Large Entity Declaration

PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number:	**11/620986**	**Current Date 18 Nov 2013**
Filing Date:	**08 Jan 2007**	
Patent Number:	**7,754,702**	
Issue Date:	**13 July 2010**	

CHANGE OF ENTITY STATUS PURSUANT TO 37 C.F.R. §1.27 (g)(2)

Commissioner for Patents
Mail Stop M Correspondence
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This communication hereby notifies the United States Patent and Trademark Office that small entity status is no longer applicable for the above-identified patent.

Respectfully submitted,

/Kathleen E. Chaffee/
Signature
Kathleen E. Chaffee
Printed Name
Patent Agent
Title

Reg. # 69,903

COMPANY or FIRM NAME AND ADDRESS:

Dentons US LLP
P.O. Box 061080
Wacker Drive Station, Willis Tower
Chicago, IL 60606

81449718\V-2

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/620,986	07/13/2010	7754702	30015730-0043	1325

26263 7590 06/23/2010

SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, WILLIS TOWER
CHICAGO, IL 60606-1080

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 403 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Mary Jane Helenek, Brookville, NY;
Marc L. Tokars, Douglassville, PA;
Richard P. Lawrence, Calverton, NY;

PTO/SB/08A (01-08)
Approved for use through 01/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | | of | |

Complete if Known	
Application Number	11/620,986
Filing Date	January 8, 2007
First Named Inventor	HELENEK, Mary
Art Unit	1623
Examiner Name	TBA
Attorney Docket Number	30015730-0043

Cdl
Ee-2-10

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/J.L./		US- 6,960,571	~~09-16-2004~~	Helenek et al. 11/2005	
/J.L./		US- 6,599,498	07-29-2003	Groman et al.	
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/Jonathan Lau/	Date Considered	05/22/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26263 7590 04/05/2010

SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, WILLIS TOWER
CHICAGO, IL 60606-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Brenda K. Nemeth	(Depositor's name)
Brenda K. Nemeth	(Signature)
28 March 2010	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043	1325

TITLE OF INVIENTION: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	07/06/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
LAU, JONATHAN S	1623	514-054000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 **Sonnenschein Nath & Rosenthal LLP**
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: **Luitpold Pharmaceuticals, Inc.**

(B) RESIDENCE: (CITY and STATE OR COUNTRY): **One Luitpold Drive Shirley, New York 11967**

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☒ Payment by credit card. Form PTO-2038 is attached.
☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature G. Harley Blosser Date 5-28-10

Typed or printed name G. Harley Blosser Registration No. 33,650

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal	
Application Number:	11620986
Filing Date:	08-Jan-2007
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Filer:	George H. Blosser/Drenda Nemeth
Attorney Docket Number:	30015730-0043
Filed as Small Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	2501	1	755	755
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1055**

Electronic Acknowledgement Receipt	
EFS ID:	7710895
Application Number:	11620986
International Application Number:	
Confirmation Number:	1325
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	George H. Blosser/Drenda Nemeth
Filer Authorized By:	George H. Blosser
Attorney Docket Number:	30015730-0043
Receipt Date:	28-MAY-2010
Filing Date:	08-JAN-2007
Time Stamp:	15:41:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1055
RAM confirmation Number	1872
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Issue Fee Payment (PTO-85B)	Issue_Fee_Transmittal_30015730_0043.pdf	49194 e7d69152acea6af5193a692eb7de06e7d5dccc28	no	1
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	31904 de110e47eaee6501aa66fe7bbc83f133bef6ba50	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	81098		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

26263 7590 04/05/2010

SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, WILLIS TOWER
CHICAGO, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 04/05/2010

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043	1325

TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	07/06/2010

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26263 7590 04/05/2010

SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, WILLIS TOWER
CHICAGO, IL 60606-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043	1325

TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	07/06/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
LAU, JONATHAN S	1623	514-054000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043	1325

26263 7590 04/05/2010

SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, WILLIS TOWER
CHICAGO, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 04/05/2010

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 217 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 217 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	Application No.	Applicant(s)	
	11/620,986	HELENEK ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Applicant's Amendment and Remarks, filed 8 Jan 2010*.

2. ☒ The allowed claim(s) is/are *1-20, 22, 23 and 26-60*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 2 pgs / 20 Jan 2010
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Harley G. Blosser on 29 Mar 2010.

The application has been amended as follows:

Amendment to the Claims

- Claims 1, 9, 31 and 33 are amended as follows:

1. (**currently amended**) A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism resulting in reduced bioavailability of dietary iron, comprising

administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron;

wherein

the iron carbohydrate complex is selected from the group consisting of an iron carboxymaltose complex, an iron mannitol complex, an iron polymaltose complex, an iron gluconate complex, and an iron sorbitol complex; and

the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component and substantially no cross reactivity with anti-dextran antibodies

wherein said disease, disorder or condition is not Restless Leg Syndrome.

9. (**currently amended**) The method of claim 1 wherein the disease, disorder, or condition is selected from the group consisting of ~~restless leg syndrome;~~ blood donation; hair loss; and attention deficit disorder.

31. (**currently amended**) The method of claim **1** ~~25~~ wherein the iron carbohydrate complex is an iron polyglucose sorbitol carboxymethyl ether complex.

33. (**currently amended**) The method of **claim 1** ~~any one of claims 1~~ wherein the iron carbohydrate complex comprises an iron core with a mean iron core size of no greater than about 9 nm.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 8 Jan 2010, in which claims 1, 9 and 58 are amended to change the scope and breadth of the claim and claim 21 is canceled.

This application is a domestic application, filed 08 Jan 2007; and claims benefit of provisional application 60/757,119, filed 06 Jan 2006.

Claims 1-20, 22, 23 and 26-60 are pending in the current application and allowed in view of the Examiner's Amendment detailed herein.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

Rejections Withdrawn

Applicant's Amendment, filed 8 Jan 2010, with respect to claims 1-23 and 26-60 rejected under 35 U.S.C. 112, first paragraph as not being enabled for the full scope of the claim has been fully considered and is persuasive, as amended claims 1, 9 and 58 do not encompass treating a disease, disorder, or condition characterized by dysfunctional iron metabolism resulting in an increased iron content, such as Parkinson's disease, amended claim 1 does not recite iron polyisomaltose complex or iron hydrogenated dextran complex, and claim 21 is canceled.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 8 Jan 2010, with respect to claim 21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite has been fully considered and is persuasive, as claim 21 is canceled.

This rejection has been **withdrawn**.

