

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 21-135**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

Strongin

OCT 30 2000

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

NDA 21-135

SUBMISSION DATE: 08/10/00

**IRON SUCROSE  
VENOFER®**

**LUITPOLD PHARMACEUTICALS, INC.  
ONE LUTIPOLD DRIVE  
SHIRLEY, NEW YORK 11967**

REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: AMENDMENT (SERIAL #B2) SUBMISSION CODE: 3S

**I. SYNOPSIS/BACKGROUND**

Amendment B2 was submitted to NDA 21-135 for iron sucrose (Venofer®), by the sponsor, on August 10, 2000. Venofer® is proposed for the treatment of adult patients with anemia associated with dialysis,

In this submission, the sponsor provides responses on the Clinical Pharmacology Comments contained in the Agency's letter of July 19, 2000 (See Attachment I).

**II. REVIEW OF SPONSOR'S RESPONSES**

Agency's Comment 1: This comment related to a study report in which red blood cell utilization of iron was evaluated in six anemic subjects each treated with a single dose of 100 mg of in the form of iron(III)-hydroxide-sucrose complex labeled with <sup>59</sup>Fe (Volume 1.15 [pages 1-144] of original NDA). The results of the study showed high "red blood cell utilization" of <sup>59</sup>Fe within 13-28 days of study initiation. The high "red blood cell utilization" of <sup>59</sup>Fe was, however, not accompanied by any appreciable increases in hemoglobin values in the study subjects. In the study report, it was stated that "red blood cell utilization" of <sup>59</sup>Fe measured as a ratio of <sup>59</sup>Fe activity in whole blood to injected <sup>59</sup>Fe activity. It was further stated that <sup>59</sup>Fe activity was measured in "plasma and packed red cells separately to define the rate of disappearance of radioactivity from plasma..." (Volume 1.15 [pages 10-11]). No information was provided in the NDA on the ratio of <sup>59</sup>Fe activity in "plasma" to injected <sup>59</sup>Fe activity or the ratio of <sup>59</sup>Fe activity in "packed red cells" to injected <sup>59</sup>Fe activity.

Accordingly, the Agency requested the sponsor (a) to explain why the high "red blood cell utilization" of <sup>59</sup>Fe observed in the six subjects was not reflected as significant, postdose hemoglobin increases and (b) to submit for review, the mean,

standard deviation and individual subject values for [i] the ratio of  $^{59}\text{Fe}$  activity in packed red cells to injected  $^{59}\text{Fe}$  activity and [ii] the ratio of  $^{59}\text{Fe}$  activity in plasma to injected  $^{59}\text{Fe}$  activity.

**Sponsor's Response on Item 1(a):** The sponsor states (i) that approximately 10 doses of intravenous iron (III)-hydroxide-sucrose complex (1000 mg iron) is needed to achieve significant increases in hemoglobin in patients and (ii) that significant hemoglobin increases in patients are not likely to occur following a single dose of Venofer<sup>®</sup> containing 100 mg of iron.

The sponsor's response seems reasonable.

**Sponsor's Response on Item 1(b):** The sponsor provided an analysis of the daily ratios of whole blood  $^{59}\text{Fe}$  activity to injected  $^{59}\text{Fe}$  activity (Attachment D). This was not consistent with the Agency's request related to the ratio of  $^{59}\text{Fe}$  activity in "packed red cells" to injected  $^{59}\text{Fe}$  activity and the ratio of  $^{59}\text{Fe}$  activity in plasma to injected  $^{59}\text{Fe}$  activity. Accordingly, the sponsor was requested to comply with the Agency's request on these issues. The sponsor satisfactorily addressed these issues in Amendment B2 submitted to the NDA on October 12, 2000.

**Agency's Comment 2:** In this Comment, the sponsor was requested to characterize the *in vitro* release of iron from iron-sucrose complex of Venofer<sup>®</sup> and submit the findings for review.

**Sponsor's Response:** The sponsor states that in a telephone conference with the Agency on Wednesday, July 26, 2000, it was agreed that characterization of the *in vitro* release of iron from the iron-sucrose complex of Venofer<sup>®</sup> be undertaken as a Phase IV commitment. At the present, the sponsor feels that such a Phase IV study is not necessary. To this end, the sponsor presents literature data suggesting (i) that *in vitro*, release of iron from Venofer<sup>®</sup> is rather limited, (ii) that over-saturation of transferrin would not occur following Venofer<sup>®</sup> administration to patients since the bulk of circulating iron "is not in a catalytically active form" and (iii) that the saccharate network in Venofer<sup>®</sup> is capable of binding a portion of its iron content until the circulating iron is adequately cleared by the mononuclear phagocytic system (see Attachment 1).

The sponsor further states that if, notwithstanding its views on this issue, the Agency still feels that the aforesaid Phase IV study is necessary, then the Phase IV study would be conducted. The Agency recommends that the Phase IV commitment be fulfilled (see Recommendation [page 3]).

APPEARS THIS WAY  
ON ORIGINAL

### III. RECOMMENDATION

Amendment B2 submitted to NDA 21-135 for iron sucrose (Venofer<sup>®</sup>), by the sponsor, on August 10, 2000 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The literature information provided in this amendment, which relates to interactions of iron from Venofer<sup>®</sup> with transferrin and the saccharate network of Venofer<sup>®</sup> and the potential of limited *in vitro* release of iron from Venofer<sup>®</sup>, is considered inadequate to replace the Phase IV commitment agreed to between the Agency and the sponsor in the telephone conference of Wednesday, July 26, 2000. Accordingly, the Agency recommends that the Phase IV commitment to characterize the *in vitro* release of iron from Venofer<sup>®</sup> be fulfilled.

The issues related to red blood cell utilization of <sup>59</sup>Fe (item 1(b) (page 2) was satisfactorily addressed in Amendment B2 submitted to the NDA on October 12, 2000.

Please convey this Recommendation, as appropriate, to the sponsor.

/S/

10/30/00

David G. Udo, Ph.D.

Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D., Team Leader:

/S/

10/30/00

cc: NDA 21-135, HFD-180, HFD-180 (Strongin), HFD-~~870~~ (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

APPEARS THIS WAY  
ON ORIGINAL

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

NDA 21-135

SUBMISSION DATE: 10/12/00

**IRON SUCROSE  
VENOFER®****LUITPOLD PHARMACEUTICALS, INC.  
ONE LUTIPOLD DRIVE  
SHIRLEY, NEW YORK 11967**

REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: AMENDMENT (#B2) SUBMISSION CODE: 3S

**I. SYNOPSIS/BACKGROUND**

Amendment B2 was submitted to NDA 21-135 for iron sucrose (Venofer®), by the sponsor, on October 12, 2000. Venofer® is proposed for the treatment of adult patients with anemia associated with dialysis.

In this submission, the sponsor provides responses on the Clinical Pharmacology information request contained in the Agency's letter dated October 5, 2000. The information requested consisted of the individual subject daily ratios of (i) <sup>59</sup>Fe activity in packed red cells to injected <sup>59</sup>Fe activity and (ii) <sup>59</sup>Fe activity in plasma to injected <sup>59</sup>Fe activity, that were obtained in the study evaluating "red blood cell utilization of iron" in six anemic subjects treated with a single dose of 100 mg of iron, in the form of iron (III)-hydroxide-sucrose complex, labeled with <sup>59</sup>Fe (Original NDA: Volume 1.15, pages 1-104 [Study Report pages 1-46]). The sponsor has submitted the requested information (see the last two pages of Attachment I).

**II. REVIEW OF SPONSOR'S RESPONSES**

The information provided by the sponsor reveals that in the above referenced study, one or more days from drug administration, <sup>59</sup>Fe activity in plasma was negligible (<sup>59</sup>Fe activity in plasma/injected <sup>59</sup>Fe activity was 0-7.5% [Table II of Attachment I]). This would mean that <sup>59</sup>Fe activity is essentially completely cleared from the plasma 24 h following drug administration.

In the original NDA, it was determined that in healthy subjects treated with a single intravenous dose of iron sucrose containing 100 mg of iron, the serum elimination half-life of iron was 6 h, approximately. Since the rate of serum elimination of iron depends on the need for iron in iron utilizing tissues of the body, it is reasonable to expect the serum elimination half-life of iron to be shorter in anemic patients.

Subsequently, complete elimination of  $^{59}\text{Fe}$  activity from the plasma in 24 h, as evidenced by the data submitted by the sponsor, seems possible.

The  $^{59}\text{Fe}$  activity cleared from the plasma is expected to be incorporated into red blood cells. It is noted that in general, for each day of the above referenced study, the ratio of  $^{59}\text{Fe}$  activity in packed red cells to injected  $^{59}\text{Fe}$  activity is essentially the same as the ratio of  $^{59}\text{Fe}$  activity in whole blood to injected  $^{59}\text{Fe}$  activity (compare Table I of Attachment I to Table 2 of Attachment II). Since the plasma has been essentially completely cleared of  $^{59}\text{Fe}$  activity as discussed in the preceding paragraph, it is reasonable to infer that the whole blood content of  $^{59}\text{Fe}$  activity is essentially the  $^{59}\text{Fe}$  activity content of its red blood cell component. Therefore, the close similarity in the ratios of  $^{59}\text{Fe}$  activity in packed red cells to injected  $^{59}\text{Fe}$  activity and  $^{59}\text{Fe}$  activity in whole blood to injected  $^{59}\text{Fe}$  activity, as deduced in this review, from the findings of the above referenced study, appears to be tenable.

Based on the foregoing discussion of, and deductions from the submitted data on packed red cell  $^{59}\text{Fe}$  activity and plasma  $^{59}\text{Fe}$  activity, the sponsor's response to the Clinical Pharmacology information is considered acceptable.

### III. RECOMMENDATION

Amendment B2 submitted to NDA 21-135 for iron sucrose (Venofer<sup>®</sup>), by the sponsor, on October 12, 2000, has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The data on packed red cell  $^{59}\text{Fe}$  activity and plasma  $^{59}\text{Fe}$  activity submitted in response to the Clinical Pharmacology information request, contained in Agency's letter dated October 5, 2000, are considered acceptable for consideration in the NDA approval decision process.

Please convey this Recommendation, as appropriate, to the sponsor.

*/S/* 10/19/00  
David G. Udo, Ph.D.  
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D., Team Leader: */S/* 10/27/00

cc: NDA 21-135, HFD-180, HFD-180 (Strongin), HFD-180 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

APPEARS THIS WAY  
ON ORIGINAL

ATTACHMENT I

**Arent Fox**  
ATTORNEYS AT LAW

October 12, 2000

**VIA MESSENGER**

Lilia Talarico, M.D., Director  
Division of Gastro-Intestinal and Coagulation Drug  
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Peter S. Reichertz  
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RE: Venofer® (Iron Sucrose Injection)  
NDA 21-135  
SPONSOR: Luitpold Pharmaceuticals, Inc.  
Response to October 5, 2000 Request  
**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS**



Dear Dr. Talarico:

This letter is written in response to the above-referenced correspondence concerning the clinical pharmacology and biopharmaceutics review of NDA 21-135 for VENOFR® (Iron Sucrose Injection).

The request has been repeated for ease of reference. It was as follows:

In the original NDA submission, in the study evaluating "red blood cell utilization" of <sup>59</sup>Fe in six anemic subjects, each treated with a single intravenous dose of 100 mg of iron in the form of iron (III)-hydroxide-sucrose complex labeled with <sup>59</sup>Fe (Volume 1.15, pages 1-104 [Study Report pages 1-46]), it was stated that "red blood cell utilization" of <sup>59</sup>Fe was measured as a ratio of <sup>59</sup>Fe activity in whole blood to injected <sup>59</sup>Fe activity". It was further stated that <sup>59</sup>Fe activity was measured in "plasma and packed red cells separately to define the rate of disappearance of radioactivity from plasma. . ." (Volume 1.15, pages 10-11 [Study Report pages 8-9]).

The individual subject daily values of the "ratio of <sup>59</sup>Fe activity in whole blood to injected <sup>59</sup>Fe activity" were provided in the original NDA (Volume 1.14, page 26 [Study Report page 26 of 53, Table 12]) and Volume 1.15, page 39 [Study Report page 37, Table 4 b]). In these Tables, the "ratio of <sup>59</sup>Fe activity in whole blood to injected <sup>59</sup>Fe activity" was referred to as "<sup>59</sup>Fe Utilization Data". However, the ratios of (i) <sup>59</sup>Fe activity in "packed red cells" to injected <sup>59</sup>Fe activity and (ii) <sup>59</sup>Fe activity in "plasma" to injected <sup>59</sup>Fe activity were not provided in the original NDA. The Agency feels that these are critical data that

Lilia Talarico, M.D.

October 12, 2000

Page 2

could further enhance our understanding of how red blood cells utilize  $Fe^{3+}$  following intravenous administration of Venofer<sup>®</sup> and need to be submitted for review. The miscellaneous clinical data provided in this amendment are not adequate for addressing the Agency's request.

**Specific Information Request:** In the same format as for Table I2 on page 26 (Study Report page 26 of 53) of Volume 1.14 of the original NDA submission, please submit the individual subject daily ratios of:

- (i)  $^{59}Fe$  activity in packed red cells to injected  $^{59}Fe$  activity
- (ii)  $^{59}Fe$  activity in plasma to injected  $^{59}Fe$  activity

that were obtained in the study evaluating "red blood cell utilization of iron" in six anemic subjects treated with a single dose of 100 mg of iron in the form of iron (III)-hydroxide-sucrose complex labeled with  $^{59}Fe$  (Original NDA: Volume 1.15, pages 1-104 [Study Report pages 1-46]).

**Luitpold's Response:**

The data on the  $^{59}Fe$  activity in packed red cells to injected  $^{59}Fe$  activity is attached as Table I.

