

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-135

ADMINISTRATIVE DOCUMENTS



Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

COMPLIANCE REVIEW

DATE: 6/14/2000

TO: Brian Strngin, Project Manager
Lilia Talarico, M.D.
Kathy Robie-Suh, M.D.
Suzane Gagnon, M.

THROUGH: David A. Lepay, M.D., Ph.D.
Director, HFD-45
Division of Scientific Investigations

FROM: Khairy W. Malek, M.D..
Good Clinical Practice 1, HFD-46
Division of Scientific Investigations

SUBJECT Evaluation of Clinical Inspections

NDA: 21-135

DRUG: Venofer Injections

SPONSOR: Luitpold Pharmaceuticals, Inc.

PROTOCOL: VENO/BGSA-VIFOR/001

THERAPEUTIC CLASSIFICATION: 2 S

USER-FEE GOAL DATE: August 6, 2000

RESULTS:

Name	City	Assigned	Inspected	Acted	Class
1. R van Zyl-Smit, M.D.	Cape Town South Africa	1/11/2000	3/13-17/2000	5/24/2000	NAI
2. M.R.Moosa, M.D.	Cape Town South Africa	1/11/2000	3/20-24/2000	6/9/2000	VAI

Site # 1

We reviewed the study-related records for all 63 subjects enrolled in this study. There were no violations observed at this site.

Site # 2

We reviewed the study records of all 41 subjects enrolled at this site. Minor violations were observed but they would not affect the reliability or integrity of the data.

CONCLUSION AND RECOMMENDATION:

Overall the minor violations observed at one site would not affect the integrity of the data.
The data appear acceptable in support of NDA # 21-135
No follow-up is needed.

Khairy W. Malek, M.D.

CONCURRENCE:

for

ISI

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research

Distribution:
HFA-224
HFD-45/Division File
HFD-45/Reading File
HFD-46/Program Management Staff (electronic Copy)
HFD-180 Talarico
HFD-180 Strongin
HFD-46 Malek
HFD-46 Huff
DSI File # 10075 & 10074

**APPEARS THIS WAY
ON ORIGINAL**

Strongin

JUN 9 2000

M.R. Moosa, M.D.
Tygerberg Hospital
Renal Unit
Cape Town, South Africa

Dear Dr. Moosa:

Between March 20 and 24, 2000, Ms. Nancy Bellamy and Dr. Khairy Malek representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #VENO/BGSA-VIFOR/001) of the investigational drug Venofer (iron sucrose injection), performed for Luitpold Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

At the close of the inspection, our personnel presented their inspectional observations listed on Form FDA 483 and discussed these observations with you and your staff. From our evaluation of: a) the inspection report, b) your oral responses to the inspectional observations, and c) Mr. Peter Reichertz' (sponsor representative) letter dated April 6, 2000, addressed to Dr. Attila Kadar, we conclude that you did not adhere to good clinical practice governing your conduct of clinical investigations and the protection of human subjects. In particular, we note that subject #13 was included in the study although the serum ferritin (520 ng/ml) was over the maximum of 200 ng/ml level allowed by the protocol. Also, all ECGs should have been done before the start of the study as required by the protocol.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Bellamy and Dr. Malek during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

for

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855

Page 2 - M.R. Moosa, M.D.

cc

HFA-224

HFD-180 Doc.Rm. NDA #21-135

HFD-180 Review Div.Dir. Talarico

HFD-180 MO. Lu

HFD-180 PM Strongin

HFD-45 Reading File

HFD-46 Chron File

HFD-46 CIB File 10074

HFD-46 CIB Reviewer Malek

HFD-46 Prager

HFR-CE750 Dempster

HFR-CE750 Bellamy

HFC-134 Kadar

FEI: 3002985460-

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI-no response required

3)VAI-response requested

APPEARS THIS WAY
ON ORIGINAL

Deficiencies noted:

inadequate informed consent

inadequate drug accountability

failure to adhere to protocol

inadequate records

failure to report ADRS _____

other

Note to Review Division and DSI Recommendation:

We reviewed the study records of all 41 subjects enrolled in the study. Minor violations observed would not affect the reliability or integrity of the data. The data appear acceptable for use in support of the NDA.