The instant invention is not taught or fairly suggested by the closest prior art as detailed herein:

Helenek et al. (US Patent Application Publication 2004/0180849, published 16 Sep 2004, of record, issued as US Patent 6,960,571, provided by Applicant in IDS mailed 24 Jan 2008) discloses the administration of iron complexes such as iron polymaltose, iron gluconate and iron sorbitol (page 3, paragraph 21) to treat restless leg syndrome wherein the dosage is high, 1000 mg/administration, about two- to ten-fold more than the dose used to treat other conditions (page 2, paragraph 11 and page 5, paragraph 51).

It would not have been obvious to one of ordinary skill in the art to apply the high dosage of iron polymaltose, iron gluconate or iron sorbitol specific to treatment of restless leg syndrome to conditions other than restless leg syndrome because Helenek et al. teaches said dosage is two- to ten-fold more than the dose to treat other conditions. Further, the ordinary level of skill taught by the state of the art teaches away from high dose iron carbohydrate complexes are provided by Applicant at page 18 of Remarks filed 26 Aug 2009 and as further detailed below.

Lawrence et al. (US Patent 5,624,668, issued 29 Apr 1997, of record) in view of Helenek et al. (US Patent Application Publication 2004/0180849, published 16 Sep 2004, of record, issued as US Patent 6,960,571, provided by Applicant in IDS mailed 24 Jan 2008) teaches as detailed in the Office Action mailed 29 May 2009.

Applicant's Remarks in view of the declaration of Richard P. Lawrence (inventor) under 37 CFR § 1.132 are persuasive that the teaching of Helenek et al. is drawn to the properties of the specific iron carbohydrate complexes taught by Helenek et al. such as release rate and dosage and the declaration of Richard P. Lawrence (inventor) is persuasive that the teaching of Helenek et al. are therefore not combinable with the teaching of Lawrence et al. with a reasonable expectation of success; Applicant's Remarks in view of the declaration of Richard P. Lawrence (inventor) under 37 CFR § 1.132 are persuasive that the combination of Lawrence et al. in view of Helenek et al. does not teach the instant invention as claimed; and the ordinary level of skill taught by the state of the art teaches away from high dose iron carbohydrate complexes are provided by Applicant at page 18 of Remarks filed 26 Aug 2009 and as further detailed below.

Macdougall (Nephrol. Dial. Transplant, 2000, 15, p1743-1745, cited in PTO-892), Andersson (British Medical Journal, 1961, p275-279, cited in PTO-892), and Fielding (British Medical Journal, 1961, p279-283, cited in PTO-892) teach as above with regard

to optimizing a lower unit dosage of an iron carbohydrate complex to minimize adverse events.

Nissenson et al. (Kidney International, 2003, 64(Supplement 87), pS64–S71, cited in PTO-892) teaches optimizing the maximum amount of iron carbohydrate complex to minimize adverse events (page S67). Nissenson et al. teaches experience with high doses of iron sucrose and iron gluconate are limited for safety reasons, that doses of iron sucrose between 200 and 400 mg may be safely infused over 120 minutes whereas doses of 400 to 500 mg are best infused over 240 minutes, and infusions of 312.5 to 500 mg iron gluconate have been safely administered but slower infusion rates may be preferable (page S67, right column, paragraph 2).

The instant invention would not have been obvious to one of ordinary skill in the art at the time of the invention because Nissenson et al. in view of the level of skill in the art teaches optimizing the maximum amount of iron carbohydrate complex to minimize adverse events and experience with high doses of iron sucrose and iron gluconate are limited for safety reasons. Therefore it would not have been obvious to one of ordinary skill in the art to increase the dosage because the reasonable expectation of increased adverse events caused by increased dosage constitutes a teaching away from increasing the dosage.

Intervening art Newnham et al. (Internal Medicine Journal, 2006, 36(10), p672-674, published online 4 Sep 2006, cited in PTO-892) discloses infusion of a mean dose of 1338 mg iron polymaltose to treat a disease, disorder, or condition characterized by

iron deficiency such as anemia (page 673, right column, paragraph 2). However, Newnham et al. was published **after** the filing date of parent provisional application 60/757,119, filed 06 Jan 2006. Support for the instant method is found, for example, specification paragraph [0012] at page 3, paragraph [0042] spanning page 11-12 and at claims 1 and 21 of parent provisional application 60/757,119.

Therefore the instant invention is not suggested or fairly taught by the prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 1-20, 22, 23 and 26-60 are allowed in view of the Examiner's Amendment detailed herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

ORIGINAL		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
514	54	A 6 1 K 31 / 715 (2006.01.01)	
		A 6 1 K 31 / 716 (2006.01.01)	

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
556	146				
536	123.1	123.12	123.13		

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	17	17	30	33	46	49								
2	2	18	18	31	34	47	50								
3	3	19	19	32	35	48	51								
4	4	20	20	33	36	49	52								
5	5		21	34	37	50	53								
6	6	21	22	35	38	51	54								
7	7	22	23	36	39	52	55								
8	8		24	37	40	53	56								
9	9		25	38	41	54	57								
10	10	23	26	39	42	55	58								
11	11	24	27	40	43	56	59								
12	12	25	28	41	44	57	60								
13	13	26	29	42	45										
14	14	27	30	43	46										
15	15	28	31	44	47										
16	16	29	32	45	48										

/Jonathan S Lau/ Examiner.Art Unit 1623 (Assistant Examiner)	3/26/10 (Date)	**Total Claims Allowed:** 57
/Shaojia Anna Jiang/ Supervisory Patent Examiner.Art Unit 1623 (Primary Examiner)	03/29/2010 (Date)	O.G. Print Claim(s) 1 and 55 O.G. Print Figure none

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

SEARCHED			
Class	Subclass	Date	Examiner
514	53, 54	3/26/2010	JSL
556	146	3/26/2010	JSL

SEARCH NOTES		
Search Notes	Date	Examiner
EAST - see attached notes	5/22/2009	JSL
Google Scholar - see attached notes	5/22/2009	JSL
EAST - inventor name search (Mary Helenek; Marc Tokars; Richard Lawrence)	5/22/2009	JSL
Google Scholar - see attached notes	12/8/2009	JSL
EAST - see attached notes	12/8/2009	JSL
EAST - inventor name search (Mary Helenek; Marc Tokars; Richard Lawrence) - updated	3/26/2010	JSL

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
514	53, 54	3/26/2010	JSL
556	146	3/26/2010	JSL

