

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-135

CHEMISTRY REVIEW(S)

Strogan

OCT 27 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-135 CHEM REVIEW #: 2 REVIEW DATE: October 27, 2000

SUBMISSION TYPE	DOCUMENT	CDER	DATES		NUM	LETTER	ST
			ASSIGNED	REVIEW			
ORIGINAL	8/6/99	8/9/99	8/12/99	5/15/00			
AMENDMENT	10/19/99	10/19/99	10/26/99	5/15/00			
AMENDMENT	6/16/00	6/19/00	6/23/00	10/27/00			

NAME & ADDRESS OF APPLICANT: Luitpold Pharmaceuticals, Inc.
One Luitpold Drive
Shirley, NY 11967

DRUG PRODUCT NAME:

Proprietary: Venofer®
Nonproprietary/USAN: Iron Sucrose Injection
Code Name/#: Antianemia, Iron Preparation/20:04.04
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY: Hematinic

INDICATION: Iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental Epoetin alfa therapy.

DOSAGE FORM: Injection

STRENGTH: 100 mg

ROUTE OF ADMINISTRATION: Intravenous

HOW DISPENSED: Rx OTC

SPECIAL PRODUCT: Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Name (BAN, proposed): Iron(III)-hydroxide sucrose complex
Name (USAN): Iron Sucrose

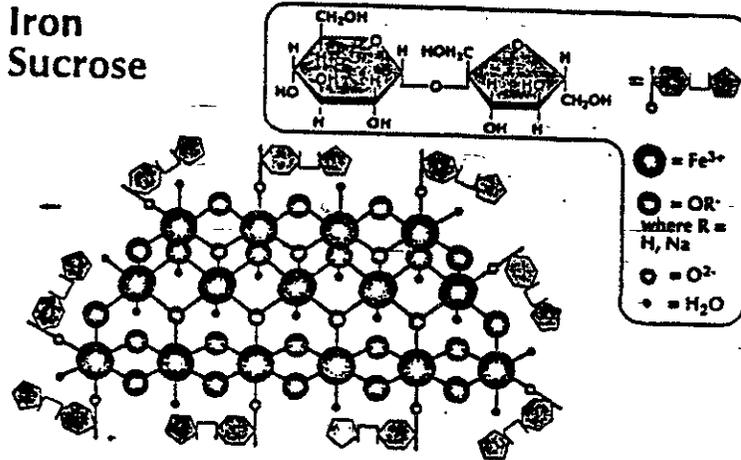
Structural Formula: Exact structure unknown. Estimated:
 $[Na_p Fe_5 O_8 (OH)_r \cdot x (H_2O)]_L \cdot m (C_{12} H_{22} O_{11})$

where: p = 2.30 ≈ 2
 r = 1.3 ≈ 1
 x = 2.70 ≈ 3

m = the number of sucrose molecules associated with the Iron (III) hydroxide.

Molecular Formula:

(proposed structure is provided on pg. 7 of volume 5 (of 80) of the submission)



Molecular weight: $M_w = 34,000 - 54,000$ daltons (D)
 $M_n = 24,000 - 36,000$ D
 $M_w/M_n = \text{NMT } 1.7$
 M_w is estimated to be 43,200 D.

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
_____	Venofex [®] Concentrate	Vifor International	Adequate		
_____	_____	_____	Adequate		
_____	_____	_____	Adequate		
_____	_____	_____	Adequate		

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

APPEARS THIS WAY
ON ORIGINAL

The microbiology/sterilization section of this NDA was consulted to HFD-805 (Microbiology Staff) for review. Review was performed by Paul Stinavage, Ph.D. (finalized on February 3, 2000). Conclusion of that review was approvable upon resolution of noted concerns. Nine (9) deficiencies were noted. Those deficiencies were addressed in this amendment. This amendment was reviewed (review finalized on August 29, 2000). In that review, approval was recommended for this application.

This drug was consulted to OPDRA for the review of the proposed proprietary name (OPDRA Consult #99-052). Review was completed December 2, 1999. Conclusion was that OPDRA had no objections to the use of the proprietary name Venofer.