O:KM\Malek

Drafted/KM 5/11/00

Revised

Final:nlp/5/18/00

final: mgk 6/5/00

Strongin

Food and Drug Administration
Rockville MD 20857

MAY 24 2000

Prof. R. van Zyl-Smit, M.D.
Renal Unit
Groôte Schuur Hospital
Cape Town, South Africa

Dear Dr. van Zyl-Smit:

Between March 13 and March 17, 2000, Ms. Nancy Bellamy and Dr. Khairy Malek, representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of a clinical study (protocol #VENO/BGSA-VIFOR/001) of the investigational drug Venofer (iron sucrose injection). You conducted this study for Luitpold Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, we conclude that you conducted your study in compliance with good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Bellamy and Dr. Malek during the inspection. Should you have any questions or concerns regarding this letter or the inspections, please contact me by letter at the address given below.

Sincerely yours,

/s/

David A. Lepay, M.D., Ph.D.
Director
Division of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

cc:

HFA-224
HFD-180 Doc. Rm. NDA 20-807/S-004
HFD-180 Review Div. Dir. Talarico
HFD-180 MO Lu
HFD-180 PM Strongin
HFD-45 Reading File
HFD-46 Chron File
HFD-46 CIB File 10075
HFD-46 CIB Reviewer Malek
HFD-46 Huff
HFR-CE750 Dempster
HFR-CE750 Bellamy
HFC-134 Kadar

FEI: 3002985457

Field Classification: NAI

Headquarters Classification:

- 1) NAI
 2) VAI-no response required
 3) VAI-response requested
 4) OAI

APPEARS THIS WAY
ON ORIGINAL

Deficiencies noted:

- Inadequate consent form
 Inadequate drug accountability
 Deviations from protocol
 Inadequate records
 Failure to report ADRs
 Other (specify)

Note to Review Division and DSI Recommendation

We reviewed the study-related records for all 63 subjects in this study. DSI recommends that the data from this study may be used in support of the NDA.

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: 021135 Trade Name: /ENOFER (IRON SUCROSE) 100MG INJECTION
 Supplement Number: 000 Generic Name: IRON SUCROSE
 Supplement Type: N Dosage Form:
 Regulatory Action: OP COMIS Indication:
 Action Date: 8/6/99

Indication # 1 Treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy.

Label Adequacy: Other - See Comments

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): November 3, 2000: This drug product is not a new molecular entity, so the December 2, 1999 Pediatric Rule does not apply. However, information regarding safety in all pediatric age groups, a PK study in adolescents, and an adequate and well-controlled study in children were requested as Phase IV commitments.

Lower Range
Adult

Upper Range
Adult

Status
Completed

Date

This page was last edited on 11/3/00

Signature -

/S/

Date

11/3/00

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-135

Food and Drug Administration
Rockville MD 20857

Luitpold Pharmaceuticals, Inc.
c/o Arent Fox Kintner Plotkin & Kahn, PLLC
Attention: Peter S. Reichertz, Esq.
1050 Connecticut Avenue
Washington, D.C., 20036-6378

NOV 3 - 1999

Dear Mr. Reichertz:

Please refer to your new drug application dated August 6, 1999, received August 9, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Venofer® (iron sucrose injection).