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4597	514/54.ccls.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:43
L2	1268	514/53.ccls.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:43
L3	967	(1 or 2) and iron	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:43
L4	89	(1 or 2) and (iron near9 complex)	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:43
L5	617	(1 or 2) and iron and (complex or conjugate)	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:44
L6	578	556/146.ccls.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:44
L7	38	6 and (carboxymaltose or mannitol or polymaltose or gluconate or sorbitol)	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:45
L12	9	((MARY) near2 (HELENEK)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:47
L13	5	((MARC) near2 (TOKARS)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:47
L14	401	((RICHARD) near2 (LAWRENCE)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:47
L15	34	14 and iron	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:48
L16	37	12 or 13 or 15	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/26 16:48

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L8	29	514/54.ccls.	UPAD	ADJ	ON	2010/03/26 16:45
L9	3	514/53.ccls.	UPAD	ADJ	ON	2010/03/26 16:45
L10	4	(8 or 9) and iron	UPAD	ADJ	ON	2010/03/26 16:45
L11	1	556/146.ccls.	UPAD	ADJ	ON	2010/03/26 16:45

3/26/2010 4:49:00 PM
C:\Documents and Settings\jlau1\My Documents\EAST\Workspaces\11620986 - iron administration.wsp

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11620986
	Filing Date	2007-01-08
	First Named Inventor	HELENEK, Mary Jane
	Art Unit	1623
	Examiner Name	LAU, Jonathan S.
	Attorney Docket Number	30015730-0043

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/J.L./	1	2007023154	WO		2007-03-01	Vifor Int. AG		☐
/J.L./	2	2004037865	WO		2004-05-06	Vifor Int. AG		☐
/J.L./	3	1997011711	WO		1997-04-03	Luitpold Pharm Inc.		☐

EFS Web 2.1.16 /Jonathan Lau/ 03/26/2010

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11620986
	Filing Date	2007-01-08
	First Named Inventor	HELENEK, Mary Jane
	Art Unit	1623
	Examiner Name	LAU, Jonathan S.
	Attorney Docket Number	30015730-0043

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/J.L./	1	European Search Report issued October 21, 2009 in connection with related European Application No. 07716309.5	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Jonathan Lau/	Date Considered	03/26/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11620986
	Filing Date	2007-01-08
	First Named Inventor	HELENEK, Mary Jane
	Art Unit	1623
	Examiner Name	LAU, Jonathan S.
	Attorney Docket Number	30015730-0043

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2007023154	WO		2007-03-01	Vifor Int. AG		☐
	2	2004037865	WO		2004-05-06	Vifor Int. AG		☐
	3	1997011711	WO		1997-04-03	Luitpold Pharm Inc.		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11620986
	Filing Date	2007-01-08
	First Named Inventor	HELENEK, Mary Jane
	Art Unit	1623
	Examiner Name	LAU, Jonathan S.
	Attorney Docket Number	30015730-0043

If you wish to add additional Foreign Patent Document citation information please click the Add button [Add]

NON-PATENT LITERATURE DOCUMENTS [Remove]

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	European Search Report issued October 21, 2009 in connection with related European Application No. 07716309.5	☐

If you wish to add additional non-patent literature document citation information please click the Add button [Add]

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11620986
	Filing Date	2007-01-08
	First Named Inventor	HELENEK, Mary Jane
	Art Unit	1623
	Examiner Name	LAU, Jonathan S.
	Attorney Docket Number	30015730-0043

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/G. Harley Blosser/	Date (YYYY-MM-DD)	2010-01-20
Name/Print	G. Harley Blosser	Registration Number	33,650

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : **A61K 33/26, 9/10**	**A1**	**(11) International Publication Number:** **WO 97/11711** **(43) International Publication Date:** 3 April 1997 (03.04.97)

(21) International Application Number: PCT/US96/14153

(22) International Filing Date: 29 August 1996 (29.08.96)

(30) Priority Data:
08/536,984 29 September 1995 (29.09.95) US

(71) Applicant: LUITPOLD PHARMACEUTICALS, INC. [US/US]; One Luitpold Drive, Shirley, NY 11967 (US).

(72) Inventors: LAWRENCE, Richard, P.; 94 Young Street, Baiting Hollow, NY 11933 (US). LANGE, Ralf, A.; P.O. Box 1967, Amagansett, NY 11930 (US). LANCE, Ralf, A.; P.O. Box 1967, Amagansett, NY 11930 (US). WU, Chin; 46 Fairlawn Court, Shirlex, NY 11967 (US). HELENEK, Mary, Jane; 19 Jean Place, Syosset, NY 11791 (US).

(74) Agents: ADLER, Reid, G. et al.; Morrison & Foerster L.L.P., 2000 Pennsylvania Avenue, N.W., Washington, DC 20006-1888 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: IRON DEXTRAN FORMULATIONS

(57) Abstract

Ferric oxyhydroxide-dextran compositions for treating iron deficiency having ellipsoidal particles with a preferred molecular weight range of about 250,000 to 300,000 daltons.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

IRON DEXTRAN FORMULATIONS

Field of the Invention

The present invention relates to improved iron dextran formulations for the treatment of iron deficiency, and to methods for preparing such formulations.

Background of the Invention

The intravenous or intramuscular injection of sterile solutions of an iron dextran complex is clinically indicated for the treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.

Iron dextran is absorbed from the injection site after intramuscular injection, for example, into the capillaries and the lymphatic system. Circulating iron dextran is cleared from the plasma by cells of the reticuloendothelial system, which split the complex into its components of iron and dextran. IMFERON®, for example, a product previously marketed by Fisons Pharmaceuticals, is released to the blood after uptake by the phagocytic activity of macrophages. See Henderson, *et al.*, *Blood* 34:357-375 (1969). The iron immediately is bound to available protein moieties to form hemosiderin or ferritin, the physiological forms of iron or, to a lesser extent, to transferrin. This iron, which is subject to physiological control, replenishes the iron component of hemoglobin and other depleted iron stores.

The major benefit of the clinical use of iron dextran is that, due to its large molecular weight (*i.e.*, greater than 70,000 daltons), the iron dextran complex is not excreted by the kidneys. Therefore almost the entire dose of iron dextran remains bioavailable as the iron dextran is metabolized in the liver. The major portion of an intramuscular injection of iron dextran is absorbed within 72 hours. Most of the remaining iron is absorbed over the ensuing 3 to 4 weeks.