The data as to  $^{59}Fe$  activity in plasma to injected  $^{59}Fe$  activity is attached as Table II.

\* \* \* \*

Please let us know if there are any questions or if additional information is needed with regard to this response.

Sincerely,



Peter S. Reichertz

cc: Mr. Brian Strongin (via facsimile)

**APPEARS THIS WAY  
ON ORIGINAL**

# BEST POSSIBLE COPY

TABLE I

The  $^{59}\text{Fe}$  Utilization Data - Packed Red Cells (PRC)

Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
Day	Activity PRC/ Injected Activity										
1		1		1		1		1		1	
2		2		2		2		2		2	
3		3		3		3		9		6	
6		6		6		6		13		8	
9		9		9		23		16		13	
13		13		13		28		20		15	
16		16		16				23		19	
20		21		21				27		22	
23		24		24							
		28		28							

Calculated from the „fraction of the given activity/g“

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TABLE II

## The $^{59}\text{Fe}$ Utilization Data -- Plasma

Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
Day	Activity Plasma / Injected Activity										
1		1		1		1		1		1	
2		2		2		2		2		2	
3		3		3		3		9		6	
6		8		6		6		13		8	
8		9		8		23		16		19	
13		13		13		28		20		15	
16		16		16				23		19	
20		21		21				27		22	
23		24		24							
		28		28							

Calculated from the fraction of the given activity/g

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ON ORIGINAL

and females and sucrose is not expected to exhibit any significant pharmacologic activity. Therefore, is considered that it is not necessary to conduct an additional study to assess the effect of gender on the kinetics of Venofer®.

**11. Is Adequate Pharmacodynamic Information Provided?**

The sponsor states that following intravenous administration of Venofer®, iron would dissociate from sucrose rapidly and would be transported to specific sites and utilized to replenish depleted iron stores and to synthesize hemoglobin, myoglobin and enzymes that contain iron.

In the study evaluating the tissue kinetics of iron sucrose containing 100 mg of iron labeled with <sup>59</sup>Fe/<sup>52</sup>Fe (0.5/20 MBq) in two patients with iron deficiency anemia, two patients with renal anemia and 2 patients with functional iron deficiency, by the PET technique (see item 2 above), utilization of radioiron (<sup>59</sup>Fe [physical t<sub>1/2</sub>=45 days]) by red blood cells was determined. Serum hemoglobin (Hb), iron (S. Fe), ferritin (S. Fer), TIBC, transferrin saturation (TS) and transferrin receptors (S.TfR) were also measured in this study. The following results were obtained:

**i. Effect of Iron Sucrose on Iron Utilization by Red Blood Cells**

Iron utilization by red blood cells increased rapidly in all patients (Table 2) and generally reached a maximum value (68-97%) 15-28 days post dose.

Table 2. Red Blood Cell Utilization of <sup>59</sup>Fe in Anemic Patients Receiving Intravenous Iron Hydroxide Sucrose Containing 100 mg of Iron labeled with <sup>52</sup>Fe/<sup>59</sup>Fe (0.5 MBq/20MBq)

Patient 1		Patient 2		Patient 3		Patient 4*		Patient 5		Patient 6	
Day	%	Day	%	Day	%	Day	%	Day	%	Day	%
1											
2											
3											
6											
9											
13											
16											
20											
23											
-											

\*Erythrocyte concentrations given on day 10 to day 13 for severe anemia and increased from the analysis after day 13, and was re-estimated on day 23.

**ii. Effects of Iron Sucrose on Hemoglobin, Serum Iron, Transferrin Saturation, Serum Ferritin, TIBC and Transferrin Receptors**

The effects of intravenous iron sucrose on hemoglobin, serum iron, serum ferritin, serum transferritin saturation, TIBC and transferrin receptors are presented in Table 3.

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

NDA 21-135

SUBMISSION DATE: 09/28/00

**IRON SUCROSE  
VENOFER®****LUITPOLD PHARMACEUTICALS, INC.  
ONE LUTIPOLD DRIVE  
SHIRLEY, NEW YORK 11967**REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: AMENDMENT

SUBMISSION CODE: 3S

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**I. SYNOPSIS/BACKGROUND**

This amendment was submitted to NDA 21-135 for iron sucrose (Venofer®), by the sponsor, on September 28, 2000. Venofer® is proposed for the treatment of adult patients with anemia associated with dialysis,

In this submission, the sponsor provides responses on the Clinical Pharmacology information request contained in the Agency's letter dated July 19, 2000 (See Attachment I).

**REVIEW OF SPONSOR'S RESPONSES**

**Clinical Pharmacology Information Request:** This information request related to a study report in which the sponsor attempted to characterize "red blood cell utilization of iron" (the Fe<sup>3+</sup> component of iron sucrose) in six anemic subjects following intravenous administration of Venofer®. In this study, each subject was treated with a single dose of 100 mg of iron in the form of iron (III)-hydroxide-sucrose complex labeled with <sup>59</sup>Fe (original NDA Volume 1.15, pages 1-104 [Study Report pages 1-46]). In the study report, it was stated that "red blood cell utilization" of <sup>59</sup>Fe was measured as a ratio of <sup>59</sup>Fe activity in whole blood to injected <sup>59</sup>Fe activity. It was further stated that <sup>59</sup>Fe activity was measured in "plasma and packed red cells separately to define the rate of disappearance of radioactivity from plasma..."

The individual subject values of the daily "ratio of <sup>59</sup>Fe activity in whole blood to injected <sup>59</sup>Fe activity" were provided in the original NDA (Volume 1.14, page 26 [Study Report page 26 of 53, Table 12] and Volume 1.15, page 39 [Study Report page 37, Table 4 b]). In these Tables, the "ratio of <sup>59</sup>Fe activity in whole blood to injected <sup>59</sup>Fe activity" was referred to as "<sup>59</sup>Fe Utilization Data". However, the daily

ratios of (i)  $^{59}\text{Fe}$  activity in "packed red cells" to injected  $^{59}\text{Fe}$  activity and (ii)  $^{59}\text{Fe}$  activity in "plasma" to injected  $^{59}\text{Fe}$  activity were not provided in the original NDA. Accordingly, the Agency requested that these data be submitted to allow the completion of the review of the Clinical Pharmacology section of the NDA.

**Sponsor's Response:** The sponsor asks (i) why the requested information is needed (ii) why such information is critical to the review of the NDA, (iii) whether the requested mean and standard deviation values of the ratios of  $^{59}\text{Fe}$  activity in packed red cells and in plasma, to injected  $^{59}\text{Fe}$  activity, refer to values "across all patients or across all patients' time-points" and (iv) whether the miscellaneous clinical data provided in this amendment are adequate to address the Agency's request (see Attachment I).

The Agency feels that the ratios of  $^{59}\text{Fe}$  activity in "packed red cells" and in "plasma" to injected  $^{59}\text{Fe}$  activity, are critical data that could enhance our understanding of how red blood cells utilize  $\text{Fe}^{3+}$  following intravenous administration of Venofer<sup>®</sup>. Accordingly, the Agency upholds the request that these data be submitted for review (see Overall Comment [page 3]).

**APPEARS THIS WAY  
ON ORIGINAL**

## II. OVERALL COMMENT

In the original NDA submission, in the study evaluating "red blood cell utilization" of  $^{59}\text{Fe}$  in six anemic subjects, each treated with a single intravenous dose of 100 mg of iron in the form of iron (III)-hydroxide-sucrose complex labeled with  $^{59}\text{Fe}$  (Volume 1.15, pages 1-104 [Study Report pages 1-46]), it was stated that "red blood cell utilization" of " $^{59}\text{Fe}$ " was measured as a ratio of  $^{59}\text{Fe}$  activity in whole blood to injected  $^{59}\text{Fe}$  activity". It was further stated that  $^{59}\text{Fe}$  activity was measured in "plasma and packed red cells separately to define the rate of disappearance of radioactivity from plasma..." (Volume 1.15, pages 10-11 [Study Report pages 8-9]).

The individual subject daily values of the "ratio of  $^{59}\text{Fe}$  activity in whole blood to injected  $^{59}\text{Fe}$  activity" were provided in the original NDA (Volume 1.14, page 26 [Study Report page 26 of 53, Table 12]) and Volume 1.15, page 39 [Study Report page 37, Table 4 b]). In these Tables, the "ratio of  $^{59}\text{Fe}$  activity in whole blood to injected  $^{59}\text{Fe}$  activity" was referred to as " $^{59}\text{Fe}$  Utilization Data". However, the ratios of (i)  $^{59}\text{Fe}$  activity in "packed red cells" to injected  $^{59}\text{Fe}$  activity and (ii)  $^{59}\text{Fe}$  activity in plasma to injected  $^{59}\text{Fe}$  activity were not provided in the original NDA. The Agency feels that these are critical data that could further enhance our understanding of how red blood cells utilize  $\text{Fe}^{3+}$  following intravenous administration of Venofer<sup>®</sup> and need to be submitted for review. The miscellaneous clinical data provided in this amendment are not adequate for addressing the Agency's request.

**Specific Information Request:** In the same format as for Table 12 on page 26 (Study Report page 26 of 53) of Volume 1.14 of the original NDA submission, please submit the individual subject daily ratios of:

- (i)  $^{59}\text{Fe}$  activity in packed red cells to injected  $^{59}\text{Fe}$  activity
- (ii)  $^{59}\text{Fe}$  activity in plasma to injected  $^{59}\text{Fe}$  activity

that were obtained in the study evaluating "red blood cell utilization of iron" in six anemic subjects treated with a single dose of 100 mg of in the form of iron (III)-hydroxide-sucrose complex labeled with  $^{59}\text{Fe}$  (Original NDA: Volume 1.15, pages 1-104 [Study Report pages 1-46]).

APPEARS THIS WAY  
ON ORIGINAL

### III. RECOMMENDATION

The amendment submitted to NDA 21-135 for iron sucrose (Venofer<sup>®</sup>), by the sponsor, on September 28, 2000 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The issues raised in the Overall Comment (page 3) need to be satisfactorily addressed by the sponsor prior to NDA approval.

Please convey this Recommendation and the Overall Comment (page 3), as appropriate, to the sponsor.

*DS* 10/04/00  
David G. Udo, Ph.D.  
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D., Team Leader:

*DS* 10/27/00

cc: NDA 21-135, HFD-180, HFD-180 (Strongin), HFD-180 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

APPEARS THIS WAY  
ON ORIGINAL

**ATTACHMENT I**



**LUITPOLD**

September 28, 2000

**VIA FACSIMILE**

Brian Strongin  
Consumer Safety Officer  
Division of Gastro-Intestinal and Coagulation Drug Products  
(HFD-180)  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

RE: Venofer® (Iron Sucrose Injection)  
NDA 21-135  
Sponsor: Luitpold Pharmaceuticals, Inc.  
Questions Regarding Request from the Biopharmaceutics Reviewer

Dear Mr. Strongin,

As you suggested during our telephone conversation today I am providing a few questions that relate to the additional information requested by the Biopharmaceutics reviewer on August 30<sup>th</sup>.

- 1) Why is this information needed? Why is it critical to the review of our NDA?
- 2) Are mean and standard deviation values to be calculated across all patients or across all patients' time-points?
- 3) Is the preliminary information (attached) helpful? Does this suffice?

Dr. Gagnon, our Vice President of R&D and-I would like to discuss these questions with the reviewer at his earliest convenience.

Thank you for your help.

Sincerely,

Marc Tokars  
Director of Clinical Operations  
Luitpold Pharmaceuticals, Inc.

CC: S. Gagnon, MD

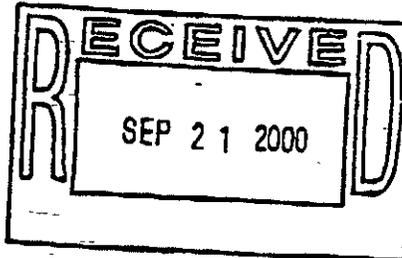
cc: P Rechenitz  
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Telex



TO: American Regent Laboratories Inc.  
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ATTN: Ms Mary Jane Helenek,  
Fax No: 001 631 824 1731  
FROM: - Dr Peter Gaisser  
cc:  
DATE: 21. September 2000 PG/FF  
PAGES: (incl. cover page) 21

Re: FDA Requested Information

Dear Ms Helenek

Please find attached the raw data of all the six patients for the study with radiolabeled Venofer (Beshara et al.).

To the table our comment is as follows:

The injected amount of <sup>59</sup>Fe is given on the top of each table. Afterwards you will find the samples, the weight of each sample and the activity in counts of each measured sample. In the next column the measured activity minus the measured background for each sample is reported. Afterwards you will find the calculated activity minus background per weight and the fraction of the given activity per gram. This is calculated by dividing the activity minus background per weight by the injected activity. The red cell utilization is then calculated by multiplying the fraction of the given activity per gram with the measured blood volume of each patient. This blood volume is given in table 3 of the original report.

We hope that this information will answer the FDA question.

If you have any further questions please do not hesitate to contact us.

Yours sincerely,  
Vifor (International) Inc.

Dr Peter Gaisser  
Head of R & D

Dr Felix Funk  
Head of Biominergetic Research

Calculation of red cell utilisation

Red cell utilisation can be determined from calculating the fraction of the injected  $^{59}\text{Fe}$  radioactivity that is circulating in the blood.

It is based on calculations made on whole blood samples.

Plasma samples were drawn in order to make sure that there is no activity left in the plasma.

The radioactivity in blood samples/g, corrected for the background radioactivity and divided by the injected radioactivity, was multiplied by the determined blood volume.

This was later corrected for the density (to compensate for the g/ml effect).