EER was submitted on October 28, 1999. The following facilities listed in subsection B4 (Manufacturers) had received Acceptable recommendations:

- ~~_____~~
- ~~_____~~
- Luitpold Pharmaceuticals (Shirley, NY)
- Vifor International (St. Gallen, Switzerland)

REMARKS/COMMENTS:

In a teleconference on October 26, 2000, representatives of Luitpold Pharmaceuticals agreed to provide any revisions to the analytical methods for this drug product that became effective between the time of this amendment and the PDUFA deadline for this application. Information regarding stability was also provided (see pages 15 and 17).

Recommendations for the labeling of this drug were provided in a division labeling meeting October 27, 2000. See section I, Labeling.

Establishment of in-vitro release test(s) and specification(s) by Biopharmaceutics division is pending.

CONCLUSIONS & RECOMMENDATIONS:

This application may be approved, from a CMC point of view.

/S/

10/27/2000

Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

/S/

10/27/

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:

NDA #

HFD-180/LTalarico

HFD-180/Div File/NDA #21-135

HFD-180/LZhou

HFD-180/RFrankewich

HFD-181/BStrongin

HFD-820/JGibbs

HFD-820/SKoepke

R/D Init by: Lzhou/10-27-00

RF/rpf Draft 10-26-00/ F/T 10-27-00

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

To: NDA-21-135 (Venofer[®])

From: Metal Complexes Working Group, David Place, Ph.D., Chairperson

Through: Frank Holcombe, Ph.D., Co-chairperson, CMCCC
Yuan-Yuan Chiu, Ph.D., Co-chairperson, CMCCC

Subject: Chemical classification code of Venofer, NDA 21-135

Date: October 18, 2000

10/19/00
10/19/00
/S/
/S/

The Metal Complexes Working Group has determined that Venofer[®], NDA 21-135, should be classified as Type 3 because it is a different formulation of the same active moiety of a drug that has been approved previously. The active moiety is the ferric (iron (III)) ion, Fe³⁺. The drug is INFeD[®] (Iron Dextran, USP; NDA 17-441). A similar drug, Ferrlecit[®] (NDA 20-955), has also been approved. That the active moiety for these drugs is iron(III) was established in a memo from this group to this NDA dated September 20, 2000.

All three of these drugs are preparations of iron(III) for parenteral administration. All three consist of a macromolecular ferric oxide-hydroxide complex or a slightly modified version thereof, stabilized by a sugar moiety (dextran in the case of INFeD, sucrose in the case of Ferrlecit and Venofer).

Literature references^{1,2} show that in INFeD the ferric oxide-hydroxide complex is bonded at its surface in a stable manner to dextran polymers, and exists as a discrete particle. This bonding does not appear to be covalent or coordinate^{2,3,4}. The ratio of iron to dextran in the iron dextran complex has been established¹. In 21 CFR 314.108(a), three separate terms that could apply to coordination complexes are used, all of which are described as "noncovalent derivatives" of an active moiety: "complex", "chelate", or "salt, including salt with hydrogen or coordination bonds". Therefore, iron dextran may be considered a complex of the active moiety, iron (III).

In the case of Ferrlecit, the ferric oxide-hydroxide complex appears to be modified by the presence of gluconate, the carboxylate function of which is believed to act as a bridging ligand for adjacent iron atoms. The complex exists in solution, with a specific molecular weight range. The complex does not appear to be bonded in a covalent or coordinate manner to the stabilizing sugar (sucrose)⁵. This complex may be thought of as a different complex of the same active moiety, iron(III), as that in INFeD. Since that active moiety had previously been approved, Ferrlecit has been considered to be Type 2.

In the case of Venofer, the ferric oxide-hydroxide complex is not modified. The complex exists in solution, with a specific molecular weight range.

Since the ferric oxide-hydroxide portions of Venofer and INFeD are similar and their differences are primarily between the stabilizing sugars, Venofer should be thought of as a different formulation than INFeD, albeit one of the same active moiety (iron (III)). With respect to INFeD, Venofer should be considered Type 3.