Iron dextran for parenteral administration currently is marketed by Steris Pharmaceuticals, Inc. under the brand name INFeD®. As formulated, this product is a dark brown and slightly viscous sterile liquid complex of ferric oxyhydroxide, beta-FeO(OH), and is a low molecular weight dextran derivative in approximately 0.9% weight per volume sodium chloride for intravenous or intramuscular use. It contains the equivalent of 50 mg of elemental iron (as an iron dextran complex) per ml. Sodium chloride may be added for tonicity. The pH of the solution is between 5.2 and 6.5.

Under electron microscopy, IMFERON® has been shown to have an inner electron-dense FeO(OH) core with a diameter of approximately 3 nm and an outer moldable plastic dextran shell with a diameter of approximately 13 nm. Almost all of the iron, about 98-99% is present as a stable ferric-dextran complex. The remaining iron represents a very weak ferrous complex.

The dextran component of conventional iron dextran products is a polyglucose that either is metabolized or excreted. Negligible amounts of iron are lost via the urinary or alimentary pathways after administration of iron dextran. Staining from inadvertent deposition of iron dextran in subcutaneous and cutaneous tissues usually resolves or fades within several weeks or months. Various studies have reported that the half life of iron dextran in iron deficient subjects ranges from 5 to more than 20 hours. Notably, these half-life values do not represent clearance of iron from the body because iron is not readily eliminated from the body. See, for example, the package inserts for IMFERON® and INFeD®, or Hamstra, *et al.* *JAMA* 243:1726-1731 (1980).

U.S. Patent No. 2,820,740 and its reissue RE 24,642 to London *et al.* describe colloidal injectable iron preparations suitable for parenteral injection formed of a nonionic ferric hydroxide, partially depolymerized dextran complex. Current commercial iron dextran products, based on these two prior patents do not have sufficient purity (see Figs. 1 and 2) and needed thermal

stability (see Figs. 3 and 4) to safeguard safety and sterility concerns. Also, these commercial products have a relatively short plasma residence time which could cause a potential risk of iron overload in specific organs. See, Carthew, R. E., *et al. Hepatology* 13(3):534-538 (1991); Pitts, T. O., *et al. Nephron* 22:316 (1978); Weintraub, L. R., *et al. Brit. J. Hematology* 59:321 (1985); and Fletcher, L. M., *et al., Gastroenterology* 97:1011 (1989).

Similarly, U.S. Patent No. 2,885,393 to Herb also discloses iron dextran complexes. The most suitable range in molecular weight of the partially depolymerized dextran for injection was found to be 30,000 to 80,000 daltons or lower. A subsequent patent to Herb, U.S. Patent No. 4,180,567, discloses other iron preparations and methods for making and administering such preparations; however, the method disclosed does not teach the heating of iron dextran complexes above 100°C.

Other methods for the production of iron dextran complexes have been described, for example, in U.S. Patent No. 4,599,045 to Muller *et al.* regarding iron (III) hydroxy/dextran complexes that are produced using an alkali carbonate, ammonium carbonate or a carbonate of an organic base added to an acid solution containing a partially depolymerized dextran and an iron (III) salt. Thereafter, an alkali metal hydroxide or ammonium hydroxide is added. The suspension so formed is then converted into a solution by heating, and the solution worked up in a known manner.

Alternatively, ferric chloride and dextran can be reacted in aqueous solution in the presence of citric acid as disclosed in U.S. Patent No. 3,697,502 or by treating reactive trivalent iron with a complex-forming agent consisting of sorbitol, gluconic acid and certain oligosaccharides, in particular proportions and amounts as taught in U.S. Patent No. 3,686,397.

U.S. Patent No. 4,749,695 and its divisional, U.S. Patent No. 4,927,756, both to Schwengers, disclose a

water-soluble iron dextran and a process for its manufacture. As disclosed, the dextran utilized has an average molar mass of from 2,000 to 4,000 daltons. Another alternative includes the complexation of ferric hydroxide with hexonic acid derivatives of dextran as in U.S. Patent No. 4,788,281 to Tosoni.

U.S. Patent No. 3,908,004 to Kitching discloses the preparation of iron compositions to treat iron-deficiency anemia. Methods of formulating these compositions include the heating of an aqueous alkaline solution of a polysaccharide with a water soluble inorganic iron compound such as ferric oxychloride. The presence of the alkali is said to be necessary to bring about the formation of the complex. However, the alkaline conditions also cause some degradation of the polysaccharide and the low molecular-weight species so formed produce iron compounds which are responsible for undesirable effects.

U. S. Patent No. 4,659,697 to Tanaka discloses a process for producing an organoiron (II) compound-containing antianemic composition which through the cultivation of a yeast in a saccharide-containing nutrient medium, such as grape juice, in the presence of an iron compound to form a cultured broth comprising an organoiron(II) compound, alcohol and water and removing the alcohol from the cultured broth to an extent that the resulting cultured broth has an alcohol content of less than about 1 % by volume, and an antianemic composition produced thereby. The antianemic composition was said to be very stable, with excellent absorbability into a living body and incorporation of iron into hemoglobin.

Iron dextran complexes also have application as imaging agents. For example, dextran/magnetite is disclosed as a particulate solution specifically noted to be stabilized by polymeric dextran. (See Hasegawa *et al.*, U.S. Pat. No. 4,101,435. Several others have used dextrans of various molecular weights as ingredients in the synthesis of magnetic colloids or particles. (See Hasegawa *et al.*, U.S. Pat. No. 4,101,435; Molday, U.S.

Pat. No. 4,454,773; and Schroder, U.S. Pat. No. 4,505,726. The resulting complexes of dextran and iron oxide have varying sizes and structures, but all have molecular weights of at least about 500,000 daltons.

The incorporation of high molecular weight dextran into magnetic particles or colloids may, however, cause some patients to experience adverse reactions to the dextran, particularly when such complexes are administered as parenteral magnetic resonance contrast agents. These adverse reactions may also be due in part to problems of high molecular weight polymers such as dextran dissociating from the metal oxide colloid upon prolonged storage or under high temperatures, thereby leaving the metal oxide free to aggregate.

Despite the variety of iron dextran formulations described in the prior act, current iron deficiency products are based on technology that has not satisfactorily resolved stability and purity concerns. What is needed in the therapeutic field of iron supplementation, is an improved next-generation iron dextran product with enhanced purity and thermal stability, as well as prolonged plasma residence time to minimize possible iron overload complications without compromising the efficacy of iron dextran therapy.

Summary of the Invention

These and other objects are achieved by the iron dextran product prepared according to this invention. It has excellent attributes and thermal stability but also has prolonged plasma residence time to minimize possible iron overload problem without compromising the efficacy of iron dextran.