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

1. examine the worldwide safety database for Venofer® for occurrence of adverse events in pediatric patients by age group (neonates, infants, children, adolescents). Attempt to obtain further information on the 5 reported cases of necrotizing enterocolitis in infants, including examination of the safety database for other similar cases. No study of Venofer® in neonates and infants is requested at this time. However, you should address possible need for and risks involved with Venofer® use in very young pediatric patients;
2. a single-dose, pharmacokinetics study of Venofer® following intravenous administration to adolescent hemodialysis patients on epoetin;
3. an adequate and well-controlled clinical trial of safety and efficacy of Venofer® in the treatment of iron deficiency in children (aged 2 to 12 years) who are on hemodialysis and receive epoetin. (Use of an active control, such as oral iron, or dose ranging comparison should be considered in designing this study.);
4. a study to provide additional safety data (e.g., incidence of allergic or anaphylactic reactions, cross-reactivity with other parenteral iron preparations);
5. develop an *in vitro* release test for Venofer® and propose specifications.

We recommend that draft protocols for the studies described above be submitted to the Agency for review and comment prior to initiation of the studies. Finalized study protocols, incorporating Agency comments and recommendations, should be submitted to IND. Please include a proposed schedule for the initiation and completion of these studies as well as the submission of final study reports or requested information. Provide the information requested in item #1 in your first annual report. Submit a prior approval supplement providing for the specification (e.g., test, acceptance criteria, and test data) requested in item #4 within one year of approval.

APPEARS THIS WAY
ON ORIGINAL

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

Sincerely yours,


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

APPEARS THIS WAY
ON ORIGINAL

NDA 21-135

Luitpold Pharmaceuticals, Incorporated
c/o Arent Fox Kintner Plotkin & Kahn, PLLC
Attention: Peter S. Reichertz, Esq.
1050 Connecticut Avenue
Washington, DC 20036-6378

SEP 9 1999

Dear Mr. Reichertz:

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

Name of Drug Product: Venofer® (iron sucrose) injection

Therapeutic Classification: Standard (S)

Date of Application: August 6, 1999

Date of Receipt: August 9, 1999

Our Reference Number: NDA 21-135

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 5, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 9, 2000 and the secondary user fee goal date will be August 9, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102© of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, contact me at (301) 827-7310.

Sincerely,

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

APPEARS THIS WAY
ON ORIGINAL

NDA 21-135

Food and Drug Administration
Rockville MD 20857

DISCIPLINE REVIEW LETTER

Luitpold Pharmaceuticals, Inc.
c/o Arent Fox Kintner Plotkin & Kahn, PLLC
Attention: Peter S. Reichertz, Esq.
1050 Connecticut Avenue
Washington, D.C. 20036-6378

JUL 19 2000

Dear Mr. Reichertz:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Venofer® (iron sucrose injection).

Our review of the clinical pharmacology and biopharmaceutics section of your submission is complete, and we have identified the following deficiencies.

- Concerning the study report entitled, "Pharmacokinetic Analysis and Red Cell Utilization of ⁵²Fe/⁵⁹Fe-Labeled Iron (III)-Hydroxide Sucrose Complex Following Intravenous Administration Using Positron Emission Tomography (PET) Study in Patients with Iron Deficiency and Renal Anaemia", Volume 1.15, pages 1-144 of the August 6, 1999 submission:

The calculated red cell radioiron utilization (as per the Data analysis section, pages 10-11 of the Study Report) and the pre-dose and post-dose hemoglobin in the evaluated anemic patients as well as the range of normal serum hemoglobin values (from clinical literature) are presented below.

Patient Number	Gender	Normal Hemoglobin Range (g/dL)	Pre-dose Hemoglobin (g/dL)	Post-dose Hemoglobin (g/dL)	Red Blood Cell Iron Utilization
6a	Female	12.0-15.6			
1a	Female	12.0-15.6			
2	Female	12.0-15.6			
5	Female	12.0-15.6			
3a	Male	14.0-17.8			
4a	Male	14.0-17.8			

a - On erythropoietin therapy

b - Patient 3, — g/dL on Day 9 only. Patient 4, ← g/dL on Day 23 only. Below baseline for the rest of the study in these patients.