In patient No 4, the ratio between determined/calculated blood volumes was also applied, since the difference was more than 10%, i.e. after multiplying by the determined blood volume which is 6969, the resulted data were multiplied by 1.1258/18142, which is the factor between the determined blood volume and the calculated blood volume (6969/6190).

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2000-09-20

JUN 16 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-135

SUBMISSION DATE: 08/06/99

IRON SUCROSE  
VENOFER®

LUHPOLD PHARMACEUTICALS, INC.  
ONE LUTIPOLD DRIVE  
SHIRLEY, NEW YORK 11967

REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: ORIGINAL NDA

SUBMISSION CODE: 3S

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I. SYNOPSIS/BACKGROUND

*What is the Drug?* This NDA is submitted for iron Sucrose (Venofer®).

*What is the Drug Product Composition?* Venofer® is supplied in 5-mL vials. Each mL contains 20 mg of elemental iron in the form of iron (III)-hydroxide (i.e., ferric hydroxide); \_\_\_\_\_ mg of sucrose and water for injection. The pH of the injection is adjusted to 10.0-11.0 \_\_\_\_\_ and its osmolarity is 1250 mOsmol/L.

*What is the Dosage?* The proposed, "usual dosage" regimen of Venofer® is as follows:

Adults: 5 mL (100 mg of iron and \_\_\_\_\_ mg of sucrose) \_\_\_\_\_ three times weekly for a total of 1000 mg of iron in \_\_\_\_\_ 10 doses (maximum tolerated dose: intravenous injection: \_\_\_\_\_ mg of iron injected over at least \_\_\_\_\_ min; intravenous infusion [if demanded by clinical circumstances]: \_\_\_\_\_ mL/kg \_\_\_\_\_ mg of iron/kg and \_\_\_\_\_ mg of sucrose/kg] infused over at least \_\_\_\_\_ h for a total dose of \_\_\_\_\_ mg of iron).



**What is the Indication?** Venofer<sup>®</sup> is proposed for the treatment of anemia associated with dialysis.

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**What is the Scientific Rationale for the Proposed Indication?** The sponsor states (i) that following intravenous administration of Venofer<sup>®</sup>, iron would dissociate rapidly from the iron sucrose complex and (ii) that the dissociated iron would be transported to specific sites and utilized to replenish depleted iron stores and for the synthesis of hemoglobin, myoglobin and enzymes that contain iron.

**What Are the Clinical Efficacy Endpoints?** The clinical efficacy endpoints proposed in the NDA are to assess increases, from baseline, of hemoglobin, hematocrit (primary endpoints), serum iron, serum ferritin and serum transferrin saturation (secondary endpoints) in patients with anemia or iron deficiency treated with intravenous Venofer<sup>®</sup>.

**What is the Adverse Event Profile?** In the NDA, it is stated that in studies evaluating Venofer<sup>®</sup> containing 100-200 mg of iron, no adverse events were observed.

**What is the Nature of Pharmacokinetic and Pharmacodynamic Studies Submitted in the NDA?** In this NDA submission, 13 literature articles on the pharmacokinetics and/or pharmacodynamics of intravenous Venofer<sup>®</sup> are provided.

**Is Adequate Information Given on the Methods of Sample Analysis?** The analytical methods are stated but some are not fully described. Appropriate assay validation data are either incomplete or not provided.

**Summary of Pharmacokinetics of Venofer<sup>®</sup>:** In healthy adults receiving intravenous Venofer<sup>®</sup>, its iron component appears to distribute mainly in blood and is rapidly cleared from serum ( $t_{1/2} \approx 6$  h,  $Cl_r \approx 1.2$  L/h). Minimal urinary elimination of iron (4.5% in 4 h [5.2% in 24 h]) also occurs. Sucrose is eliminated mainly by renal excretion (68.3% in 4 h and 75.4% in 24 h). In patients with anemia or iron deficiency treated with Venofer<sup>®</sup>, the bone marrow appears to be an iron trapping compartment and not a reversible volume of distribution.

**Summary of Pharmacodynamics of Venofer<sup>®</sup>:** In patients with anemia or iron deficiency receiving a single dose of Venofer<sup>®</sup> containing 100 mg of iron, serum iron, serum transferrin saturation and serum ferritin increase within 24 h. In anemic, hemodialysis patients on recombinant erythropoietin therapy receiving the same dose of Venofer<sup>®</sup>, thrice weekly, significant increases in hemoglobin, hematocrit, serum iron, serum ferritin or decreases in total iron binding capacity (TIBC) occurred beginning the fourth week of treatment.

**What is the Recommendation?** From a Pharmacokinetic and Pharmacodynamic perspective, the NDA is considered acceptable for approval considerations.

APPEARS THIS WAY  
ON ORIGINAL

## II. SUMMARY OF INFORMATION ON PHARMACOKINETICS, PHARMACODYNAMICS, METABOLISM, ETC.

### 1. *Is Adequate Serum Pharmacokinetic Information Provided?*

The pharmacokinetics of iron and sucrose was evaluated in 12 normal adult subjects (3 men and 9 women; see Appendix I [page 25] for subject demography) receiving a single dose of iron sucrose (Venofer<sup>®</sup>) containing 100 mg of iron and 1510 mg of sucrose (Reference 3)<sup>1</sup> and in 11 normal adult subjects receiving Venofer<sup>®</sup> containing 50 mg of iron (Reference 4)<sup>2</sup>. The amount of sucrose in the Venofer<sup>®</sup> formulation used in this study was not specified. In Reference 3, pharmacokinetic analysis was performed by compartmental and non-compartmental methods. In this study, a compartmental analysis which includes a Michaelis-Menten term was also performed. This analysis allowed an estimation of the amount of iron transported by transferrin. Details of pharmacokinetic methods for this study are presented in Appendix I (pages 26-27). The serum iron profiles for the compartmental analyses are presented in Figs. 1 and 2. The summary of the pharmacokinetic results provided in Reference 3 include some molar units and are presented in Appendix I (pages 28-30). These results, with the molar units converted to metric units by this reviewer, are summarized in Table 1. A summary of the pharmacokinetic data provided in Reference 4 is included in Table 1.

Fig. 1 Plot of Mean+SD Serum Iron ( $\mu\text{M/L}$ ) Versus Time for Evaluation of Iron Kinetics by Compartmental Analysis following Intravenous Injection of Venofer<sup>®</sup> Containing 100 mg of Iron, over Five Minutes, to Normal Subjects

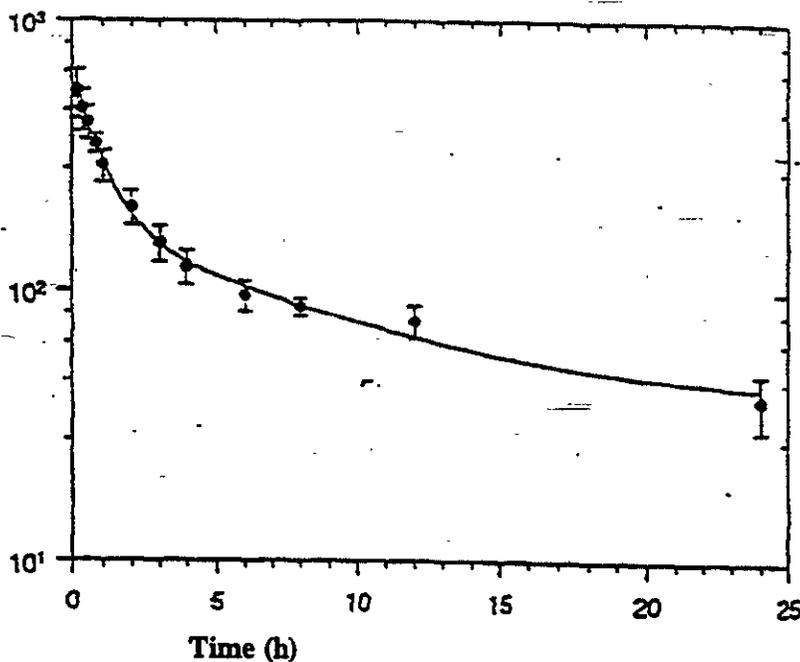


Fig. 2 Plot of Mean+SD Serum Iron Concentration ( $\mu\text{M/L}$ ) Versus Time for Evaluation of Iron Kinetics by Compartmental Analysis with Michaelis-Menten Term following Intravenous Injection of Venofer<sup>®</sup> Containing 100 mg of Iron, over Five Minutes, to Normal Subjects

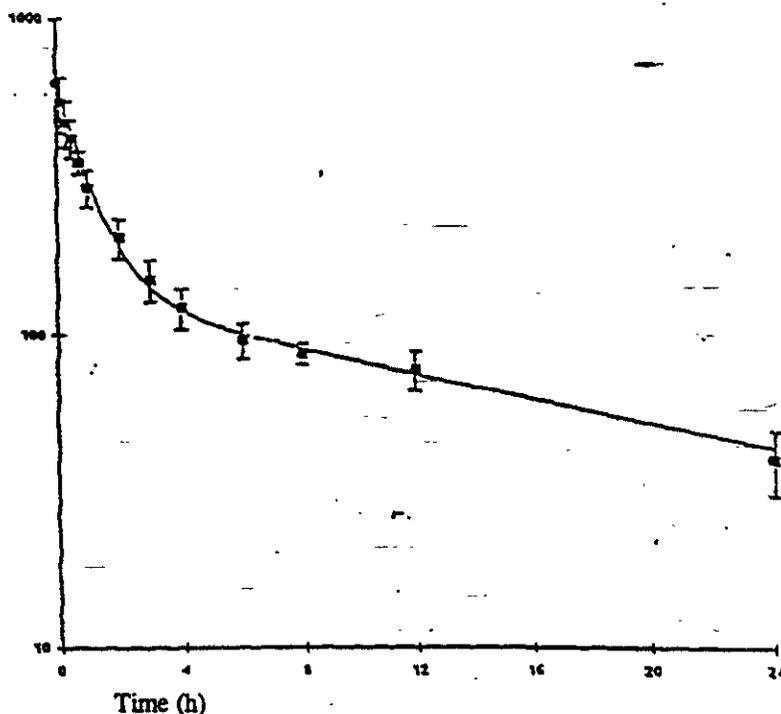


Table 1. Mean +SD Pharmacokinetic Parameters of Iron Following Intravenous Injection of Venofer<sup>®</sup> Containing 100 mg of Iron, over Five Minutes, to Normal Subjects

Ref. #	n	Dose (mg)	PK <sup>a</sup> Parameter	NC <sup>b</sup>	C <sup>c</sup>	MM <sup>d</sup>
3	12	100	C <sub>0</sub> ( $\mu\text{g/mL}$ )	32.6+8.6	33.9+9.0	35.3+8.2
			C <sub>max</sub> ( $\mu\text{g/mL}$ )	30.0+6.0	NR <sup>e</sup>	NR <sup>e</sup>
			t <sub>1/2</sub> (h)	7.0+3.2	6.3+3.4	5.3+1.6
			MRT (h)	8.2+4.2	7.1+3.6	5.3+1.2
			AUC ([mg/L]h)	94.4+31.3	86.7+20.3	83.3+11.8
			AUMC ([mg/L]h <sup>2</sup> )	846.4+652.7	673.3+520.2	465.5+146.2
			Cl <sub>r</sub> (L/h)	1.11+0.23	1.20+0.23	1.23+0.22
			V <sub>c</sub> (L)	3.3+0.8	3.1+0.8	3.2+0.7
			V <sub>d(are)</sub> (L)	10.4+2.8	10.0+4.1	9.2+2.3
			V <sub>d</sub> (L)	8.4+2.5	7.9+2.7	7.3+2.1
4	11	50	Tf-Iron <sup>f</sup> (mg)	N/A <sup>g</sup>	N/A <sup>g</sup>	31.0+6.6
			C <sub>0</sub> ( $\mu\text{g/mL}$ )		3.7+0.8	
			t <sub>1/2</sub> (h)		9.3+6.8	
			Cl <sub>r</sub> (L/h/kg)		0.074+0.086	
			V <sub>d(are)</sub> (L/kg)		0.395+0.117	
			AUC ([ $\mu\text{g/mL}$ ]h)		24.3+ 15.6	

<sup>a</sup>Pharmacokinetic, <sup>b</sup>Non-compartmental, <sup>c</sup>Compartmental, <sup>d</sup>Michaelis-Menten, <sup>e</sup>Not Reported, <sup>f</sup>Iron Transported by Transferrin in 24 h, <sup>g</sup>Not applicable.

To determine suitability of the pharmacokinetic data from the submitted literature articles for use in the drug product labeling, the overall quality of information in the study in each article was assessed. In Reference 4, adequate information is not provided on the study design, sample analysis and pharmacokinetic analysis. It is not clearly stated whether the analytical method measured the iron in the drug complex or free iron that has dissociated from the drug complex. Individual subject data are also not provided in this reference. In Reference 3, the study design and the method of pharmacokinetic analysis are adequately described (see Appendix I [pages 26-28]). The precision of the assay method for iron analysis in serum is stated as 5.6% (n=63). However, the limit of quantification, accuracy and specificity of the analytical method as well as stability data for iron and sucrose in stored samples are not provided. Nevertheless, the pharmacokinetic parameters obtained by compartmental and non-compartmental analyses are in agreement. For compartmental analysis with or without the Michaelis-Menten term, individual subject data are provided which yield insight into the goodness of fit of individual subject plots. However, since the Michaelis-Menten term does not usually feature in equations for determining pharmacokinetic parameters, the compartmental pharmacokinetic data obtained without the Michaelis-Menten term are considered more suitable for use in the drug product labeling.