It is an object of the present invention to provide methods for synthesizing iron dextran compositions useful in the treatment of iron deficiency. Associated compositions also are disclosed. Such compositions include aqueous colloidal suspensions or solutions of a ferric oxyhydroxide-dextran complex, having an average molecular weight of about 100,000 to 600,000 daltons and

a substantially uniform size distribution. Physiologically acceptable carriers for these compositions also are contemplated. The administration of such compositions to humans and other mammals for the treatment of iron deficiency or, in the case of non-human mammals, for medicinal as well as investigational purposes also are described.

In a preferred embodiment of the present invention, the molecular weight range of the iron dextran compositions are about 150,000 to 350,000 daltons, and more particularly preferred are compositions with a molecular weight range of about 250,000 to 300,000 daltons.

It is a further object of the present invention to provide iron dextran compositions having a beta-FeO(OH) core. A further object of the invention is to provide ellipsoidal iron-dextran particles with a length in the range of about 25 to 45 nanometers, more preferably about 31.5 to 36.5 nanometers, and a width of about 3.5 to 5.5 nanometers, more preferably about 4 to 5 nanometers.

It is a further object of the present invention to provide methods for synthesizing iron-dextran compositions as described above. The process of the present invention involves the initial production of iron-dextran particles by conventional methods. Applicants, however, have discovered that superior particles may be produced by the following process. Generally, as discussed in greater detail below, iron-dextran particles are purified by conventional techniques to remove various impurities, in particular, chloride iron, but also including any toxic by-products, uncomplexed dextran and, generally, any component of the initial iron-dextran reaction mixture which would not be appropriate or permitted to be administered to patients in an approvable composition.

Brief Description of the Drawing Figures

Figure 1 shows a HPGPC chromatogram of an iron dextran formulation according to the present invention demonstrating its uniform molecular weight distribution.

Figure 2 shows the HPGPC chromatogram of two commercial preparations of iron dextran demonstrating a significant heterogeneity relative to the formulations in Figure 1.

Figure 3 shows the HPGPC chromatogram of an iron dextran formulation according to the present invention assessed over a period of seven days, demonstrating the stability of formulations.

Figure 4 shows the HPGPC chromatogram of a commercial iron dextran formulation assessed over a period of seven days, demonstrating a significant instability relative to the formulation of Figure 3. At a magnification of 140,000 times.

Figure 5 shows that an electron photomicrograph of iron dextran particles according to the present invention at a magnification of 140,000 x.

Figure 6 shows electron photomicrograph of particles sold under the brand name INFeD® at a magnification of 140,000 x.

Description of the Preferred Embodiments

The present inventors have found that iron dextran formulations prepared according to the following specifications are surprisingly more temperature stable and/or exhibit a much greater degree of homogeneity than is evidenced by or would have been expected from iron dextran formulations of the prior art such as IMFERON® and INFED®. The improved methods and compositions disclosed for the preparation of these iron dextran formulations achieve uniform molecular weight distribution. Safety, reliability and quality of iron dextran injectable and infusible products can be significantly improved over previous products. Our product now in development is called DEXFERRUM®. DEXFERRUM® is a pharmaceutically-equivalent iron dextran

characterized by a higher mean molecular weight (266,608 ± 1.4 % daltons).

In the following discussion and examples, certain calculations as set forth below are required to determine the amounts of active and inactive ingredients:

The amount of iron dextran is based on its iron (Fe^{3+}) content. The amount in mg/ml is calculated by dividing the desired iron concentration in mg/ml of elemental iron by the powder's % w/w iron content divided by 100. This amount is then multiplied by the batch size in liters for the amount required in grams for that batch size. This value is then corrected for its moisture content.

In general, a suitable iron III salt, such as ferric chloride, is neutralized with a suitable alkali to which a modified dextran is added either before, concomitantly or after neutralization to produce an iron dextran complex with a molecular weight in the range of about 100,000 to about 600,000 daltons. The resulting solution is purified of excess dextran, salts, toxic impurities, etc., such as are identified in Table 2 by any suitable method to produce an iron dextran aqueous concentrate or powder with an elemental iron concentration of between about 5% to about 50%. Purified iron dextran powder or concentrate is then used in the preparation of a final solution made of the foregoing iron dextran composition, with an elemental iron content of about 25 to about 100 mg/ml.

We have observed that in solution, dextran is not tightly bound to the iron core, and complexes formed of aggregates in which, e.g., two cores might be bound to the same dextran molecule, can be observed. The dextran serves to stabilize the core, but the purification process associated with the initial preparation of iron dextran particules in which, e.g., chloride iron is removed, also tends to remove some of the dextran.

To a final solution made of the foregoing iron-dextran composition, an appropriate amount of oxidized dextran is added to provide a desired final ratio of the

content of iron to dextran in the final iron dextran composition in a range from about 1:2 to 1:5, but preferably about 1:4 as described in greater detail below. The iron-dextran and oxidized dextran mixture is heated and reacted for an appropriate length of time with a suitable alkali. Generally, an appropriate length of time is not less than about one hour. The actual amount of time required to complete the reaction is dependent on the amounts and ratios of starting materials. Determination of the end point may be measured by the absence of dextran enhancement of the LAL endotoxins test. We have determined that oxidized dextran enhances the LAL gel clot method for assessing endotoxins, whereas reacted material, prepared according to our disclosure, demonstrates no such enhancement. Thus, in our manufacturing procedure, the reaction end point is determined by this technique to be complete when the amount of unreacted dextran does not exceed about 0.05 percent. After cooling and dilution to a final volume, the pH of the solution is adjusted to a physiologically acceptable pH range. This adjusted solution is then aseptically filled and/or terminally sterilized for administration, such as by injection.

We believe that the reaction of the iron dextran complex with an oxidized dextran under alkaline conditions converts the terminal unit of oxidized dextran from δ-Gluconolactone to sodium gluconate. The resulting solution contains dextran that is both bound and unbound to the iron complex where the molecular weight distributions of the bound and unbound dextrans are in equilibrium. Without wishing to be bound by any particular mechanism of action, we believe that the oxidized dextran at this stage of processing of iron dextran compositions minimizes or substantially eliminates aggregate complexes in which two iron cores might be bound to the same dextran molecule. Moreover, oxidized dextran has a terminal carboxyl group and has superior chelating abilities.