- A. Clarify why the high utilization of iron by red blood cells in all patients is not reflected as significant post-dose hemoglobin increases during the 13-28 days of the study.
 - B. Submit the mean±standard deviation and the individual subject values for the ratios of ^{59}Fe activity in red blood cells and plasma to injected ^{59}Fe activity calculated in this study.
2. Characterize the *in vitro* release of iron from iron sucrose and submit the findings for Agency review:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,


Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Strongin

NDA 21-135

JUL 10 2000

Luitpold Pharmaceuticals, Inc.
c/o Arent Fox Kintner Plotkin & Kahn, PLLC
Attention: Peter Reichertz, Esq.
1050 Connecticut Avenue
Washington, D.C., 20036-6378

Dear Mr. Reichertz:

We acknowledge receipt on July 3, 2000 of your June 30, 2000 amendment to your new drug application for Venofer® (iron sucrose injection).

This amendment includes a study report entitled, "The Natural History of Iron Deficiency in Patients with Dialysis-Associated Anemia (Van Wyck): Analysis of the First 10 Weeks Without Iron and Comparison to LU98001". Under 21 CFR 314.60, this is a major amendment received by the Agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is November 6, 2000.

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

Sincerely yours,

/s/ 7-10-00

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

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-135

Food and Drug Administration
Rockville MD 20857

DISCIPLINE REVIEW LETTER

Luitpold Pharmaceuticals, Inc.
c/o Arent Fox Kintner Plotkin & Kahn, PLLC
Attention: Peter S. Reichertz, Esq.
1050 Connecticut Avenue
Washington, D.C., 20036-6378

JUN - 8 2000

Dear Mr. Reichertz:

Please refer to your August 6, 1999 new drug application for Venofer® (iron sucrose injection).

We also refer to your submission dated October 19, 1999.

Our review of the chemistry, manufacturing, and controls section of your submission is complete, and we have identified the following deficiencies:

Redacted

2

pages of trade

secret and/or

confidential

commercial

information

H. Environmental Assessment (EA)

Determine whether or not Venofer® would qualify for a categorical exclusion from the EA requirement as stated in 21 CFR §25.31(b) by clarifying whether or not the estimated concentration of it at the point of entry into the aquatic environment will be below 1 part per billion. The CDER Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements, which was released in November 1995, may be consulted for more information.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,


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

APPEARS THIS WAY
ON ORIGINAL



LUITPOLD

Patent Certification – No Relevant Patents

In the opinion, and the best knowledge of Luitpold Pharmaceuticals, Inc., there are no patents that claim the drug or drugs on which the investigations that are relied upon in this application (NDA 21-135) were conducted or that claim the use of such drug or drugs.

Mary Jane Helenek

MaryJane Helenek, R.Ph., M.S., M.B.A.
Senior Vice President
Luitpold Pharmaceuticals, Inc.

Dated: May 21, 1999

**APPEARS THIS WAY
ON ORIGINAL**

d) Did the applicant request exclusivity?

YES / / NO / /

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

Five Years

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

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES / X / NO / ___ /

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

NDA # 17-441; INFED (iron dextran, USP 50 mg elemental iron/ml)

NDA # 20-955; Ferrlecit® (sodium ferric gluconate complex in sucrose injection)

IF THE ANSWER TO QUESTION 1 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of

reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / ___ NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / ___ NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug

product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO 7 X /

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO / X /

If yes, explain: _____

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Study LU98001

Investigation #2, Study # Study LU98002

Investigation #3, Study # Study VIFOR/001

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO / X /

Investigation #2 YES /___/ NO / X /

Investigation #3 YES /___/ NO /_X_/

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1, Study # LU98001

Investigation # 2, Study # LU98002

Investigation # 3, Study # VIFOR/001

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /_X_/ NO /___/ Explain:

Investigation #2

IND # _____ YES / / NO / / Explain: _____

Investigation #3

IND # _____ YES / / NO / / Explain: Study VIFOR/001 was a non-IND study conducted/sponsored by Vifor International.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 N/A

YES / / Explain _____ NO / / Explain _____

Investigation #2 N/A

YES / / Explain _____ NO / / Explain _____

Investigation #3

YES / / Explain _____ NO / / Explain The sponsor obtained the right to reference all safety and efficacy data from the sponsor of Investigation #3. The sponsor did not provide substantial support for this study.

