during pregnancy is beneficial in improving clinical outcome in the mother, fetus or newborn.[2] However, iron absorbed from the diet, together with that mobilized from stores, is usually insufficient to meet the demands imposed by pregnancy. Since iron needs during pregnancy cannot be met by diet only, the American College of Obstetricians and Gynecologists and obstetric textbooks recommend routine supplementation with a daily dose of 30 mg of elemental, ferrous iron during the second and third trimesters.[3,4]

[Intravenous iron administration in pregnancy] should be considered for patients with severe iron-deficiency anemia who cannot benefit from oral preparations.

The absorption of iron from oral supplements is influenced by dose, the patient's iron stores and the relation to meals. High doses are associated with decreased absorption and increased side effects. Iron is best absorbed when the stomach is empty in a patient with decreased iron stores. Therefore, the required amount should be reached gradually, divided and administered three times a day to increase absorption, decrease side effects and hence increase patient compliance.[1] Maximum absorption occurs when iron tablets are taken between meals or at bedtime.[3]

Even when these guidelines are followed, some patients develop severe side effects or simply cannot absorb oral preparations. In these patients the alternatives are parenteral administration or blood transfusion. Blood transfusion carries a risk of a febrile reaction, hemolytic reaction, anaphylaxis, alloimmunization and graft versus host disease.[5] Of primary concern currently is the infectious risks associated with blood transfusion. These risks include viruses, such as hepatitis B and C, the human immunodeficiency virus, and protozoal and bacterial infections.[5]

There is controversy in the literature regarding intravenous iron administration. Therefore, the objective of this study was to determine the safety and efficacy of maternal intravenous iron administration to avoid blood transfusion in patients who could not use oral preparations.

Materials and Methods

This clinical study was performed during a three-year period (August 1992–July 1995). Patients with iron-deficiency anemia who had one of the following indications were included in this study: severe gastrointestinal side effects from oral preparations (13 patients), lack of clinical improvement or increase in hemoglobin despite oral iron intake (5 patients) or history of gastrointestinal operations (3 patients). All patients were referred with severe symptoms of anemia. These symptoms included fatigue, dyspnea, palpitations (particularly following mild physical activity), inability to tolerate exertion, dizziness, headache, irritability, difficulty sleeping and concentrating, anorexia and bowel irregularities. In all patients a serious trial of oral iron supplementation was attempted, including a trial of ferrous sulfate syrup. Before considering intravenous treatment, we verified with all the patients the severity of the symptoms and verified repeat laboratory results of serum hemoglobin showing < 8.5 g/dL, and serum iron and ferritin levels below normal. All patients were otherwise healthy, without renal or other disease. Informed consent was obtained from each patient after explaining the risks and benefits of intravenous iron administration. Although iron preparation is an approved medication in Europe and no official institutional review board approval was necessary, all appropriate safeguards were met as required by our human investigation committee.

The total iron amount needed to regenerate iron stores was calculated according to the hemoglobin and patients' weight. The formula that was used for calculation (given by the manufacturer) was 0.3 × body weight (lb) × (100 − hemoglobin [g/dL] × 100/14.8). Hemoglobin, hematocrit, mean corpuscular volume, serum iron, transferrin and ferritin were evaluated at the start and conclusion of therapy as well as two weeks afterward.

Extra precautionary measures (more than recommended by the manufacturer) were taken during the first treatment. With the patient in a supine position, an intravenous line was placed and normal saline infusion started. The product that was

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used was a ferrous-sodium-gluconate complex, 62.5 mg/5 mL (Ferrlecit, Rhone-Poulenc-Rorer, Cologne, Germany). A test dose of 0.5 mL was given, following which the patient was observed for one hour. A second test dose was given following the same protocol. After two hours of observation with repeat test doses, the rest of the vial (4 mL) was administered, and the patient was observed for another one-hour period. If the first day of treatment was successful, continuous daily therapy was given on an outpatient basis. In the first five patients, two to three vials (125–187.5 mg) per day were given. After it was noticed that the side effects were dose dependent, we limited the dose to one vial (62.5 mg) per day. The 5 mL was given over a five-minute interval via heparin lock, following which the patient was observed for half an hour. The patient was then discharged if no side effects were reported.

Statistical analysis of the data was performed using analysis of variance and multiple comparison test (Scheffe's comparisons) when applicable. $P < .05$ was considered significant.

Results

Twenty-six patients were included in this study; four of them delivered during the therapy course. One patient developed mild signs of allergy (urticaria) after the test dose and was excluded from the study. The remaining 21 patients (mean maternal age 31.2 ± 7.5 years) completed the therapy course. The patients' mean gestational age was 28.1 ± 8.8 weeks at the start of therapy; mean gravidity and parity were 2.5 ± 1.1 and 1.5 ± 0.9, respectively.