The amount of oxidized dextran required to produce the desired product meeting its desired nonvolatile residue is calculated by subtracting the calculated # mg/ml iron dextran (dry weight) from the theoretical total weight based on the nonvolatile residue of the desired product. That is, for a nonvolatile residue of 28-43 % w/v, the theoretical total weight would range from 280 to 430 mg/ml. The value obtained is then corrected for the oxidized dextran's loss on drying by dividing this value by (1-(loss on drying/100)). This amount is then multiplied by the batch volume in liters for the amount of grams for that batch size.

The amount of alkali (such as sodium hydroxide) is dependent on the amount of oxidized dextran since it reacts with the alkali to form a carboxylic acid. The reaction is 1:1. To determine the appropriate amount of alkali (such as NaOH) in grams, the molecular weight of the alkali is multiplied by the number of grams of oxidized dextran required for the desired product which is then divided by the average molecular weight of the oxidized dextran.

A maximum limit for the hydrochloric acid used to adjust pH is calculated using the desired product's upper limit for chloride content. The amount of chloride supplied by the starting materials (iron dextran and oxidized dextran) is calculated, then the maximum amount of hydrochloric acid added is determined by subtracting the total amount of chloride supplied from the starting materials from the desired product's upper limit for chloride content, then multiplying the value obtained by the batch size in liters, divide this value by the atomic weight of chloride (35.5) and then divide by the normality of the hydrochloric acid solution to be used for the final value.

The low molecular weight carbohydrates of the invention must be oxidized in order to avoid problems in lack of uniformity and with the presence of endotoxins. Such carbohydrates preferably have a molecular weight in the range of about 2,000 to 15,000 daltons, most

preferably around 6,000 to 7,000 daltons. The preferred concentrations of the carbohydrates of the invention which effectively impart stabilization to the carrier phase of the metal oxide composition are in the range of about 0.001 M to about 2 M, most preferably about 0.05 M to about 0.5 M, but optimal concentrations can be determined by those skilled in the art according to conventional techniques.

Some preferred low molecular weight stabilizing agents include, but are not limited to, mannitol, sorbitol, glycerol, inositol, dextran 1 (Pharmacia Inc., Piscataway, N.J.) and ascorbate. Other useful agents include dextrins, celluloses, hydroxyethylstarches, heparins, starches, dextran sulfates, carboxylmethylated dextran and carboxymethyl cellulose. In the case of dextran 1, which has a molecular weight of about 1,000 daltons, the same compound can both stabilize the colloid or particulate suspension against unwanted physical changes and block possible adverse reactions. The simultaneous injection of dextran 1 and a complex of dextran and the magnetic iron oxide decreases adverse reactions to high molecular weight dextran alone.

Preferred methods of manufacture of iron dextran solutions involve the neutralization of ferric chloride solution with an alkaline solution of dextran. The mixture is heated, then cooled to room temperature and clarified by centrifugation. The resulting solution is then concentrated to the desired iron content by dialysis against running water. The iron dextran is composed of a beta-FeO(OH) core formed by the neutralization of an acidic ferric chloride/dextran solution with alkaline sodium bicarbonate. The by-products of this reaction are sodium chloride and carbon dioxide. During neutralization, the modified dextran is absorbed (complexes) to the iron core's surface where the dextran's hydroxyl groups provide the "OH" needed for stabilization of the core's beta-FeO(OH) structure.

Examples

Experimental studies describing the use of low molecular weight carbohydrates as stabilizing agents for metal oxide compositions prepared according to the present invention are presented below. These examples are to be considered as illustrative of the present invention rather than limitative of its scope in any way.

The preferred dextran formulation for the production of iron dextran formulations according to the present invention are prepared by fermentation of sucrose using *Leuconostoc mesenteroides* bacteria (NRRL B-512 (F)). The crude dextran is precipitated, hydrolyzed, and fractionated by conventional means. The dextran fraction is oxidized with an oxidizing agent under alkaline conditions, then purified.

Studies on the structure of the iron dextran complex report that it is composed of a beta-FeO(OH) core complexed with low molecular weight dextrans ranging from 3,500 to 7,500 daltons. The oxidized dextran used in this invention is the dextran which is depolymerized to an average molecular weight ranging from 3,500 to 7,500 daltons. The dextran's terminal unit, D-glucose, is then oxidized to gluconolactone. During the manufacturing process described in this invention the oxidized dextran's terminal unit, gluconolactone, is converted to D-glucuronic acid via alkaline hydrolysis.

The oxidized dextran used to produce iron dextran products according to the present invention has the following physical properties as set forth in Table 1:

Table 1	
Parameter	**Tolerance**
Description	White, amorphous powder
Odor	Odorless
Loss on Drying (w/w %)	Not more than 5.0 %
Sodium chloride content (w/w %)	Not more than 2.0 %
Nitrogenous Impurities	Not more than 0.015 %
Bromide content	Less than 5 ppm
Alcohol and Related Impurities	Less than 0.05 % w/w
Relative Viscosity of a 10 % sol	Less than 4.0 centistokes
Average Molecular Weight	Between 3,000 and 7,000
Phosphate (w/w %)	Not more than 0.28 %
Reducing Sugars (w/w %)	Not more than 7.0 %
Pyrogen Test	Passes test

The characteristics and physical properties of the preferred iron dextran powder used to produce iron dextran formulations of the present invention are as follows in Table 2. This composition is commercially available from Laboratorien Hausmann AG in Switzerland, and U.S. Patent No. 4,599,405, discussed above, is relevant to the preparation of such compositions. U.S. Patent No. 3,697,502 also is relevant.

Table 2	
Parameter	**Tolerance**
Description	Brown, amorphous powder
Identification	Complies
Loss on Drying (w/w %)	Not more than 10.0 %
Sodium chloride content (w/w %)	Not more than 6.0 %
Dextran content	Between 29.0 and 36.0 %
Iron Content	Between 28.0 and 35.0 %
Bromide content	Less than 5 ppm
Alcohol and Related Impurities	Less than 0.05 % w/w
pH of a 5 % Solution	5.2 to 6.5
Molecular Weight Determination by GPC M_W M_n M_W/M_n	 Between 255,000 - 520,000 Between 200,000 - 365,000 Not more than 1.7
Arsenic	Not more than 2 ppm
Lead	Not more than 100 ppm
Copper	Not more than 100 ppm
Zinc	Not more than 100 ppm
Bacterial Endotoxins	Passes test

Example 1

Preparation of Iron dextran Compositions

In a 200 liter steam-jacket reaction vessel, 114 liter of hot (70°C - 90°C) water was added. Next, 30.0 kg of iron dextran, satisfying the parameters described above, along with 28.3 kg oxidized dextran, also satisfying the parameters discussed above. The mixture was diluted up to 175 liters. Next, 185 g of NaOH was added and mixed with the iron dextran mixture. The vessel was sealed and then heated to a range of 110°C - 115°C using a steam jacket for three hours. The vessel was then cooled to approximately 25°C and vented during

the cooling process. The pH was tested and adjusted to the range of 5.7 - 6.0.