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all

rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

/S/

Signature of Preparer
Title: _____

11/3/00
Date

/S/

Signature of Office of Division Director

11-3-00
Date

CC:
Archival NDA
HFD-180/Division File
HFD-180/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

APPEARS THIS WAY
ON ORIGINAL



LUITPOLD

Debarment Certification

Luitpold Pharmaceuticals, Inc., hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 21-135).

Mary Jane Helenek
MaryJane Helenek, R.Ph., M.S., M.B.A.
Senior Vice President
Luitpold Pharmaceuticals, Inc.

Dated: May 21 1999

APPEARS THIS WAY
ON ORIGINAL

NDA 21-135

Venofer® Iron Sucrose Injection

Certification Made Pursuant To The Generic Drug Enforcement Act of 1992

Pursuant to Section 306(k) of the Generic Drug Enforcement Act of 1992, Luitpold Pharmaceuticals, Inc. hereby certifies that Luitpold has not used, is not using and will not use in any capacity, the services of any person debarred pursuant to subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Luitpold Pharmaceuticals, Inc. further certifies that during the past five years, Luitpold has not sustained a conviction described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992. To the best of Luitpold's knowledge, no person affiliated with Luitpold, responsible in whole or in part for the development or submission of this application, has been convicted of any offense as described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992.



Richard P. Lawrence
Manager, Product Development

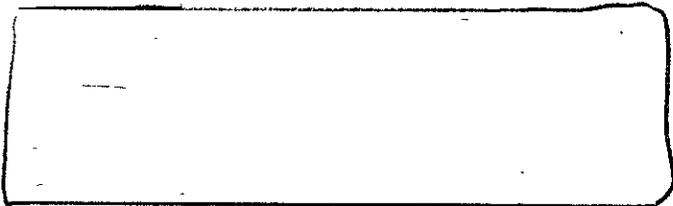
4/22/99
Date

APPEARS THIS WAY
ON ORIGINAL



Debarment Certification

_____, the contract research organization assisting Luitpold Pharmaceuticals, Inc. in the preparation and submission of NDA 21-135, hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA 21-135.



Senior Director
Regulatory Affairs

5/18/99
Date

APPEARS THIS WAY
ON ORIGINAL



CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	C. Charytan, M.D.	J. Roman-LaTorre, M.D.
	I.M. Cohen, D.O., F.A.C.P.	S. Zeig, M.D.
	N. Levin, M.D.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Mary Jane Helenek, R.Ph., M.S. M.B.A.	TITLE Senior Vice President
FIRM/ORGANIZATION Luitpold Pharmaceuticals, Inc.	
SIGNATURE <i>Mary Jane Helenek</i>	DATE July 29, 1999

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research



PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 29, 1999
NDA# 21-135
NAME OF DRUG: Venofer (Iron Sucrose Injection) 20 mg/mL
NDA HOLDER: Luitpold Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) to review the proposed proprietary drug name, Venofer, regarding potential name confusion with existing proprietary/generic drug names.