Based on the findings of the study in Reference 3, following intravenous administration of Venofer® to healthy adults, the elimination half-life of its iron content is 6 h, the total clearance is 1.11 L/h, the total area under the plasma versus time curve is 86.7 mg/L\*h, the apparent volume of distribution in the plasma compartment is 3.1 L, the non-steady state apparent volume of distribution is 10.0 L and the steady state apparent volume of distribution is 7.9 L. The standard deviations of the main pharmacokinetic parameters (Table 1) represent mild to moderate (19.2-45.7%) inter-individual pharmacokinetic variability.

The serum elimination half-life of 6 h suggests that in healthy adults, receiving intravenous Venofer®, its iron content is essentially completely cleared from the serum in 24 h. This is supported by the sponsor's findings of a mean  $\pm$  SD 24 h serum iron concentration of  $39.5 \pm 9.5 \mu\text{M/L}$  (n=12) which was not significantly different baseline values ( $35.7 \pm 12.6 \mu\text{M/L}$  [n=12]). Thus, significant iron accumulation in serum may not occur in healthy adults receiving daily Venofer® doses containing 100 mg of iron.

The potential for iron accumulation in individuals receiving multiple doses of Venofer® containing 100 mg of iron was further investigated by this reviewer using the formula  $R = 1/(1-e^{-k\tau})$ , where R is the accumulation ratio (factor), k is the elimination rate constant and  $\tau$  is the dosing interval (24 h). For  $t_{1/2} = 6-7$  h,  $R = 1.07-1.10$  suggesting minimal (7-10%) accumulation of iron in serum.

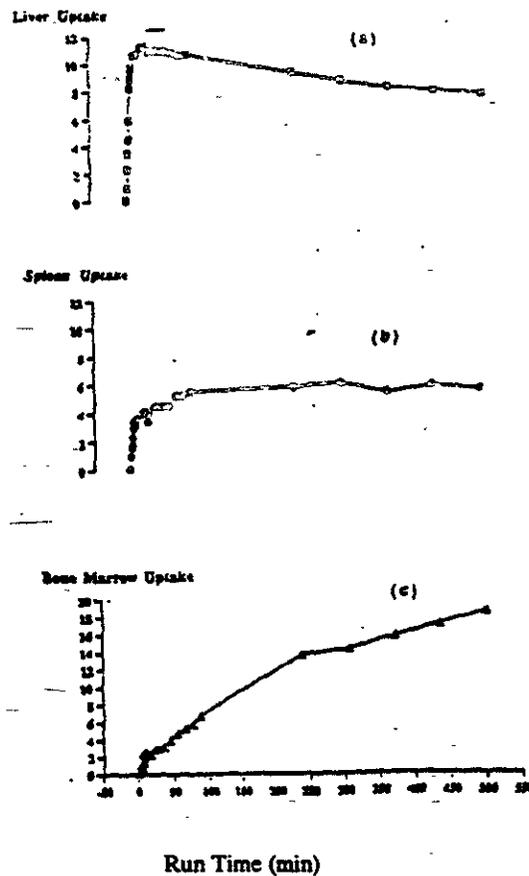
In healthy adults receiving Venofer® containing 100 mg of iron, 31.0% of the iron is transported by transferrin within 24 h suggesting ready systemic availability of iron from intravenous Venofer®.

Since iron elimination from the serum depends on its need at the sites of utilization and storage, it is reasonable to expect a faster iron clearance and, subsequently, a lower chance of iron accumulation in the target patient population receiving the labeling recommended multiple dosage regimen of Venofer®.

## 2. Is Adequate Tissue Pharmacokinetic Information Provided?

The tissue kinetics of iron hydroxide sucrose containing 100 mg of iron labeled with  $^{52}\text{Fe}/^{59}\text{Fe}$  (0.5/20 MBq) was evaluated, via  $^{52}\text{Fe}$  uptake, in two patients with iron deficiency anemia, two patients with renal anemia, 2 patients with functional iron deficiency using the positron emission tomography (PET) technique (Reference 5)<sup>3</sup>. Patients 1, 3, 4, and 6 were on recombinant human erythropoietin therapy (see Appendix I [page 31]) prior to this study. Levels of  $^{52}\text{Fe}$  (physical  $t_{1/2} = 8.3$  h) rose rapidly to a maximum standardized uptake values (SUV) of about 11 in the liver within 60 min and 5.5 in the spleen within 100 min. Thereafter, spleen radioactivity was essentially unchanged while the liver values declined slowly. Bone marrow  $^{52}\text{Fe}$  rose rapidly to an SUV of about 2 within 30 min and, then increased more slowly (Fig 3).

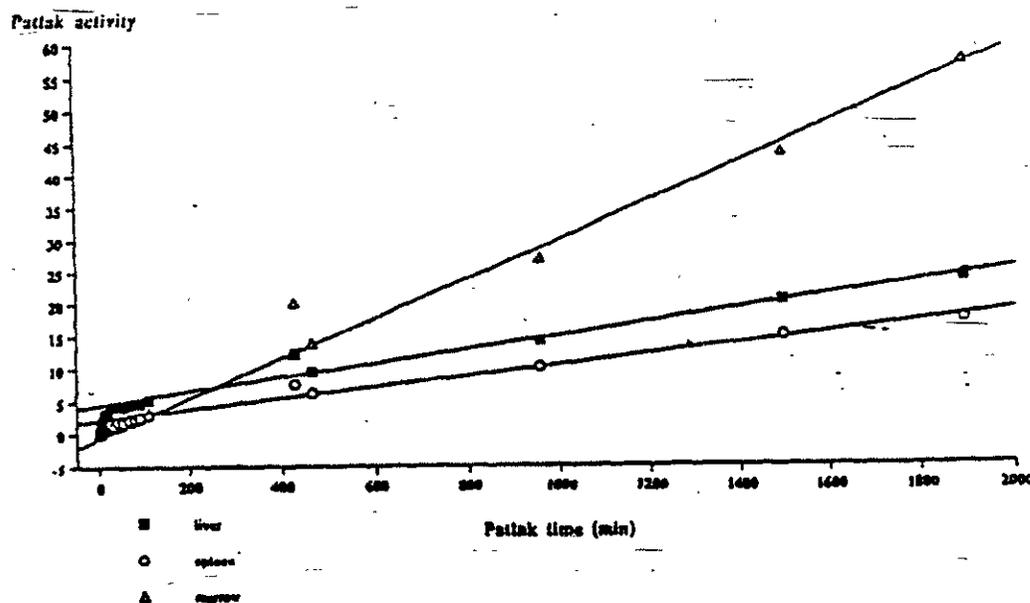
Fig. 3. Plots of Liver, Spleen and Bone Marrow  $^{52}\text{F}$  Activity Uptake (SUV) Versus Time in One Anemic Patient Receiving Intravenous Iron Hydroxide Sucrose Containing 100 mg of Iron labeled with  $^{52}\text{Fe}/^{59}\text{Fe}$  (0.5 MBq/20MBq)



A Patlak plot (of Patlak activity versus Patlak time) yields intercepts of approximately 0 (zero), 2 and 4 for radioactivity in the bone marrow, the spleen and the liver, respectively (Fig.4). Furthermore, the slope of the plot for the bone marrow is much greater than those for the liver and the spleen.

The intercept of the Patlak plot represents the size of the reversible iron pool (distribution volume) and the slope the rate constant that describes the rate of flow of iron from the blood into the distribution volume (see Appendix I, page 34). In Fig. 4, the intercepts for the plots of the liver and spleen radioactivity are stable, positive values suggesting that these organs constitute reversible iron pools. The intercept for the plot of bone marrow radioactivity approximates zero suggesting that the bone marrow is not a reversible iron pool. This means that once iron enters the bone marrow, it does not return to the general circulation but is trapped for utilization in erythropoiesis. Furthermore, iron flows from the blood into the bone marrow at a higher rate as compared to the liver and the spleen. This is evidenced by the larger slope for the plot of bone marrow Patlak activity versus Patlak time as compared to those of the liver and the spleen.

Fig 4. Patlak Plots of Liver, Spleen and Bone Marrow  $^{52}\text{Fe}$  Activity in One Anemic Patient Receiving Intravenous Iron Hydroxide Sucrose Containing 100 mg of Iron labeled with  $^{52}\text{Fe}/^{59}\text{Fe}$  (0.5 MBq/20MBq)



### 3. Is Adequate Information Provided on Drug Distribution?

In healthy adults receiving intravenous doses of Venofer<sup>®</sup>, its iron content appears to distribute mainly in blood and only to some extent in extravascular fluid. This is evidenced by a non-steady state apparent volume of distribution of 10 L and a steady state apparent volume of distribution of 7.9 L.

#### **4. Is Adequate Information Provided on Drug Metabolism?**

The sponsor proposes that *in vivo*, the iron sucrose complex in Venofer<sup>®</sup> would dissociate to iron and sucrose and that the iron would be readily utilized for erythropoiesis and replenishment of depleted iron stores. In the submitted literature studies, there is evidence that the dissociation is mediated, at least in part, by macrophages in the liver and other tissues as well as by hepatocytes. Iron forms complexes with apotransferrin to form transferrin and is transported to the bone marrow for hemoglobin synthesis. Iron also complexes with the protein ligand, apoferritin, in the mitochondria of the liver and other tissues, to form ferritin (the iron storage molecule). Myoglobin and enzymes that contain iron may also be synthesized with the iron from Venofer<sup>®</sup>. Significant metabolism of intravenously administered sucrose is not expected as sucrose is not known to be converted to fructose and glucose outside the gastrointestinal tract or to be utilized in the synthesis of glycogen.

#### **5. Is Adequate Information Provided on Drug Elimination?**

In healthy 12 adults receiving intravenous Venofer<sup>®</sup> containing 100 mg of iron and 1510 mg of sucrose (Reference 3), its sucrose content was eliminated primarily in urine (68.3% in 4 h and 75.4% in 24 h [see Appendix I, page 32]). Small amounts of its iron content were also eliminated in urine (4.5% in 4 h and 5.2% in 24 h [see Appendix I, page 33]). In another study (Reference 6)<sup>4</sup>, two doses of iron sucrose (one containing 500 mg of iron, the other containing 700 mg of iron) were administered by intravenous infusion over 3 days, to patients with iron deficiency anemia (n=26 [3 men and 23 women; age range=16-60 years]). In this study, similar 24 h urinary elimination of iron (4.5% and 4.8% for the 500 mg and 700 mg doses, respectively) was observed. Based on these data, urinary excretion is the main route of Venofer<sup>®</sup> elimination.

#### **6. Is Adequate Plasma Protein Binding Information Provided?**

No studies were conducted to evaluate the plasma protein binding of Venofer<sup>®</sup>. An independent literature review by this reviewer yields no information that would suggest that iron or sucrose could be significantly plasma protein bound. Accordingly, it is considered that an additional study to evaluate the plasma protein binding of Venofer<sup>®</sup> is not necessary.

#### **7. Is Adequate Information Provided on Drug-drug Interactions?**

No studies were conducted to investigate possible drug-drug interactions involving Venofer<sup>®</sup>. In the drug product labeling, under the sub-section, Drug Interactions, the sponsor states that "Venofer<sup>®</sup> should not be administered concomitantly with oral iron preparations since the absorption of iron is reduced". The sponsor further states that in patients already on oral iron therapy, oral iron needs to be discontinued prior to initiation of treatment with Venofer<sup>®</sup>.

### 8. Is Adequate Information Provided on Pharmacokinetics in Special Populations?

No information is provided on the kinetics of Venofer<sup>®</sup> in special populations. In the Contraindication section of proposed drug product labeling, the sponsor states that Venofer<sup>®</sup> is contraindicated in patients with iron overload or disturbances in iron utilization. It is noted that the sucrose component of Venofer<sup>®</sup> is eliminated primarily by renal mechanisms. However, sucrose is not expected to exhibit any significant pharmacologic activity. Therefore, prolonged elimination in patients with renal impairment is not expected to result in classical drug type toxicity. From a pharmacokinetic perspective, it is considered that an additional study to evaluate the kinetics of Venofer<sup>®</sup> in patients with renal impairment is not necessary. The medical officer is advised to examine the findings of the Phase III safety and efficacy studies for evidence of kidney damage in any participating patients with renal impairment and make safety related comments as appropriate (see General Comment 1).

### 9. Is Adequate Information Provided on Effects of Age on Pharmacokinetics?

No information is provided on the effects of age on the kinetics of Venofer<sup>®</sup>. In the Dosage and Administration section of the drug product labeling, the "usual dosage" of Venofer<sup>®</sup>

### 10. Is Adequate Information Provided on the Effect of Gender on Pharmacokinetics?

No studies were conducted to evaluate the effect of gender on the kinetics of Venofer<sup>®</sup>. However, this reviewer re-analyzed the compartmental pharmacokinetic data in Reference 3 (males=3; females=9) in an attempt to provide insight into gender differences in the kinetics of Venofer<sup>®</sup>. The following results were obtained:

$t_{1/2}$ : \_\_\_\_\_ h in males and \_\_\_\_\_ h in females  
 Clr: \_\_\_\_\_ L/kg in males and \_\_\_\_\_ L/kg in females  
 AUC: \_\_\_\_\_  $\mu\text{M/L}\cdot\text{h}$  in males and \_\_\_\_\_  $\mu\text{M/L}\cdot\text{h}$  in females  
 $V_{\text{dis}}$ : \_\_\_\_\_ L in men and \_\_\_\_\_ L in women  
 24 h Renal Elimination of Iron: \_\_\_\_\_ in males and \_\_\_\_\_ in males  
 24 h Renal Elimination of Sucrose: \_\_\_\_\_ in males and \_\_\_\_\_ in females.