The reaction solution was prefiltered through a 1.0 micron membrane into a holding vessel. Next, the filtered solution was passed through a 0.2 micron filter into sterilized receiving vessels, and depyrogenated vials were filled and stoppered with aliquots of the sterilized solution.

Example 2

Evaluation of Process Results to Determine Molecular Weight Using HP-GPC

The molecular weight of the iron dextran complex of Example 1 was determined by gel permeation chromatography in a HP-GPC system equipped with a differential refractometer as the detector and an integrator with a GPC program for molecular weight calculations. The HP-GPC column was packed with porous particles of polyacrylic acid containing pore sizes up to 1000 angstroms. The pores act as sieves where smaller molecules permeate through in the packing's pores while the larger molecules are excluded from the packing and are eluted by the more mobile phase. Thus, macromolecules elute from the columns, from largest to smallest.

Figs. 1-4 show comparisons between the iron dextran formulations of the present invention and two commercial preparations. These figures present data generated by a refractive index detector. This detector measures the concentration of the iron dextran, dextran and other molecules and the integrator's GPC program interprets the data and calculates the relative: weight average molecular weight (Mw), number average molecular weight (Mn) and polydispersity index (Mw/Mn) of the sample. The reported values are based on polyethylene-glycol (PEG) and polyethylenoxide (PEO) standards used for calibration of the instrument, and are considered relative molecular weights which should be within 5% of the actual values.

Ellipsoidal particles of the present invention are shown in Fig. 5. This shows DEXFERRUM® at a magnification of about 140,000 x. In comparison, Fig. 6 shows particles sold under the name INFeD®. The unique conformation and consistency of the DEXFERRUM® particles, as compared with another iron dextran supplement product, is evident from the foregoing figures and comparative electron photomicrographs. This information is consistent with the literature analyses of prior art iron-dextran complexes as reflected in the paper by Cog, *et al*, from *J. Pharm. Pharmac* 24:513-517 (1972).

The DEXFERRUM® particles typically range in length from about 31.5 to about 36.5 nanometers and are approximately 4.5 nanometers in width. The IMFERRON® particles by photomicrograph have a core also in an ellipsoid shape but ranging in size from about 13.5 to 18 nanometers in length with a width ranging from about 9 to about 13.5 nanometers. These electron photomicrographs are not shown. Fig. 6, which shows the INFeD® product, reveals iron cores also in the form of thin ellipsoids with a length of about 13.5 to 18 nanometers with an average width of about 4.5 nanometers. As Fig. 5 indicates, the DEXFERRUM® particle is substantially uniform in terms of particle size and shape. Fig. 6 shows a relative heterogeneity of the comparable INFeD® product.

Example 3

Human Plasma Residence Time

The following Table 3 demonstrates that the plasma residence time of the new iron dextran prepared according to the present invention is significantly longer than that of other commercial iron dextran formulations.

Table 3 Plasma Residence Time of Iron Dextrans*	
Products	**Half life (hours)**
IMFERON	5.9
INFED	34.2
DEXFERRUM	58.9

*The plasma half-life figures assume a standard intravenous dose of 100 mg of elemental iron. IMFERON® determination used a radio-isotope label of iron ^{59}Fe, while INFeD® and DEXFERRUM® had direct measurement of iron dextran in plasma.

Example 4

Comparison of Indicators of Iron Dextran Efficacy

Measurements of transferrin, plasma ferritin and hemoglobin levels are the major indicators of iron dextran efficacy. The following Tables 4 and 5 demonstrate that the iron dextran according to the present invention are biologically comparable to an existing commercial preparation. Levels of hemoglobin, serum ferritin, serum iron and total iron binding capacity (the serum iron divided by the total iron binding capacity times 100 %) were determined by standard CLIA monitored commercial clinical laboratory assays.

Table 4 Comparison of Transferrin Levels Transferrin AUC 0 - 96 hours (ug*hr/dL)	
Iron Dextran Invention	**Commercial # 2**
11,510	11,316

Table 5
Comparison of Hemoglobin and Ferritin Levels

Days	Hemoglobin Comm. #2	Hemoglobin New Iron Dextran	Ferritin Comm. #2	Ferritin New Iron Dextran
0	10.7	10.3	122.8	104.1
7	10.9	11.1	255.5	619.8
14	11.3	11.2	205.8	233.8
21	11.0	11.4	186.8	213.3
28	11.0	11.4	194.5	193.2

Example 5

Comparison of Biological Equivalence Between INFeD® and DEXFERRUM®

To examine the pharmacokinetics of iron dextran in hemodialysis patients, we serially determined iron dextran concentrations in the serum of 20 patients after 100 mg IV (intravenous) iron dextran was administered. By this study, we determined whether treatment with DEXFERRUM® versus INFeD® was biologically equivalent for the pharmacokinetic parameters, since DEXFERRUM® is an iron dextran preparation, according to the process of the present invention. DEXFERRUM® has a higher average molecular weight than INFed®, *i.e.*, about 300,000 daltons to 180,000 daltons. The clinical design was a 2-period crossover study with patients randomized to receive either DEXFERRUM® followed by INFed® or INFeD® followed by DEXFERRUM®. Blood samples were obtained at specified times after the end of drug infusion.

A comparison of the results for area-under-the-curve suggested a statistically significant difference between the two treatments, with no statistically significant difference in the observed maximum blood concentration. Analysis of secondary parameters, suggested a statistically significant difference in the half-lives, but no difference in the volumes observed for the two treatments.

Iron deficiency in dialysis-associated anemia is heralded by a falling hematocrit, or increasing Epoetin alfa requirements to maintain target hematocrit, coupled with a declining serum transferrin saturation and serum ferritin. See, *e.g.*, Van Wyck DB, Iron Balance in Dialysis Patients, Healthmark, New York (1989); Eschbach, J. W. *et al.*, *Ann. Intern. Med.* 11:992 (1989); McEvory, G. K. ed. AHES: Drug Information '92, American Society of Hospital Pharmacists, pages 766-768 (1992); and Gimenez, L. F. *et al.*, *Hematology/Oncology Clinics* 8:913 (1995).