Patients received a mean amount of 1,000 ± 131.1 mg of elemental iron. The changes in hemoglobin, hematocrit, mean corpuscular volume, serum iron, transferrin and ferritin by the end of the therapy course as well as two weeks after treatment are presented in Table I. Analysis of variance revealed a statistically significant difference in all parameters presented in Table I ($P < .0001$). The results of the multiple comparison test are presented in Table I. Ferritin, representing iron stores, was increased by more than 40 times at the last day of treatment. These stores continued to serve as a source of hemoglobin production as the levels of hemoglobin were increased and those of ferritin decreased after two weeks of discontinuing of treatment.

Only mild and transient side effects were occasionally reported. These include sinus tachycardia, palpitation, shortness of breath and hot flushes. All these symptoms were transient, disappeared spontaneously after a few minutes and were dose dependent. After decreasing the daily dose to one vial (62.5 mg of iron), almost no side effects were reported.

Discussion

This study demonstrated the relative safety of intravenous iron administration in iron-deficient pregnant women who cannot use oral preparations. Caution was taken in carefully selecting the patients; that is one of the reasons why the number of patients included in the study was not very large.

Table I *Positive Effect of Maternal Intravenous Iron Administration on the Blood Test Profile (mean ± SD; [a]P < .05)*

	Time of treatment		
Profile	First day	Last day	Two weeks after last day of treatment
Hemoglobin (9.7–12.3 g/dL)	8.4 ± 1.0[a]	10.1 ± 0.6[a]	10.9 ± 0.6
Hematocrit (29–37 %)	27.1 ± 3.1[a]	31.6 ± 2.3[a]	33.7 ± 2.0
Mean corpuscular volume (80–94 fL)	79.1 ± 9.1[a]	78.6 ± 5.0	80.3 ± 5.6
Serum iron (7–25 umol/L)	3.9 ± 2.0[a]	15.5 ± 7.2	15.0 ± 7.1
Transferrin (21–46 umol/l)		41.4 ± 5.3	37.1 ± 11.8
Ferritin (10–160 ng/mL)	2.9 ± 2.7[a]	122.8 ± 87.1	109.4 ± 90.7

[a]First day was different from the last day and two weeks, $P < .01$
[b]Last day was lower than two weeks, $P < .01$
[c]Last day was lower than two weeks, $P < .05$
Values in parentheses are the normal range

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Extra precautions were also taken in administration of the iron. Indeed, the only patient who developed a mild form of anaphylaxis was identified right from the start, and the infusion was discontinued, without further complications. According to our experience, increased side effects were reported with higher doses. When the dose was reduced to one vial a day, almost no side effects were reported. It is possible that when a high dose of iron is given, the serum transferrin is fully occupied, resulting in increased levels of serum-free iron, which can cause increased side effects.

Intravenous iron administration proved to be successful in all patients who completed the course of therapy. Hemoglobin was significantly increased and continued to rise even after the conclusion of treatment. Iron stores were regenerated as well. In all patients anemia symptoms and signs subsided very quickly upon initiation of therapy. The patients felt stronger and reported a better ability to perform their daily tasks as well as carrying the pregnancies to term. However, since we did not have a control group of untreated patients, the actual benefits from our treatment in terms of maternal-fetal outcomes remain unproven.

Intravenous iron administration is indicated in patients who do not absorb oral preparations or develop severe side effects.[4] It was recommended that the intravenous iron dextran be given undiluted in a single syringe. A test dose of 0.5 mL should be given first, a two-minute wait should occur for a sensitivity reaction, then an additional 9.5 mL should be given over the next five minutes. Most of the reactions appeared immediately, usually during the test dose.[6] Symptoms reported include flushing, headache, arthralgia and lymphadenopathy, most of which were mild and transient. No effect on pregnancy was seen in patients in which reactions occurred.[6]

Oral and intravenous iron supplementation has been administered to hemodialysis patients.[7] In that study the intravenous route was found to be the most efficient to correct iron-deficiency anemia. The authors also noticed no side effects with its use; therefore, the intravenous route was recommended.[7] Pascual et al[8,9] reported their excellent experience with intravenous iron administration for iron-deficiency patients on hemodialysis.

Pritchard studied hemoglobin regeneration in severe iron deficiency anemia patients.[10] The average hemoglobin concentration was compared among women who were treated with oral agents and intramuscular injections and patients who received intravenous iron infusion. Oral iron treatment was satisfactory in most cases of severe iron-deficiency anemia, with occasional side effects of abdominal cramping, constipation or diarrhea. Intramuscular treatment was associated with local soreness, which lasted hours to days, and the rate of regeneration was no better than that with the oral route. The intravenous route was associated with a more rapid rate of increased hemoglobin concentration than did the oral or the intramuscular route. Furthermore, the slow intravenous iron infusion produced no serious local or systemic side effects.[10]

Hamstra et al[11] reported on their experience with intravenous iron dextran administration to 481 patients (46 obstetric patients). They used imferon in the usual dose of 250–500 mg per injection. Hemoglobin production was higher after intravenous than oral or intramuscular injection if the hemoglobin was <9 g/dL. Three severe immediate and eight delayed anaphylactoid reactions were observed; however, no death occurred. Delayed reactions were less frequent in pregnancy. The conclusion of these investigators was that iron dextran is acceptable treatment when the alternatives are either not to treat or to give blood transfusion.