A conclusive statement as to differences in the kinetics of intravenous Venofer<sup>®</sup> between males and females cannot be made on the basis of this analysis due to the small number of male subjects. Iron is a micro-nutrient needed to varying extents by males

and females and sucrose is not expected to exhibit any significant pharmacologic activity. Therefore, is considered that it is not necessary to conduct an additional study to assess the effect of gender on the kinetics of Venofer®.

#### 11. Is Adequate Pharmacodynamic Information Provided?

The sponsor states that following intravenous administration of Venofer®, iron would dissociate from sucrose rapidly and would be transported to specific sites and utilized to replenish depleted iron stores and to synthesize hemoglobin, myoglobin and enzymes that contain iron.

In the study evaluating the tissue kinetics of iron sucrose containing 100 mg of iron labeled with  $^{59}\text{Fe}/^{52}\text{Fe}$  (0.5/20 MBq) in two patients with iron deficiency anemia, two patients with renal anemia and 2 patients with functional iron deficiency, by the PET technique (see item 2 above), utilization of radioiron ( $^{59}\text{Fe}$  [physical  $t_{1/2}=45$  days]) by red blood cells was determined. Serum hemoglobin (Hb), iron (S-Fe), ferritin (S-Fer), TIBC, transferrin saturation (TS) and transferrin receptors (S.TfR) were also measured in this study. The following results were obtained:

##### i. Effect of Iron Sucrose on Iron Utilization by Red Blood Cells

Iron utilization by red blood cells increased rapidly in all patients (Table 2) and generally reached a maximum value (68-97%) 15-28 days post dose.

Table 2. Red Blood Cell Utilization of  $^{59}\text{Fe}$  in Anemic Patients Receiving Intravenous Iron Hydroxide Sucrose Containing 100 mg of Iron labeled with  $^{52}\text{Fe}/^{59}\text{Fe}$  (0.5 MBq/20MBq)

Patient 1		Patient 2		Patient 3		Patient 4*		Patient 5		Patient 6	
Day	%	Day	%	Day	%	Day	%	Day	%	Day	%
1											
2											
3											
6											
9											
13											
16											
20											
23											
-											

\*Erythrocytic concentrations given on day 10 to day 13 for severe anemia and excluded from the analysis after day 13, and was re-included on day 23.

##### ii. Effects of Iron-Sucrose on Hemoglobin, Serum Iron, Transferrin Saturation, Serum Ferritin, TIBC and Transferrin Receptors

The effects of intravenous iron sucrose on hemoglobin, serum iron, serum ferritin, serum transferrin saturation, TIBC and transferrin receptors are presented in Table 3.

Table 3. Hematological and Iron Parameter in Anemic Patients Treated with a Single Intravenous Dose of Iron Hydroxide Sucrose Containing 100 mg of Iron Labeled with  $^{52}\text{Fe}/^{59}\text{Fe}$  (0.5 MBq/20MBq)

Patient	Day	Hb (g/L)	S. Fe ( $\mu\text{M/L}$ )	S. Fer ( $\mu\text{g/L}$ )	TIBC ( $\mu\text{M/L}$ )	TS (%)	S.TfR (mg/L)	
1 (female)	0							
	1							
	2							
	3							
	6							
	9							
	13							
	16							
	20							
	23							
	27							
	2 (female)	0						
		1						
2								
3								
6								
9								
13								
16								
21								
24								
28								
3 (male)	0							
	1							
	2							
	3							
	6							
	9							
	13							
	15							
	21							
	24							
28								

Normal Range: Hb (g/dL): 12.0-15.6 (f), 14.0-17.8 (m); S.Fe ( $\mu\text{g/dL}$  [ $\mu\text{M/L}$ ]): 65-165 [11.64-29.55] (f); 75-175 [13.43-31.34] (m); S. Fer. (ng/mL): 20-120 (f), 20-300 (m); TIBC ( $\mu\text{g/dL}$ ): 250-450 (m & f); TS (%): 20-50 (m & f); (m = males; f = females).

Table 3 (contd.). Hematological and Iron Parameters in Anemic Patients Treated with a Single Intravenous Dose of Iron Hydroxide Sucrose Containing 100 mg of Iron Labeled with  $^{52}\text{Fe}/^{59}\text{Fe}$  (0.5 MBq/20MBq).

Patient	Day	Hb (g/L)	S. Fe ( $\mu\text{M/L}$ )	S. Ferritin ( $\mu\text{g/L}$ )	TIBC ( $\mu\text{M/L}$ )	TS (%)	S.TfR (mg/L)
4 (male)	0						
	1						
	2						
	3						
	6						
	23						
	24						
	5 (female)	0					
1							
2							
9							
13							
16							
20							
23							
6 (female)	0						
	1						
	2						
	6						
	8						
	13						
	15						
	19						
26							

Normal Range: Hb (g/dL): 12.0-15.6 (f), 14.0-17.8 (m); S.Fe ( $\mu\text{g/dL}$  [ $\mu\text{M/L}$ ]): 65-165 [11.64-29.55] (f); 75-175 [13.43-31.34] (m); S. Fer. (ng/mL): 20-120 (f), 20-300 (m); TIBC ( $\mu\text{g/dL}$ ): 250-450 (m & f); TS (%): 20-50 (m & f); m= males; f = females.

Generally, serum iron, serum transferrin saturation and serum ferritin increased significantly with 24 h of drug administration. However, in some patients, some of these increases occurred much later (e.g., Patient 3: serum iron on Days 13-15 and serum transferrin saturation on Days 6, 13-15 and 24-28). In Patient 5 with markedly low serum iron and serum transferrin saturation, serum transferrin receptor levels were higher than those of the other patients. This would be expected in this patient as iron utilizing cells would produce more transferrin receptors in an effort to extract iron from the serum to meet their needs. TIBC values were generally not significantly affected by intravenous iron hydroxide sucrose in this study. These findings suggest that following intravenous administration of iron hydroxide sucrose to patients with iron deficiency anemia, renal anemia and functional iron deficiency, its iron component is readily available systemically and is efficiently transported to appropriate sites to replenish iron

stores. The hemoglobin values and red cell iron utilization, in these anemic patients, were further analyzed by this reviewer (see Table 4).

Table 4. Hemoglobin in Anemic Patients Receiving a Single Intravenous Dose of Iron Hydroxide Sucrose Containing 100 mg of Iron Labeled with  $^{52}\text{Fe}/^{59}\text{Fe}$  (0.5 MBq/20MBq).

Patient	Gender	Normal Hb Range (g/dL)	Pre-dose Hb (g/dL)	Postdose Hb (g/dL)	Red Blood Cell Iron Utilization (%)
6 <sup>a</sup>	Female	12.0-15.6			
1 <sup>a</sup>	Female	12.0-15.6			
2	Female	12.0-15.6			
5	female	12.0-15.6			
3 <sup>a</sup>	Male	14.0-17.8			
4 <sup>a</sup>	Male	14.0-17.8			

On erythropoietin therapy; — g/dL on Day 9 only (Patient 3), — g/dL on Day 23 only (Patient 4), below baseline for the rest of the study

Modest hemoglobin increases, above baseline, were observed in 3 of 6 patients (Patients 6, 1 and 2). In one patient (Patient 5), hemoglobin values were essentially unchanged throughout the study. In 2 of 6 patients (Patients 3 and 4), hemoglobin values were at or above baseline on only one day (Day 9 for Patient 3 and Day 23 for Patient 4) and was below baseline for the rest of the study. It is considered that significant enhancement of hemoglobin values in anemic patients treated with a single intravenous dose of Venofer<sup>®</sup> containing 100 mg of iron cannot be concluded based on the findings of this study.

It is noted that the iron utilization value, calculated as a ratio of whole blood  $^{59}\text{Fe}$  activity to injected  $^{59}\text{Fe}$  activity following  $^{59}\text{Fe}$ -labeled iron sucrose administration, does not correlate with changes in hemoglobin levels in this study. Therefore, such red cell iron utilization values cannot be used as an indicator of hemoglobin formation following intravenous iron sucrose administration. Accordingly, it would be necessary to monitor individual patients in the course of iron sucrose therapy to determine whether hemoglobin levels are increasing, especially in cases where hemoglobin levels require therapeutic intervention (Hb < 10.5  $\mu\text{g}/\text{dL}$  [males and females; based on literature information]). The sponsor is requested to submit the mean and individual subject data on the ratios of  $^{59}\text{Fe}$  activity in red blood cells and plasma to injected  $^{59}\text{Fe}$  activity to the Agency for review (see Overall Comment).

Intravenous iron sucrose containing 100 mg of iron, administered over 5-10 min, was evaluated in hemodialysis patients with iron deficiency (n=22) or without iron deficiency (n=29) (Reference 10)<sup>5</sup>. This dose was administered three times per week. In the same study, iron sucrose containing 500 mg of iron was administered over 1-4 h, once weekly, to hemodialysis patients with iron deficiency (n=42) or without iron

deficiency (n=16). Each dose was administered, based upon hemoglobin levels, until a total target dose of 1000 mg of iron was reached. A maximum of 5-10 doses was administered to each patient. For each dose level, hematological and iron parameters were determined once weekly. The iron deficient and iron non-deficient groups had been on recombinant human erythropoietin therapy ( $\leq 100$  IU/kg and 50 IU/kg, respectively) administered three times weekly for at least 8 weeks. Only the mean data are reported in this literature article. Individual subject data are not provided. The results are presented in Table 5.

Table 5. Hematological and Iron Parameters in Hemodialysis Patients on Recombinant Human Erythropoietin Therapy Treated with Intravenous Iron Sucrose Containing 100 mg Three times Weekly or 500 mg Once Weekly for Three Weeks.

Test	Group 1 - "High Dose" - 500 Mg Iron (N=58)				Group 2 - "Low Dose" - 100 Mg Iron (N=31)			
	Iron Deficient (n=42)		Non-Iron Deficient (n=16)		Iron Deficient (n=22)		Non-Iron Deficient (n=29)	
	A <sup>†</sup>	B	A	B	A	B	A	B
Hb (g/dL)	8.3±0.7	11.0±0.7	8.8±0.6	11.6±0.6	8.5±0.3	11.1±1.0	8.5±0.8	11.2±1.0
Hct (%)	24.9±2.3	33.0±2.1	26.5±2.1	35.0±1.9	25.7±1.8	33.4±2.8	25.4±2.6	34.1±2.9
MCV (fL)	71.7±4.7	81.4±3.5	83.7±4.2	83.7±3.0	68.2±4.5	75.4±4.4	84.7±4.2	85.2±3.8
MCH (pg)	24.5±2.7	30.9±1.5	31.4±0.9	31.1±0.8	22.1±2.5	28.4±1.5	32.1±1.2	31.9±1.1
Fe (umol/L)	11.0±2.9	18.7±4.6	19.8±2.9	21.6±2.1	7.2±3.2	15.2±2.4	19.9±3.8	21.1±3.4
TIBC (umol/L)	80.4±5.3	57.9±9.8	50.8±5.7	48.7±5.6	97.7±6.4	55.5±9.4	55.5±8.1	47.6±6.0
Ferritin (ng/mL)	18.6±11.8	52.2±25.3	165.0±46.3	200.0±38.3	12.8±6.0	88.7±23.0	107.5±38.5	177.5±66.5

<sup>†</sup>A = Before iron sucrose therapy; B = Four weeks after beginning iron sucrose therapy.

\*p<0.001 (Student's paired "t" test for B vs A).

Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; Fe: iron; TIBC: total iron binding capacity  
g/dL: gram per deciliter, umol/L: micromolar, ng/mL: nanogram per milliliter, mg: milligram.

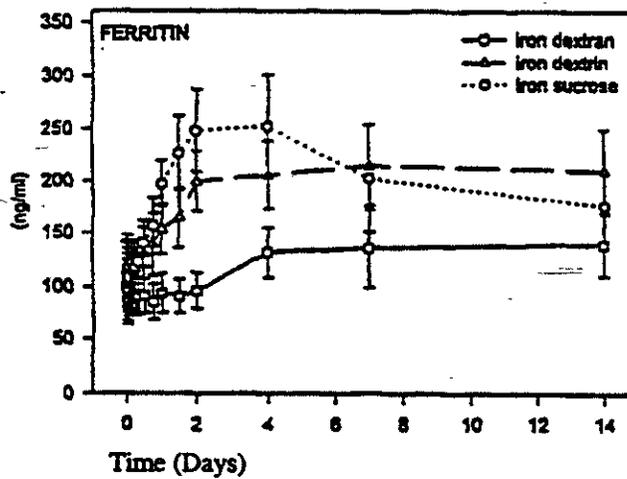
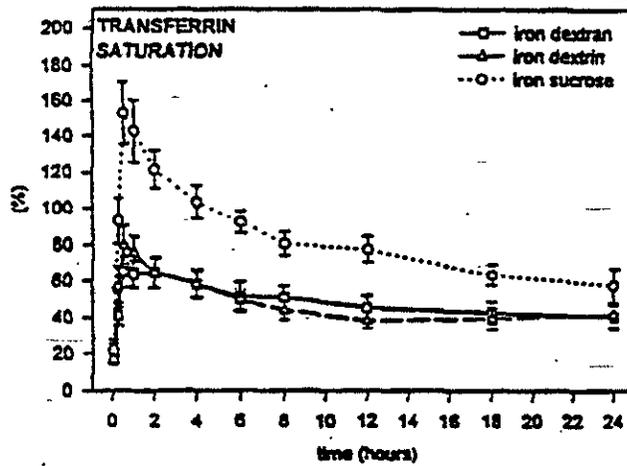
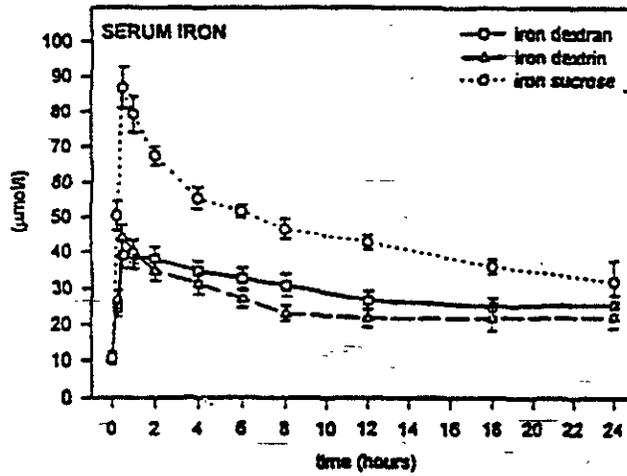
These results suggest that in iron deficient patients on erythropoietin therapy treated with intravenous iron sucrose containing 100 mg of iron, thrice weekly, or 500 mg of iron, once weekly, significant increases in hemoglobin, hematocrit, serum iron and serum ferritin or significant decreases in TIBC are not attained until the fourth week of treatment. In the iron non-deficient patients on erythropoietin therapy treated with the same iron sucrose dosage regimens, only hemoglobin and hematocrit levels may increase significantly in the fourth week following the initiation of treatment.