It should be noted that the role of the gluconate groups in the structure of Ferrlecit was believed to have been established when the drug was approved, but is less certain at this time. It is anticipated that information that is to be requested from the firm will clarify 1) the extent of gluconate bonding in the ferric oxide-hydroxide complex and 2) the manner in which such bonding occurs. If it is shown that the gluconate groups do not significantly modify the ferric oxide-hydroxide core, it may be necessary to re-consider the status of the ferric oxide-hydroxide portion of Ferrlecit as a different complex with respect to that of INFeD, and consider a Type 3 classification for Ferrlecit. The determination of a Type 2 classification is based on the proposed structures and on information held currently.

This Working Group has recommended changes to the language presently in SMG 4820.3, in order to clarify the assignment of chemical classification codes for coordination complexes. Among them are guidelines illustrating when a coordination complex may be considered an active moiety. The proposed language states that, in order to be considered an active moiety, the coordination complex 1) must be sufficiently stable *in vivo* to be responsible for its physiological or pharmacological action; 2) must be of clearly defined stoichiometry 3) must contain coordinate covalent bonds. It is the intent of this Working Group to propose further changes that will more correctly describe a coordination complex where the metal ion and not the complex is the active moiety.

References

1. Ricketts, C. R.; Cox, J. S. G.; Fitzmaurice, C.; Moss, G. F. *Nature*, 208(5007), 237-239 (1965).
2. Cox, J. S. G.; Kennedy, G. R.; King, J.; Marshall, P. R.; Rutherford, D. J. *Pharm. Pharmac.*, 24, 513-517 (1972).
3. Jacobs, P. CACE Special Seminar, 9/21/00.
4. Bremner, I.; Cox, J. S. G.; Moss, G. F. *Carbohydrate Research*, 11, 77-84 (1969).
5. NDA 20-955 and CMC Review (5/18/98). The label claim of sucrose is assayed by diluting the drug product in water and chromatographing it, using an _____ column and water as mobile phase (reverse-phase conditions).
6. DMF _____ (in particular, vol. 4.1, pg. 27).

See also CMC Review (5/5/00).

Reviewed by:

CMCCC

HFD-103/F. Houn

HFD-103/V. Raczkowski

HFD-40/R. Temple

HFD-102/J. Jenkins

GCF-1/D. Goldsmith

GCF-1/K. Dettelbach

GCF-1/E. Dickinson

HFD-007/W. Mitchell

cc:

HFD-800/Y. Chiu

HFD-600/G. Buehler

HFD-180/Division File

HFD-180/L. Talarico

HFD-180/S. Aurecchia

HFD-180/L. Zhou

HFD-180/B. Strongin

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

To: NDA 21-135 (Venofer®)

From: David Place, Ph.D., Chairperson */S/ 9/22/00*
Metal Complexes Working Group

Through: Frank Holcombe, Ph.D., Co-chairperson, CMCCC */S/ 9/21/00*
Yuan-Yuan Chiu, Ph.D., Co-chairperson, CMCCC */S/ 9/22/00*

Subject: Evaluation of the chemical classification code of Venofer®, NDA 21-135

Date: September 20, 2000

The Metal Complexes Working Group has determined that Venofer®, NDA 21-135, should not be classified as Type 1 because the active moiety of this drug is the ferric (iron(III)) ion, Fe^{3+} , which is not a new molecular entity. Two NDA applications approved previously, NDA 17-441 (INFeD®), and NDA 20-955 (Ferrlecit®) contain the same active moiety.

All three of these drugs are preparations of iron(III) for parenteral administration. All three consist of a ferric oxide-hydroxide complex or a slightly modified version thereof, stabilized by a sugar moiety (dextran in the case of INFeD, sucrose in the case of Ferrlecit and Venofer).

Literature references (in the case of INFeD)^{1,2}, an assay protocol from the Ferrlecit IND³ and descriptive information from the Venofer NDA⁴ indicate that when each of these drugs is administered, the iron introduced is taken up by apotransferrin to form transferrin, after which it is transported to various parts of the body either for use or storage.