PRODUCT INFORMATION

Venofer is a brown, aqueous solution for intravenous use containing an alkaline iron (III)-hydroxide complex as the active ingredient. Administration of iron sucrose reconstitutes tissue iron stores, reverses iron depletion and iron deficient erythropoiesis, and corrects or prevents iron deficiency anemia. Serum ferritin levels increase significantly after 8-10 hours and double after 24 hours. The terminal half-life is 5.3 hours and total serum clearance is 20.5 mL/min. Venofer is renally excreted and serum iron returns to predose iron levels in 24 hours. Venofer is indicated in the treatment of: dialysis-associated anemia,



The usual adult dosage is 100 mg _____ iron administered one to three times per week to a total dose of 1000 mg in _____ 10 doses, repeat if needed. Frequency of dosing should be no more than three times weekly.



Venofer will be supplied in 5 mL single dose vials containing 100 mg of elemental iron (20 mg/mL). Administration of a test does is not necessary. Venofer must only be administered intravenously by slow injection directly into the dialysis line or by infusion. To reduce the risk of hypotensive episodes Venofer may also be administered by drip infusion. The contents of each vial must be diluted exclusively in a maximum of 100 mL of 0.9% NaCl, immediately prior to infusion.

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II. RISK ASSESSMENT:

In order to predict the potential for medication errors and to determine the degree of Confusion associated with the proposed name, Venofer, with other approved and unapproved drug names, the medication error staff of OPDRA searched MICROMEDEX Healthcare Intranet Series, 1999, which includes the following published texts: DrugDex, Poisindex, Martindale, Emergindex, Reprodisk, Index Nominum, and Physicians' Desk Reference (1999). Additional publications utilized to search for potential sound-alike or look-alike names to approved drugs were the American Drug Index (43rd Edition); Drug Facts and Comparisons (Updated Monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. OPDRA also searched several FDA databases for potential sound-alike or look-alike names to unapproved/approved drugs (Establishment Evaluation System (EES), Drug Product Reference File (DPR), Decision Support System (DSS) and the LNC database. In addition, OPDRA conducted an internal study of written and verbal analysis of the proposed proprietary name, involving health care practitioners within OPDRA, to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

A) STUDIES CONDUCTED WITHIN OPDRA

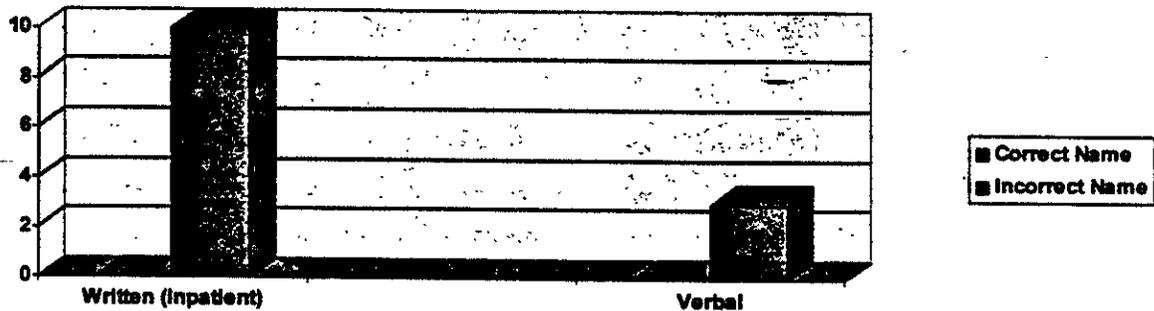
Methodology:

This study involved 20 health professionals comprised of pharmacists, physicians, and nurses within OPDRA to determine the degree of confusion of these names with other drug names due to the similarity in handwriting and verbal pronunciation of the name. OPDRA staff members wrote two inpatient orders, each consisting of known drug products and a prescription for Venofer. These prescriptions were scanned into the computer and a random sample of the written orders, were then delivered to the participating health professionals via e-mail. In addition, two pharmacists recorded the inpatient orders on voice mail. The voice mail messages were then sent to the participating health professionals for their review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

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Results:

We received responses from thirteen out of twenty participants, none of which interpreted the name correctly. Ten participants interpreted inpatient prescription orders and three interpreted verbal orders. The results are as follows:



None of the participants interpreted the name correctly. The following represents the incorrect responses:

Written

Venafer
Venafen
Venafir

Verbal

Zenifer
Zenofer
Venifer

B) FOCUS GROUP FINDINGS

The group did not uncover any existing drug names that could cause confusion with Venafer and thus pose a significant safety risk.