Based on these results, therapy with intravenous iron sucrose containing 500 mg of iron given once weekly or 100 mg of iron, given thrice weekly, would probably not be ideal where rapid (i.e., in <4 weeks), significant increases in hematological or iron parameters are needed in patients on human erythropoietin therapy.

### 12. Does Iron Sucrose Have any Pharmacodynamic Advantage over Iron Dextran and Iron Dextrin?

The levels of serum iron, serum transferrin saturation and serum ferritin were assessed in three groups of dialysis patients (n=20 per group) receiving single intravenous doses of iron sucrose, iron dextran and iron dextrin, each containing 200 mg of iron, in a parallel design (Reference 1)<sup>6</sup>. The results of the study are presented in Fig. 5.

Fig.5. Mean  $\pm$  SE Iron Parameters in Anemic, Dialysis Patients Receiving Intravenous Iron Sucrose, Iron Dextran and Iron Dextrin Each Containing 200 mg of Iron



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Within 24 h of dose administration, serum iron and serum transferrin saturation levels for iron sucrose were significantly higher as compared to iron dextran and iron dextrin whereas iron dextran and iron dextrin were similar in these iron parameters. It is noted that for iron sucrose, serum transferrin saturation exceeded 100% (i.e., exceeded the total iron binding capacity of transferrin) within the first 5 h of dose administration. The sponsor attributes this to a release of iron (which is indistinguishable from the iron released from transferrin) from other macromolecules, that is also detected by the chromogen used in the transferrin saturation analysis. In this study, hemoglobin and hematocrit were not determined.

The mean serum ferritin for iron sucrose increased rapidly reaching a maximum of approximately 245-255 ng/mL 2-4 days postdose and declined to approximately 180 ng/mL at 14 days postdose. The mean serum ferritin for dextrin increased rapidly to approximately 200 ng/mL at 2 days postdose and then increased gradually to 220 ng/mL at 14 days postdose. Serum ferritin levels for iron sucrose and iron dextrin were not significantly different throughout the study. For iron dextran, the mean serum ferritin remained essentially at baseline up to 2 days postdose. It increased to approximately 125 ng/mL at 4 days postdose but remained below 150 ng/mL up to 14 days postdose. Throughout the study, serum ferritin levels for iron dextran were significantly lower as compared to those for iron sucrose and iron dextrin.

The findings of this study suggest that in anemic dialysis patients, intravenous iron sucrose results in higher serum iron and serum transferrin saturation levels as compared to iron dextrin and in higher serum iron, serum transferrin saturation and serum ferritin levels as compared to iron dextran.

### **13. *What Is the Adverse Event Profile of Venofer®?***

Across studies, in subjects receiving Venofer® containing 100-200 mg of iron, it is stated, in the NDA, that no adverse events were observed. It is further stated (i) that 2 of 58 hemodialysis patients treated with Venofer® containing 500 mg of iron experienced fever, nausea and hypotension that responded to treatment with antihistamines and hydrocortisone within a few hours and (ii) that three other patients in this study experienced headache, nausea and skin discomfort during Venofer® infusion which resolved when infusion was stopped.

### **14. *Is Pharmacokinetic/Pharmacodynamic Relationship Adequately Explored?***

In the NDA, it is stated that the selection of the labeling recommended dose of Venofer® was based on practical experience, which showed "100 mg iron given intravenously as iron sucrose" to be "safe and effective" (for the proposed label use), and not on "classical dose-ranging studies with clinical efficacy endpoints". Most of the studies in the NDA utilized one Venofer® dose level. In the few studies using more than

one dose level, sufficient serum iron data are not provided to allow a meaningful assessment of relationship between iron dose and hematological or iron parameters.

In a study evaluating a single intravenous dose of iron sucrose containing 100 mg of iron labeled with  $^{52}\text{F}/^{59}\text{F}$  in 6 anemic patients (Reference 5), significant increases from baseline, in serum iron, serum ferritin and serum transferrin, which lasted 24 h or longer, were observed in 5 of 6 patients (see Table 3 above). In this study, the high rate of irreversible influx of iron into the bone marrow of the patients following iron sucrose administration, suggested by the pharmacokinetic findings (see Figs. 3(c) and 4), resulted in only minimal hemoglobin increases above baseline in 3 of 6 patients (see Table 3). The postdose values in the other three patients were at or below baseline. Thus, a correlation cannot be established between the amount of iron in the bone marrow and the hemoglobin values in the patients evaluated in this study. A lack of increase in hemoglobin in the presence of large amounts of iron in the bone marrow could possibly be related to erythropoietin deficiency in the bone marrow of the patients.

**15. Are the Methods of Sample Analysis Adequately Described?**

The following information on analytical methodology is provided for the major studies on which the clinical pharmacology section of the drug product labeling is based:

**A. Reference 3 Evaluating Venofer<sup>®</sup> Kinetics in Healthy Subjects:**

(i) **Serum Iron and Iron(III)-hydroxide Sucrose Complex:** Serum iron and iron(III)-hydroxide complex in blood and urine were measured as elemental iron using the method of \_\_\_\_\_ The analyses were performed at the \_\_\_\_\_ The sponsor states (i) that precision of the analytical method was 5.6% (mean-25.8  $\mu\text{M}/\text{L}$ , SD=1.44  $\mu\text{M}/\text{L}$ , n=63) and (ii) that regular internal precision and accuracy checks and external quality control were performed in accordance with the recommendations of the Nordic Committee of the Scandinavian Society of Clinical Chemistry. The limit of quantification, linearity range, accuracy, specificity and data on analyte stability in stored samples are not provided for the analytical method.

(ii) **Iron and Sucrose:** Iron was measured in urine samples using \_\_\_\_\_ Sucrose was measured in urine samples using a \_\_\_\_\_ Both analyses were performed at Vifor International, Inc., St. Gallen, Switzerland. The analytical methods are not fully described and no assay validation information is provided.

(iii) **Serum Transferin Saturation, Serum Ferritin and Hemoglobin:** Serum transferrin saturation, serum ferritin and hemoglobin were analyzed by standard clinical laboratory methods.

**B. Reference 5 Evaluating Venofer<sup>®</sup> in Anemic Patients by the PET Method:**

(i) **PET Imaging:** PET imaging was performed using the

The standardized supine position was selected to ensure that the heart, liver, and spine are situated in the field of view. Measurement times were one minute for the first 15 frames and 15 minutes for the rest of the frames. Intercalibration of the tomograph versus ionizing chamber and well counters was performed regularly. Emission scans were performed for the first 90 min followed by scans at 3, 4, 5, 6 and 8 postdose.

(ii) **Measurement of <sup>52</sup>F Activity in Blood Samples:** Each blood sample was divided into two portions. Plasma was obtained from one portion. The other portion remained as whole blood. Radioactivity in the whole blood and the plasma was measured by counting in a well counter that was cross calibrated with the scanners.

(iii) **Correction for <sup>52</sup>Mn in Blood Samples:** To correct for <sup>52</sup>Mn (the positron emitting decay product of <sup>52</sup>Fe), blood samples obtained at 1 and 2 h postdose were placed in a well-type NAI (T1) detector. At higher energies, a measuring window was obtained which provided information on the activity from <sup>52</sup>Mn. This allowed for a correction of total radioactivity for <sup>52</sup>Mn activity.

(iv) **Measurement of Radioiron (<sup>59</sup>Fe) for Assessment of Red-Cell Iron Utilization:** Blood samples were obtained thrice weekly for the first week and twice weekly for the remaining two weeks. Each blood sample was divided into two portions. Plasma and red blood cells were obtained from one portion. The other portion remained as whole blood. Radioactivity per gram was measured in whole blood, plasma and red blood cells. Red cell utilization of iron was estimated as a ratio of the <sup>59</sup>Fe activity in whole blood to the administered <sup>59</sup>Fe activity.

(v) **Measurement of Iron Parameters and Hematological Parameters:** Serum iron, serum transferrin saturation, serum ferritin, TIBC and hemoglobin were determined using standard clinical laboratory methods.

(vi) **Measurement of Serum Transferrin Receptors:** Serum transferrin receptors were determined using \_\_\_\_\_ The analytical method is not fully described and no assay validation information is provided.

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**C. Reference 10 Evaluating Venofer<sup>®</sup> in Hemodialysis Patients Treated with Recombinant Human Erythropoietin:**

(i) **Measurement of Hematological Parameters:** Hematological parameters were measured using a \_\_\_\_\_

(ii) **Measurement of Serum iron and TIBC:** Serum iron and TIBC were measured using \_\_\_\_\_

(iii) **Measurement of Serum Ferritin:** Serum Ferritin was measured by \_\_\_\_\_

Details of these analytical methods are not provided.

**16. *Are the Methods of Pharmacokinetic Analysis Adequately Described?***

Pharmacokinetic analyses were performed by standard compartmental and non-compartmental methods as well as by a compartmental method with a Michaelis-Menten term which allowed the estimation of the amount of iron transported by transferrin (see Appendix I [pages 26-28]). The pharmacokinetic methods were adequately described.

**17. *Are the Methods of Pharmacodynamic Analysis Adequately Described?***

No dose ranging studies were conducted to determine the dosage regimen recommended in the drug product labeling (see item 14 [page 16]). Subsequently, no classical pharmacodynamic analysis was performed. The pharmacodynamic endpoints consists of hematological and iron parameters. The measurements of these parameters are covered under Sample Analysis (item 15 [pages 17-19]).

**18. *What are the Pharmacokinetic and Pharmacodynamic Results?***

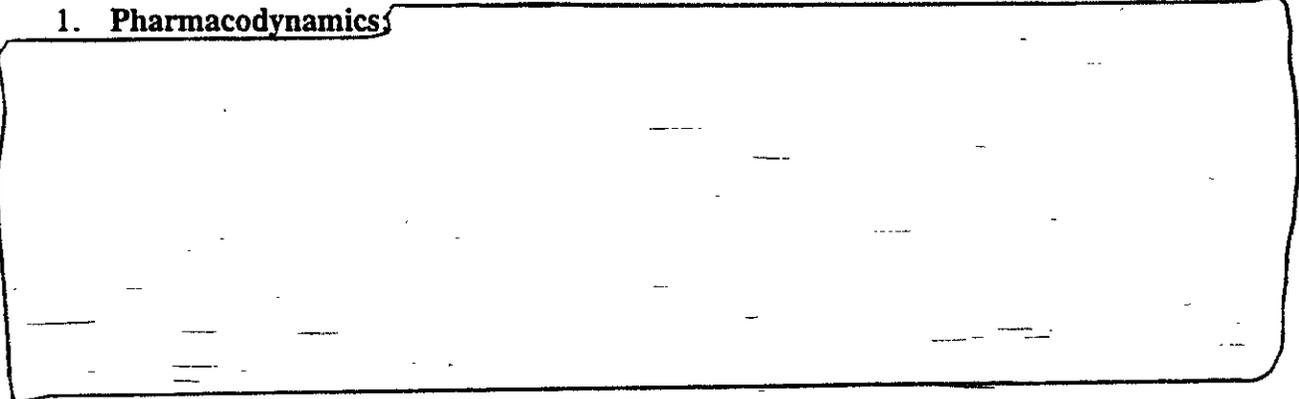
See pages 3-17.

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### III. LABELING COMMENTS

The Clinical Pharmacology section of the proposed drug product labeling should be modified to reflect the following:

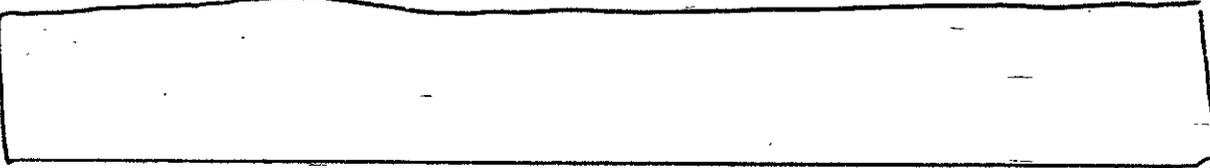
#### 1. Pharmacodynamics:



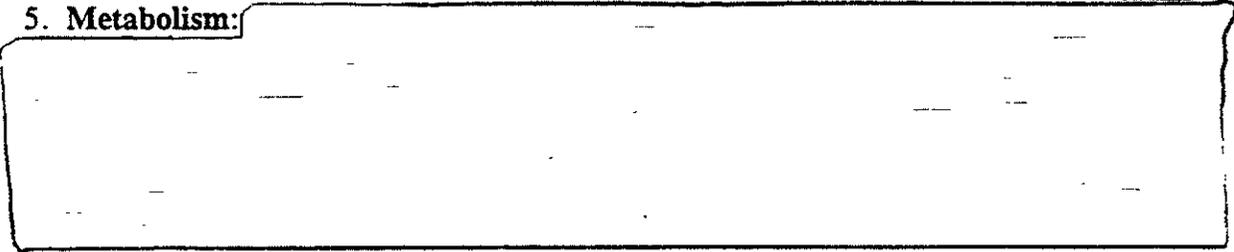
2. Pharmacokinetics: In healthy adults treated with intravenous doses of Venofer<sup>®</sup>, its iron component exhibits first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, non-steady state apparent volume of distribution of 10.0 L and steady state apparent volume of distribution of 7.9 L. Since iron disappearance from serum depends on the need for iron in the iron stores and iron utilizing tissues of the body, serum clearance of iron is expected to be more rapid in \_\_\_\_\_ patients treated with Venofer<sup>®</sup> as compared to healthy individuals.