Apotransferrin is an iron-binding transport glycoprotein found in the blood. It contains two Fe(III) binding sites involving two or three tyrosyl residues^{5,6}. Since this protein binds iron(III) specifically, the iron must be present as iron(III) in order to be transported to the appropriate locations within the body where its primary uses occur (i. e., formation of hemoglobin and myoglobin).

It should be noted that, with other metal-ion complexes that have been approved as drugs (such as radioimaging compounds), the entire complex, not just the metal ion, is transported to the appropriate location within the body where it is used⁷. Also, different complexes of the same metal have been used in different parts of the body for different functions^{7,8}.

References

1. Henderson, P. A.; Hillman, R. S. *Blood*, 34(3) 357 - 375 (1969).
2. Jacobs, J. C.; Alexander, N. M. *Clin. Chem.*, 36(10) 1803-1807 (1990).
3. IND _____ & CPB review, 11/15/99. Also see pharmacokinetic study submitted to NDA 20-955/S-003, 8/2/00 (review pending). —
4. CPB review, NDA 21-135, 6/16/00
5. Douglas, B.; McDaniel, D. H.; Alexander, J. J. *Concepts and Models of Inorganic Chemistry*, 2nd Ed., John Wiley & Sons, Inc., 1983. Pp. 732-733.
6. Aisen, P.; Leibman, A. "Transport by Transferrin" in *Bioinorganic Chemistry II*, K. N. Raymond, Ed. *Adv. Chem. Ser.*, 1977, 162, p. 104.
7. Piace, D. A.; Leutzinger, E. "Stability by Design: Transition Metal Complexes in Medical Imaging and Diagnosis". Paper presented to CMCCC 12/15/99; presented to MPCC 1/31/00.
8. Jones, A.; Davidson, A. *J. Nucl. Med.* 23, 1041-1043 (1982).

Reviewed by:

CMCCC

HFD-103/F. Houn

HFD-103/V. Raczkowski

HFD-40/R. Temple

HFD-102/J. Jenkins

GCF-1/D. Goldsmith

GCF-1/K. Dettelbach

GCF-1/E. Dickinson

HFD-007/W. Mitchell

cc:

HFD-800/Y. Chiu

HFD-600/G. Buehler

HFD-180/Division File

HFD-180/L. Talarico

HFD-180/S. Aurecchia

HFD-180/L. Zhou

HFD-180/B. Strongin

APPEARS THIS WAY
ON ORIGINAL

STROGIN - MAY 18 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-135 CHEM REVIEW #: 1 REVIEW DATE: May 15, 2000

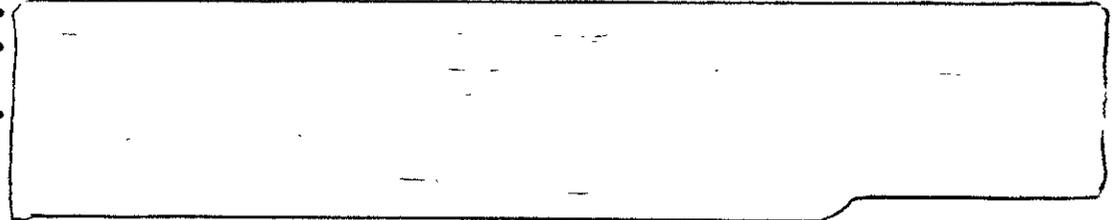
SUBMISSION TYPE	DOCUMENT	CDER	DATES		NUM	LETTER	ST
			ASSIGNED	REVIEW			
ORIGINAL	8/6/99	8/9/99	8/12/99	5/15/2000			
AMENDMENT	10/19/99	10/19/99	10/26/99	5/15/2000			

NAME & ADDRESS OF APPLICANT: Luitpold Pharmaceuticals, Inc.
One Luitpold Drive
Shirley, NY 11967

DRUG PRODUCT NAME:
Proprietary: Venofer®
Nonproprietary/USAN: Iron Sucrose Injection
Code Name/#: Antianemia, Iron Preparation/20:04.04
Chem. Type/Ther. Class: 3S (proposed)