The main concern about intravenous iron administration is the danger of anaphylaxis. This, indeed, is a very serious problem and may outweigh the advantages of the intravenous route. However, according to our experience and those experiences reported in the literature, when taking strict precautions, this risk can be minimized. In most cases these patients can be identified in the beginning, before the severe reaction of anaphylaxis develops. Furthermore, parenteral iron should be administered for the right indications. We concur with Pritchard in that intravenous iron administration should be "limited to those situations in which effective oral iron preparations are poorly tolerated by the gastrointestinal tract or where the patient after appropriate instruction is judged incapable of taking oral medication."[10]

When the right indications and precautions are taken, intravenous iron administration during pregnancy is an effective method of regenerating hemoglobin and iron stores. It should be considered for patients with severe iron-deficiency anemia who cannot benefit from oral preparations.

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ficiency anemia in women of childbearing age. Prim Care Update Ob/Gyns 1995;2:135–137

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[redacted]

[redacted]

Pharmaceutical Research Associates, Inc.

May 20, 1998

Brian Strongin
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

RE: **NDA # 20-955 – 120-Day Update**
Ferrlecit® (sodium ferric gluconate in sucrose) Injection
R&D Laboratories, Inc.

Dear Mr. Strongin:

This letter is to advise you that there were no additional safety data obtained in the 120-day period since the filing of the above-referenced NDA. There are no clinical studies currently in progress, and all spontaneously reported adverse events of which we are aware have been reported in the NDA.

If you have additional questions about this update, please do not hesitate to call me.

Sincerely yours,

Howard M. Smith
Director, Regulatory Services

[redacted]
APPEARS THIS WAY ON ORIGINAL

2400 Old Ivy Road ▪ Charlottesville, Virginia 22903-4826 USA
Tel: 804 977-2772 ▪ Fax: 804 293-7084

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20955 **Trade Name:** FERRLICIT (SODIUM FERRIC GLUCONATE COMPL

Supplement Number:

Generic Name: SODIUM FERRIC GLUCONATE COMPLEX IN SUCRO

Supplement Type:

Dosage Form: Injectable; Injection

Regulatory Action: AP

Proposed Indication: Iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoetin therapy.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? YES

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) _X_ Children (25 months-12 Years)

____Infants (1-24 Months) _X_ Adolescents (13-16 Years)

[redacted]

Label Status	ADEQUATE Labeling for SOME PEDIATRIC ages
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant has COMMITTED to doing them
Study Status	Protocols are submitted and under review

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:
2/5/99 - This NDA will be approved upon completion of Office level review of the action package. Phase IV commitments include a clinical study in children, a PK study in adolescents, and a request for waivers in neonates and infants.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, BRIAN STRONGIN

/S/ [redacted]

Signature

2/5/99

Date

[redacted]

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/PLA/PMA # NDA 20-955 Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

D-180 Trade and generic names/dosage form: Ferrlecit (sodium ferric gluconate complex in sucrose injection) Action: AP (AE) NA

Applicant R & D Labs, In Therapeutic Class 1 P

Indication(s) previously approved None

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___ N/A

Proposed indication in this application Iron deficiency anemia in chronic hemodialysis patients

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolescents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- ___ c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing.
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

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X 5. **PEDIATRIC LABELING MAY NOT BE ADEQUATE.**

- X a. Pediatric studies are needed. (See Division Director's Memo dated May 21, 1998.)
- ___ b. Pediatric studies may not be needed but a pediatric supplement is needed.

___ 6. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ [redacted]

Signature of Preparer and Title

5/21/98

Date

cc: Orig NDA/PLA/PMA # NDA 20-955
HF D-180/Div File
NDA/PLA Action Package
HFD-006/ KRoberts (include labeling for all NME approvals;either draft or final)

(revised 8/15/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

EXCLUSIVITY SUMMARY FOR NDA # 20-955

Trade Name: Ferrlecit

Generic Name: sodium ferric gluconate complex in sucrose injection

Applicant Name: R& D Laboratories. Incorporated

HFD -180

Approval Date If Known _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

The applicant requested five years of exclusivity in their March 9, 1998 submission.

e) Has pediatric exclusivity been granted for this Active Moiety?

___No_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /__/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC

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monograph. but that was never approved under an NDA. is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

/S/

Signature

3/5/99

Date

Title

/S/

Signature of Office/
Division Director

2-5-99

Date

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ON ORIGINAL

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 20-955

Trade Name: Ferrlecit

Generic Name: sodium ferric gluconate complex in sucrose injection

Applicant Name: R& D Laboratories. Incorporated

HFD -180

Approval Date If Known _____

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a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

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___No_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /__/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA#_____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC

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monograph. but that was never approved under an NDA. is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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/S/

Signature

2/5/99

Date

Title

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Signature of Office/ Division Director

2-5-99

Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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