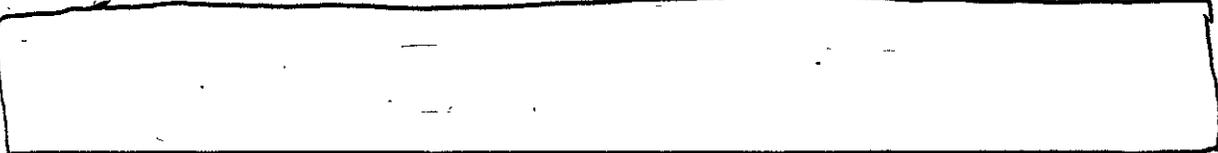
3. Distribution: In healthy adults receiving intravenous doses of Venofer<sup>®</sup>, its iron component appears to distribute mainly in blood and to some extent in extravascular fluid \_\_\_\_\_

\_\_\_\_\_ A study evaluating Venofer<sup>®</sup> containing 100 mg of iron labeled with <sup>52</sup>Fe/<sup>59</sup>Fe in patients with \_\_\_\_\_ iron deficiency shows that a significant amount of the administered iron distributes in the liver, spleen and bone marrow and that the bone marrow is an iron trapping compartment and not a reversible volume of distribution.

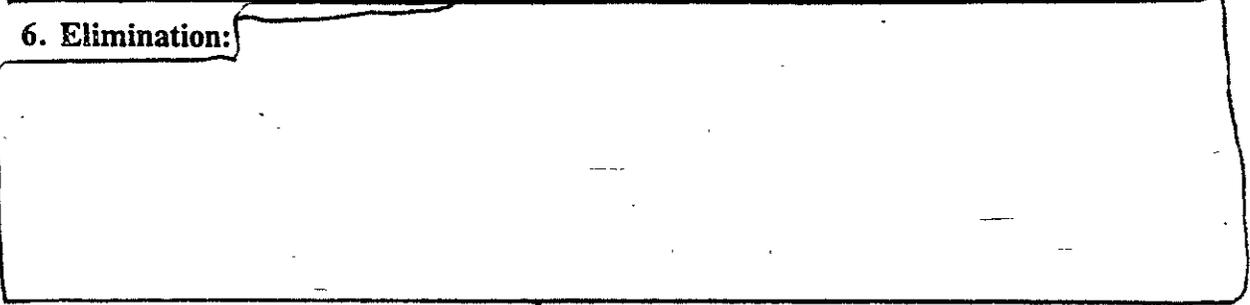


#### 5. Metabolism:

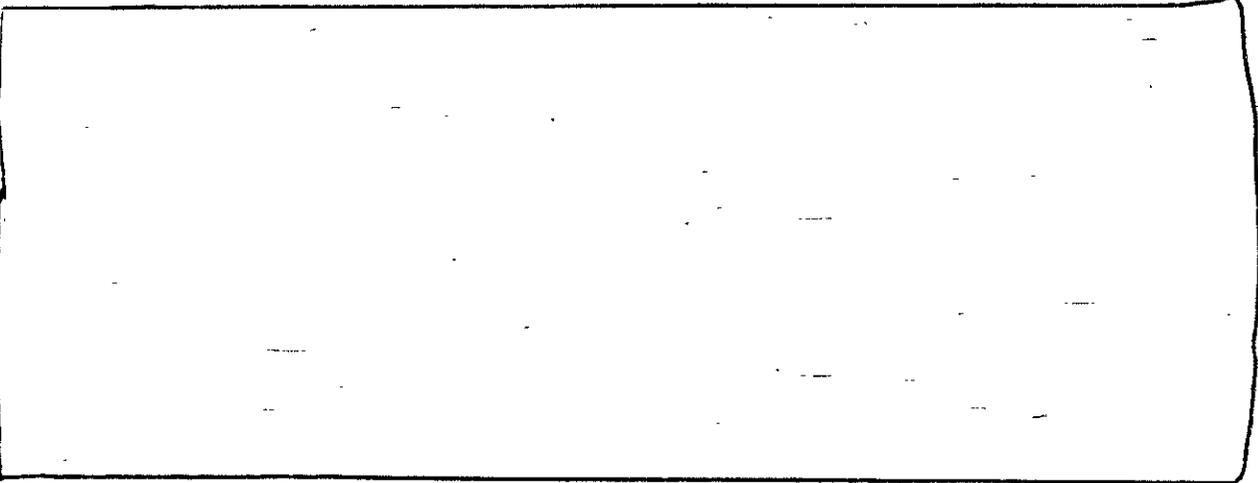




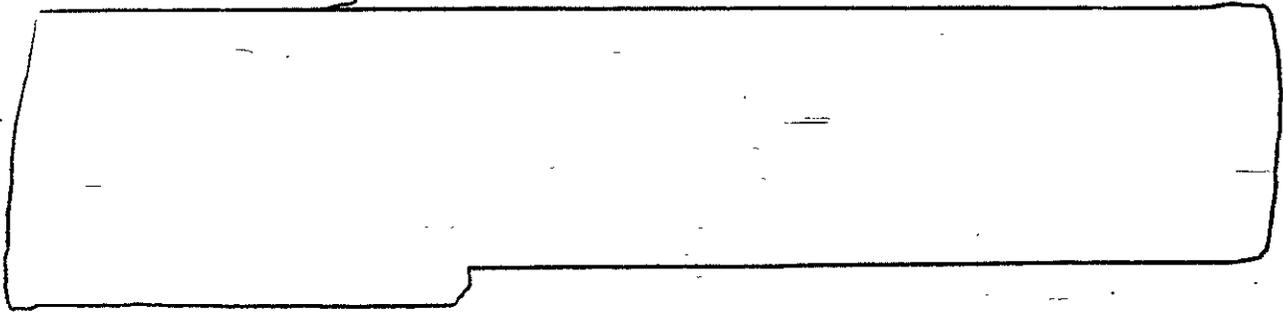
**6. Elimination:**



**7. Drug-drug Interactions:** Drug-drug interactions involving Venofer<sup>®</sup> have not been studied. However, like other parenteral iron preparations, Venofer<sup>®</sup> would reduce the absorption of concomitantly administered oral iron preparations.



**11.** The following relate to the **Dosage and Administration** section of the labeling:

- (a) The term, \_\_\_\_\_ should be replaced with **Recommended Dosage**. Under the sub-section, \_\_\_\_\_ the first sentence should be modified as follows:
- 

#### IV. OVERALL COMMENTS

In the NDA (Volume 1.15 [pages 10-11]), regarding the estimation of red blood cell utilization of radioiron ( $^{59}\text{Fe}$ ), it is stated that "radioactivity per gram was measured in whole blood, plasma and packed red cells separately to define the rate of disappearance of radioactivity from the plasma, so that the whole blood activity represents the radioiron red cell incorporation". It is further stated that "red blood cell radioiron utilization was calculated as the ratio of  $^{59}\text{Fe}$  activity per mL of whole blood for the total blood volume on a given day to the injected  $^{59}\text{Fe}$  activity".

The calculated red cell radioiron utilization and the pre-dose and postdose hemoglobin in the evaluated anemic patients as well as the range of normal serum hemoglobin values (from clinical literature) are presented below.

Patient	Gender	Normal Hb Range (g/dL)	Pre-dose Hb (g/dL)	Postdose Hb (g/dL)	Red Blood Cell Iron Utilization (%)
6 <sup>a</sup>	Female	12.0-15.6			
1 <sup>a</sup>	Female	12.0-15.6			
2	Female	12.0-15.6			
5	female	12.0-15.6			
3 <sup>a</sup>	Male	14.0-17.8			
4 <sup>a</sup>	Male	14.0-17.8			

<sup>a</sup>On erythropoietin therapy; — g/dL on Day 9 only (Patient 3), — g/dL on Day 23 only (Patient 4), below baseline for the rest of the study in these patients.

(a) The Agency seeks to understand why the high utilization of iron by red blood cells in all patients is not reflected as significant postdose hemoglobin increases during the 13-28 days of study.

(b) It is requested that the mean + SD and individual subject values for the ratios of  $^{59}\text{Fe}$  activity in red blood cells and plasma to injected  $^{59}\text{Fe}$  activity, that were calculated in this study (Reference 5) and the related raw data, be submitted to the Agency for review.

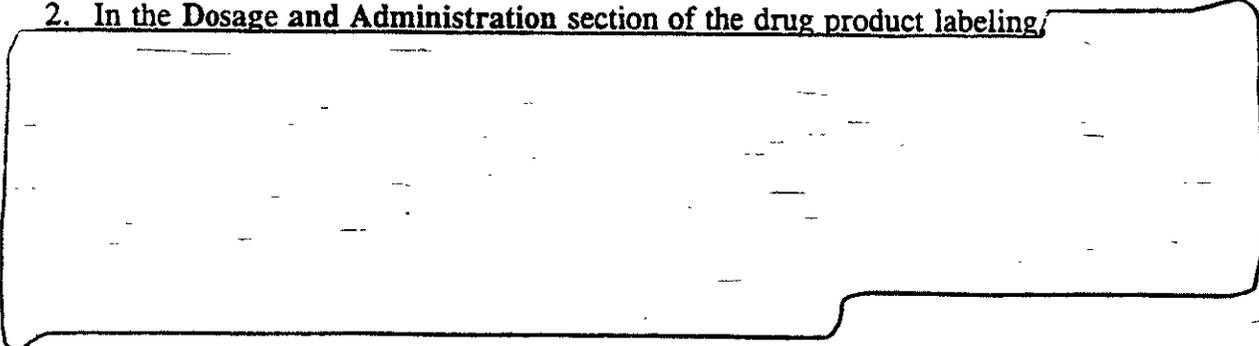
2. The *in vitro* release of iron from iron sucrose should be satisfactorily characterized and the findings should be submitted to the Agency for review.

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**V. GENERAL COMMENTS**

1. It is noted that the sucrose component of Venofer<sup>®</sup> is eliminated primarily in urine (68.3% in 4 h and 75.4% in 24 h). However, from a clinical pharmacology perspective, since sucrose is not expected to be pharmacologically active, a classical type drug toxicity is not expected if its elimination is prolonged. Therefore, in this review, it is considered that it is not necessary to request the sponsor to conduct an additional study to evaluate Venofer<sup>®</sup> in patients with renal impairment. If, in the Phase III clinical safety and efficacy studies, structural damage to the kidney was observed in subjects with renal impairment, safety related comments can be made as appropriate.

2. In the Dosage and Administration section of the drug product labeling,



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## VI. RECOMMENDATION

NDA 21-135 submitted for iron sucrose (Venofer<sup>®</sup>), by the sponsor, on August 6, 1999, has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The pharmacokinetic and pharmacodynamic information provided by the sponsor is acceptable for consideration in the process of making the NDA approval decision. However, the issues raised in Labeling Comments 1-11 (pages 20-21) and Overall Comments 1 and 2 (page 22) need to be satisfactorily addressed by the sponsor prior to NDA approval.

Please convey this Recommendation, Labeling Comments 1-11 (pages 20-21) and Overall Comments 1 and 2 (page 22), as appropriate, to the sponsor. General Comments 1 and 2 (page 23) should be brought to the attention of the reviewing medical officer.

*/s/*

06/16/00

David G. Udo, Ph.D.

Division of Pharmaceutical Evaluation II

*/s/*

6/16/00

Concurrence: Suresh Doddapaneni, Ph.D. \_\_\_\_\_

Clinpharm/Biopharm Briefing: 06/15.00 at 3.30 p.m. (Attendees: Huang [HFD-870], Hunt [HFD-870], Robie-Suh [HFD-180], Sandip [HFD-870], Al-Fayoumi [HFD-870] and Doddapaneni [HFD-870]).

cc: NDA 21-135, HFD-180, HFD-180 (Strongin), HFD-870 (M. Chen, Huang, Hunt, Doddapaneni and Udo), CDR (Attn: Zorn Zadeng).

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## APPENDIX I

Table 6

Demographic characteristics of the healthy volunteers

Initials	No	Age	Sex	Weight	Height
—	1	40	F	55	164
—	2	35	F	63	164
—	3	32	F	68	174
—	4	33	M	83	178
—	5	52	F	77	161
—	6	47	F	65	163
—	7	48	F	75	169
—	8	35	F	60	170
—	9	43	M	84	191
—	10	36	F	50	168
—	11	50	F	83	171
—	12	34	M	93	186
Mean ± SD		40.4 ± 7.3		71 ± 13	172 ± 9

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### 3.2. Non-compartmental pharmacokinetic analysis

The measured iron concentrations (Table 1) were corrected by subtraction of the individual baseline value. The baseline data was evaluated by considering the individual predose concentrations determined from two predose samples per subject as well as the respective iron concentrations after 24 hours where also two samples were available per subject.