C) DISCUSSION:

The results of the verbal and written analysis studies demonstrate thirteen out of twenty participants interpreted the proprietary name Venofer incorrectly. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health professionals are not familiar with the name. The inaccurate interpretations of the proposed name did not overlap with any existing approved drug products. The proprietary name does not contain any USAN stems. In addition, the searches conducted within OPDRA did not reveal any existing drug names that would render the name objectionable.

III. CHEMISTRY AND SAFETY RELATED LABELING/PACKAGING ISSUES

In the review of the packaging and the labeling of Venofer, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current labels and labeling available and offer the following comments for improvement, which might minimize potential user error:

The expression of strength appears very small and is difficult to read. We recommend the firm be requested to increase the prominence of this statement on both the container label and carton labeling.

OCT 23 2000

Division of Gastrointestinal & Coagulation Drug Products

PROJECT MANAGER'S REVIEW

Application Number: NDA 21-135

Name of Drug: Venofer® (iron sucrose injection)

Sponsor: Luitpold Pharmaceuticals, Inc.

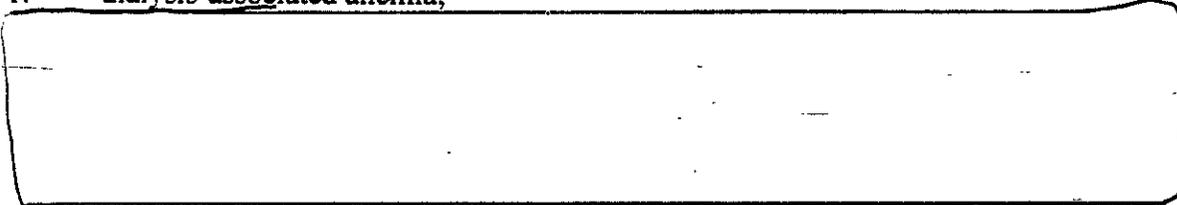
Material Reviewed

Submission Date: August 6, 1999 (draft immediate container and carton labels)

Receipt Date: August 6, 1999

Background and Summary Description: NDA 21-135 for Venofer® (iron sucrose injection) was submitted August 6, 1999 for the following indications:

1. dialysis-associated anemia;



Draft labeling (package insert, immediate container, and carton) was included in Volume 1.2 of the August 6, 1999 submission of the NDA. Marked-up draft labeling is being prepared for the package insert and it will be conveyed to the firm when appropriate. Luitpold Pharmaceuticals, Inc. proposes to market Venofer® in cartons of 10 x 5mL vials. This review concerns the vial and carton labels.

Review

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

Per Review Chemist, Ray Frankewich, Ph.D., dispensing Venofer® in a special container (glass, light resistant, etc.) is unnecessary so no additional statement is necessary.

2. Per 21 CFR 201.17 the expiration date shall appear on the immediate container and carton label unless it is easily legible through the carton label.

Luitpold Pharmaceuticals should be directed to provide a space for the expiration date.

3. Per 21 CFR 201.18 the lot number should appear on the immediate container and carton label.

Luitpold Pharmaceuticals should be directed to provide a space for the lot number.

Conclusions

Luitpold Pharmaceuticals should be requested to add a space for the lot number and expiration date to the vial and carton labels.

/S/

Project Manager */10-20-00*

cc:

NDA 21-135

HFD-180/Div.File

HFD-180/B.Strongin

HFD-180/L.Talarico

Drafted by: BKS/October 20, 2000

Final: BKS/October 20, 2000

PM REVIEW

**APPEARS THIS WAY
ON ORIGINAL**