PHARMACOLOGICAL CATEGORY: Hematinic

INDICATION: • Dialysis-associated anemia



DOSAGE FORM: Injection

STRENGTH: 100 mg

ROUTE OF ADMINISTRATION: Intravenous

HOW DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Name (BAN, proposed): Iron(III)-hydroxide sucrose complex
Name (USAN): Iron Sucrose

Structural Formula: Exact structure unknown. Estimated:
 $[Na_pFe_5O_8(OH)_r \cdot x(H_2O)]_L \cdot m(C_{12}H_{22}O_{11})$

where: p = 2.30 ≈ 2
 r = 1.3 ≈ 1

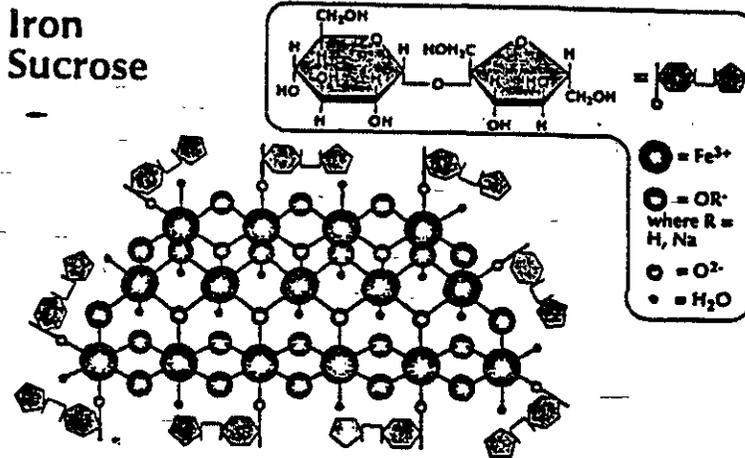
$x = 2.70 \approx 3$

L = the degree of iron polymerization

m = the number of sucrose molecules associated with the Iron (III) hydroxide.

Molecular Formula:

(proposed structure is provided on pg. 7 of volume 5 (of 80) of the submission)



Molecular weight:

$M_w = 34,000 - 54,000$ daltons (D)

$M_n = 24,000 - 36,000$ D

$M_w/M_n = \text{NMT } 1.7$

M_w is estimated to be 43,200 D

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
_____	Venofer® Concentrate	Vifor International	Deficient	3/16/2000	
_____	_____	_____	Adequate	3/31/2000	-

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

The microbiology/sterilization section of this NDA was consulted to HFD-805 (Microbiology Staff) for review. Review was performed by Paul

Stinavage, Ph.D. (finalized on February 3, 2000). Conclusion of that review was approvable upon resolution of noted concerns. Nine (9) deficiencies were noted.

EER was submitted on October 28, 1999. The following facilities listed in subsection B4 (Manufacturers) had received Acceptable recommendations (based on profile):

• _____
• _____
Both acceptable recommendations were dated October 29, 1999.

As of May 15, 2000, the last milestone for following facility listed in subsection B4 was "Inspection Scheduled":

- Luitpold Pharmaceuticals (Shirley, NY)

As of May 15, 2000, the last milestone for following facility listed in subsection B4 was "Assigned Inspection to IB":

- Vifor International (St. Gallen, Switzerland)

REMARKS/COMMENTS:

In this review deficiencies are noted in the following sections:

- Drug Substance
- Drug Product/Composition
- Drug Product/Specification & Methods for Drug Product Ingredients
- Drug Product/Methods of Manufacturing & Packaging
- Drug Product/Regulatory Specifications
- Drug Product/Container/Closure System
- Drug Product/Microbiology
- Drug Product/Stability
- Environmental Assessment
- Methods Validation
- Labeling
- Establishment Inspection

Establishment of in-vitro release test(s) and specification(s) by Biopharmaceutics division is pending.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

This applicatio- is Not Approvable.

/S/

5/18/2000

Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

/S/

5/18/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:

NDA #
HFD-180/LTalarico
HFD-180/Div File/NDA #21-135
HFD-180/LZhou
HFD-180/RFrankewich
HFD-181/BStrongin
HFD-820/JGibbs
HFD-820/SKoepe
R/D Init by:

**APPEARS THIS WAY
ON ORIGINAL**