It was observed that the predose values ( $35.7 \pm 12.5 \mu\text{M/l}$ ) and the values measured after 24 hours ( $40.0 \pm 8.7 \mu\text{M/l}$ ) were not statistically significantly different (paired t-test,  $p > 0.05$ ).

Hence, for each subject, the respective baseline value was calculated as the average of all predose and 24-hour samples. The baseline values varied from 27.3 to  $50.3 \mu\text{M/l}$  with a mean of  $37.9 \pm 8.0 \mu\text{M/l}$ .

For the non-compartmental analysis, these baseline values were subtracted for each subject. The resulting corrected iron concentrations (Table 2) were used for the calculations. The elimination rate constant ( $k_e$ ) was determined by linear regression as the negative slope of the natural logarithm of the concentrations in the terminal phase (3 - 12 h). The half-life ( $t_{1/2}$ ) was calculated as  $\ln(2)/k_e$ . The initial concentration  $C_0$  at time 0 was backextrapolated using the natural logarithms of the concentrations at 10 and 20 minutes. The area under the curve (AUC) was determined from the concentrations using the trapezoidal rule. The terminal part of the area was extrapolated as  $C_x/k_e$  where  $C_x$  is the last measured concentration. The area under the first moment curve (AUMC) was calculated using the trapezoidal rule as the AUC of a plot of the products of concentrations and respective time (Ct) versus time. The terminal part of the AUMC was extrapolated as  $C_x t_x/k_e^2 + C_x/k_e$  where  $C_x$  is the last measured concentration at time  $t_x$ . The mean residence time (MRT) was determined as  $\text{AUMC}/\text{AUC}$ .

The total body clearance (CL) was determined as  $D/\text{AUC}$  where the dose (100 mg) was converted into  $\mu\text{Mol}$  ( $1790.5 \mu\text{Mol}$ ; MW 55.85). The volume of distribution of the central compartment ( $V_d$ ) was determined as  $D/C_0$ .

The volume of distribution at steady state ( $V_{d_{ss}}$ ) was calculated as  $\text{CL} \cdot \text{MRT}$ . The volume of distribution during elimination ( $V_{d_{area}}$ ) was calculated as  $\text{CL}/k_e$ . The results are summarized in table 3.

### 3.3. Compartmental pharmacokinetic analysis

The serum concentration time profile without any baseline correction was fitted to an open two-compartment body system with an underlying predose baseline level:

$$C = ae^{-\alpha t} + be^{-\beta t} + C_B$$

where C is the iron serum level, a, b,  $\alpha$  and  $\beta$  hybrid constants and  $C_B$  the iron predose baseline level. The data was fitted up to 24 hours using the nonlinear regression program SCIENTIST with a weight factor of 1. Each subject was fitted individually, using the average of the two predose iron levels as the baseline value. The following parameters were calculated from the resulting hybrid constants: The half-life ( $t_{1/2}$ ) was calculated as  $\ln(2)/\beta$ . The initial concentration  $C_0$  at time 0 was

calculated as  $a+b$ . The area under the curve (AUC) was determined by integration as  $a/\alpha + b/\beta$ . The area under the first moment curve (AUMC) was determined by integration as  $a/\alpha^2 + b/\beta^2$ . The mean residence time (MRT) was determined as  $AUMC/AUC$ . The total body clearance (CL) was determined as  $D/AUC$  where the dose (100 mg) was converted into  $\mu\text{Mol}$  (1790.5  $\mu\text{Mol}$ ; MW 55.85).

The volume of distribution of the central compartment ( $V_c$ ) was determined as  $D/C_0$ . The volume of distribution at steady state ( $V_{d_{ss}}$ ) was calculated as  $D \cdot (a\beta^2 + b\alpha^2)/(a\beta + b\alpha)^2$ . The volume of distribution during elimination ( $V_{d_{area}}$ ) was calculated as  $CL/\beta$ . The results are summarized in table 4.

#### 3.4. Compartmental pharmacokinetic analysis using a Michaelis - Menten model.

Due to the results of *in vitro* measurements of total iron binding capacity (TIBC) after addition of iron(III)-hydroxide sucrose complex a compartmental pharmacokinetic analysis including Michaelis - Menten model (MM) was performed. This is based on the fact that practically all the transferrin present is saturated with iron from iron(III)-hydroxide sucrose complex.

The serum concentration time profile without any baseline corrections was fitted to an open two compartment body system with an underlying baseline level as well with an underlying Michaelis - Menten term:

$$C = ae^{-\alpha t} + be^{-\beta t} + C_b - k_0 t$$

where  $C$  is the serum iron level,  $a$ ,  $b$ ,  $c$  and  $\beta$  the hybrid constants,  $C_b$  the iron predose level and  $k_0 t$  the Michaelis - Menten term. Because the transferrin is readily saturated with iron and the serum levels are not statistically significant different between before injection (0 h) and at 24 hours after injection, for the MM-term  $V_{max} = k_0 t$  can be used.  $V_{max}$  reflects the transferrin measured during the 24 hours observation time as well the TIBC measured before injection. That means that  $k_0 t$  runs between the transferrin and serum iron level, what is equal with the latent iron binding capacity.

For calculations for each subject individually and for the mean of all 12 patients  $c$  and  $a$  resp.  $\beta$  and  $b$  values were determined by optimal linear regression as the negative slope of the natural logarithm of the concentration phase 0,16 - 1 h and 3 - 12 h resp: after correction with the baseline  $C_b$ , the TIBC and the Michaelis - Menten term  $k_0 t$ . The area under the curve (AUC) was determined by integration as  $a/\alpha + b/\beta + k_0 t^2/2$ .  $k_0$  was optimised by minimising the sum of the squares of the differences between model and measurements and by minimising the difference of AUC and AUMC between the algebraic and trapezoidal integration.  $C_0$  was calculated from the intercept of the  $\alpha$ -function by addition of  $C_b$ .

The area under the first moment curve (AUMC) was determined by integration as  $a/\alpha^2 + b/\beta^2 + k_0 t^3/6$ . The mean residence time (MRT) was determined as  $AUMC/AUC$ . The total body clearance (CL) was determined as  $D/AUC$  where the dose (100 mg) corresponds to 1790.5  $\mu\text{Mol}$  Fe. The volume of distribution of the central compartment ( $V_c$ ) was determined as  $D/(C_0 - C_b)$ . The volume of distribution at steady state ( $V_{d_{ss}}$ ) was calculated as  $CL \cdot MRT$ . The volume of distribution during elimination ( $V_{d_{area}}$ ) was calculated as  $CL/k_0$ , whereby  $k_0$  is not included. The amount of iron transported by saturated transferrin was calculated as a fraction of  $AUC/k_0 t^2/2$  multiplied by the dose (100 mg). The results are summarised in table 5.

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Table 3 Non-compartmental pharmacokinetic parameters for each of the 12 subjects

Non-compartmental analysis	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD
CL (L/h)														
CL <sub>R</sub> (L/h)														
CL <sub>CR</sub> (L/h)														
AUC <sub>0-∞</sub> (ng·h/mL)														
AUC <sub>0-t</sub> (ng·h/mL)														
AUMC <sub>0-∞</sub> (ng·h <sup>2</sup> /mL)														
AUMC <sub>0-t</sub> (ng·h <sup>2</sup> /mL)														
ME (h)														
CE (%)														
CV (%)														
CV (%)														
CV (%)														

Table 4

Compartmental pharmacokinetic parameters for each of the 12 subjects

Compartmental data analyzed	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD
CL														
CL <sub>R</sub>														
CL <sub>CR</sub>														
CL <sub>INT</sub>														
CL <sub>INT</sub> /V <sub>D</sub>														
CL <sub>INT</sub> /V <sub>D</sub> + k <sub>12</sub>														
CL <sub>INT</sub> /V <sub>D</sub> + k <sub>21</sub>														
CL <sub>INT</sub> /V <sub>D</sub> + k <sub>12</sub> + k <sub>21</sub>														
CL <sub>INT</sub> /V <sub>D</sub> + k <sub>12</sub> + k <sub>21</sub> + k <sub>10</sub>														
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**Table 1a. Baseline characteristics of the patients**

No.	Age (y)	Gender	Diagnosis	Hb (g/l)	S-creatinine ( $\mu\text{mol/l}$ )	S-Fe ( $\mu\text{mol/l}$ )	S-ferritin ( $\mu\text{g/l}$ )	TIBC ( $\mu\text{mol/l}$ )	TS (%)	S-TfR (ng/l)	rHuEpo therapy	
											dose (U/kg/w)	duration (m)
1	63	f	polycystic kidney + RA	112	653	9	81	42	22	3.01	51	4
2	38	f	medullary sponge kidney + IDA	109	72	12	3	101	12	3.52	-	-
3	52	m	diabetic nephro- pathy + FID	121	261	11	95	58	18	2.45	31	44
4	24	m	status post renal transplantation + RA	77	253	30	501	46	65	1.72	90	12
5	55	f	ulcerous colitis, renal stones + IDA	100	86	3	8	85	4	6.19	-	-
6	38	f	congenital cystic disease + FID	116	157	7	37	51	14	1.96	150	2

S-Fe = serum iron; TIBC = total iron binding capacity; TS = transferrin saturation; S-TfR = serum transferrin receptor; rHuEpo = recombinant human erythropoietin; U/kg/w = unit/kg/week; IDA = iron deficiency anaemia; RA = renal anaemia; FID = functional iron deficiency.



Table 20

Iron content (mg) in urine

	0-24h	24-48h	48-72h	72-96h	96-120h	120-144h	144-168h	168-192h
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean		0.51	4.64	0.27	0.16	0.20	6.19	4.00
SD		0.33	1.16	0.11	0.12	0.13	1.28	1.31

Δ = difference between Fe excretion in urine during 24 hours post and 24 hours pre injection of 100 mg Fe as iron sucrose complex

A Multiple Graphical Plotting method, used to investigate PET kinetic data, was then applied to determine the net influx from the plasma to the tissues as well as the sizes of the reversible pools (Patlak et al., 1983; Patlak et al., 1985). According to this method, known as "the Patlak method", the different compartments for the tracer distribution consist of the reversible region which freely communicate with the blood and the irreversible compartment where the tracer can enter but cannot leave the region. The different rate constants  $k_1$ ,  $k_2$  and  $k_3$  are the rate constants from the blood to the reversible pool, from the reversible pool to the blood and from the reversible pool to the trapping compartment, respectively. After an initial distribution phase, which is variable for the different tracers in the different tissues, increasing accumulation of the ligand into the trapping compartment can be seen. After a certain time, dividing the integrals of the tissue concentration by the blood concentration gives a linear part. This linear part represents a state of dynamic equilibrium between the blood and the trapping compartment.

The way to analyze the kinetic information from the PET tomograph (tissue concentration C) and the blood curve measurements ( $C_b$ ) can be set as follows:

$$\frac{C}{C_b} = \frac{k_1}{k_2 + k_3} + \frac{k_2}{k_2 + k_3} + \frac{k_1 \cdot k_3}{k_2 + k_3} \cdot T$$

where  $k_1$ ,  $k_2$  and  $k_3$  are the rate constants between the different compartments, and T is a dimension time (Patlak time, min); which represents the transformation of the physical time into a physiological time.

According to this model, the intercept of the linear part of the Patlak plot represents the distribution volume, while the slope represents the influx constant i.e. a rate constant which describes the rate of the flow of the iron from the blood into the accumulation compartment.

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## REFERENCES

1. (Sponsor's Reference 3) Danielson BG, et al. Pharmacokinetics of Iron (III)-hydroxide Sucrose Complex (Venofer<sup>®</sup>) after Single Intravenous Dose in Healthy Volunteers. Internal Report. 7.7.1995. *Arzneim-Forsch./Drug Res.* 1996; 46(1); 6:615-621.
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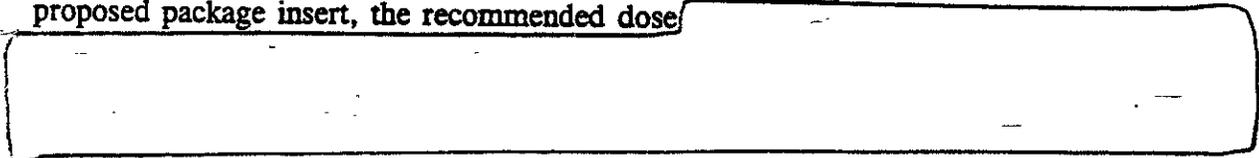
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MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF CLINICAL PHARMACOLOGY  
AND BIOPHARMACEUTICS  
DIVISION OF PHARMACEUTICAL EVALUATION II

Date: September 21, 1999  
To: Mei-Ling Chen, Ph.D., Director  
John Hunt, Deputy Director  
- David J. Lee, Ph.D., Team Leader  
From: David G. Udo, Ph.D., Reviewer  
Subject: Pre-45 Day Filing Meeting for NDA 21-135 for iron sucrose injection  
(Venofer®)

SYNOPSIS/BACKGROUND

NDA \_\_\_\_\_ was submitted for sucrose iron injection (Venofer®) by the sponsor, Luitpold Pharmaceuticals, Inc. on August 6, 1999. Venofer® is proposed for intravenous injection for the treatment of \_\_\_\_\_ (see the Indication section of the attached, proposed package insert for specific cases). In the Dosage and Administration section of the proposed package insert, the recommended dose:



The sponsor states (i) that Venofer® is formulated as an aqueous solution of ferric hydroxide-sucrose complex with an osmolality of 1250 mosm/L and a pH of 10.5-11.1, (ii) that pH adjustment is accomplished by addition of \_\_\_\_\_ (iii) that each vial of drug product contains 100 mg of iron in 5 mL of aqueous solution and (iv) that the drug formulation contains no preservative.

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