Unfortunately, oral iron supplements do not reliably restore iron balance, probably because intestinal absorption of low doses is limited, high doses promote GI toxicity and noncompliance, and any benefit to body iron balance is outstripped by iron deficits due to dialysis-associated or pathologic blood loss. When oral supplementation fails to prevent iron deficiency in dialysis-associated anemia, therapy with intravenous iron dextran is indicated. See, Eschbach, J.W. *et al.*, cited above; and Van Wyck, D. B., *et al.*, *Kid. Int.* 35:712 (1989).

The effective bioavailability of iron dextran given intravenously depends on clearance of the iron dextran colloid from the plasma space. Previous information in patients with normal renal function has shown that radiolabelled iron dextran after IV administration is removed from the plasma by the reticuloendothelial system. See, Eschbach, J.W. *et al.*, and Henderson, *et al.*, cited above. Though iron deficiency in patients with dialysis-associated anemia is a frequent indication for iron dextran therapy, information on pharmacokinetics of iron dextran in patients with renal failure is lacking. Nor are data available describing pharmacokinetics of an unlabelled product.

The physiologic response to anemia in individuals with normal renal function is characterized by increased production of erythropoietin by the kidney. In chronic renal failure, erythropoietin production fails, and progressive anemia routinely ensues. Prior to the

introduction of recombinant human erythropoietin (in North America, Epoetin alfa; produced by Amgen and OrthoBiotech), virtually all chronic hemodialysis patients suffered dialysis-associated anemia, and 25 % required frequent transfusions to maintain the hematocrit in a life-sustaining range.

The use of Epoetin alfa successfully reverses transfusion dependency and raises hemoglobin and hematocrit into a range compatible with health. Nevertheless, the therapeutic efficacy of Epoetin alfa is frequently thwarted in practice by the development of iron deficiency. Iron deficiency in dialysis-associated anemia is heralded by a falling hematocrit, or an increasing Epoetin alfa requirement to maintain target hematocrit, coupled with a declining serum transferrin saturation and serum ferritin.

Several other factors also contribute to the ongoing negative iron balance experienced by hemodialysis patients. First and foremost, the dialysis procedure itself is associated with blood loss, from the needle stick and from retention of red cells within the dialyzer microtubules. Though the volume lost with each dialysis is small, the cumulative loss of iron is estimated to amount to greater than 1 gram annually. Since the diet of the dialysis patient is restricted by prescription in the foods richest in iron (red meat), little iron is available to dialysis patients from nutritional sources.

Oral iron is commonly prescribed. However, despite the observation that intestinal iron absorption in chronic renal failure is intact, meals, antacids, a multiplicity of medications, and a high incidence of gastritis and constipation conspire against the effectiveness of oral iron supplements. Iron deficiency marked initially by a fall in ferritin level, followed by a drop in the transferrin saturation, and eventually, as iron deficiency erythropoiesis slows red cell production, by iron deficiency anemia or an increasing demand for Epoetin alfa. When oral supplementation fails to prevent

iron deficiency in dialysis-associated anemia, therapy with intravenous iron dextran is indicated.

Evidence in patients with iron deficiency anemia and normal renal function suggests that recovery of iron for hemoglobin synthesis or iron stores early after intravenous iron dextran infusion is incomplete. Our previous retrospective analysis in patients with dialysis-associated anemia confirmed that quantitative iron utilization for hemoglobin or ferritin-related stores is highly variable and incomplete within the first 90 days after iron dextran infusion.

To forestall declining hematocrit or increasing Epoetin alfa doses, iron dextran is administered early in iron deficiency, whenever the ferritin falls below 100 ug/L or the transferrin saturation falls below 20 %. Our data confirm that, when iron dextran is given in this early stage of iron deficiency, when storage iron depletion is present but worsening anemia or Epoetin alfa resistance has not yet occurred, therapeutic efficacy is marked by a rise in serum ferritin, signifying repletion of iron stores, without a concomitant increase in hemoglobin.

In the current study, we examined iron utilization after infusion of five 100 mg infusions of iron dextran, INFeD®, in iron deficient patients receiving Epoetin alfa for dialysis-associated anemia. We compared results with those seen in patients after an equimolar dose of iron dextran, DEXFERRUM®. The 500 mg is a standard therapeutic dose for iron deficiency in iron anemic dialysis patients.

This was an active treatment control study using a randomized, unblinded design. The purpose of the study was to determine whether treatment with DEXFERRUM®, when compared with INFeD®, is biologically equivalent for hemoglobin synthesis and ferritin-related stores in patients undergoing hemodialysis for end-stage renal disease who meet the requirements for parenteral iron supplementation. The primary study outcome was the percent mobilization of iron from iron dextran. Results

after iron dextran INFeD® (Schein Pharmaceuticals, Phoenix, AZ) were compared to those after equimolar administration of DEXFERRUM® (Luitpold Pharmaceuticals, Shirley, NY).

Secondary study outcomes included serum ferritin, total body iron, hemoglobin, serum iron, total iron binding capacity (TIBC), and serum transferrin saturation. We also examined adverse events after administration of each test dose and each therapeutic dose of iron dextran, and compared results after DEXFERRUM® to those after INFeD®. Five (5) single 100 mg IV doses (total dose: 500 mg) of each drug were administered to the patients in each group during five sequential dialysis sessions (see Figure 1 in section titled "Study Design").

Example 6

Iron Mobilization Early After Iron Dextran Infusion in Hemodialysis Patients

To determine the reliability of serum iron indices and the degree of iron utilization early after iron dextran infusion, we measured iron status before and at weekly intervals after a total course of 500 mg IV iron dextran INFeD® in 11 iron-deficient patients receiving chronic hemodialysis and Epoetin alfa for dialysis associated anemia. Oral iron therapy was withheld and evidence of bleeding, infection, inflammation, recent surgery or transfusions was absent. Mobilization was calculated by expressing the increase in body iron as a percent of total iron administered (Van Wyck, *et al.* cited above):

Iron stores = 400 x [log(ferritin) - log(3)]

Red cell iron = 150 x (Hbg)

% Mobilization = $\{[(A_0-A_1)!(B_0-B_1)]/500\}$ = 100%

where A_0 and B_0 are values for stores and red cell iron, respectively, at time zero, and A_1 and B_1 are values at intervals afterwards. Results ± SD) are as follows in Table 6:

Table 6				
Day	Hgb	%Saturation	Ferritin	%Mobilization
0	10.8 ± 0.9	17.2 ± 7.4	104.7 ± 84	-
7	11.1 ± 1.1	22.1 ± 9.5	215.6 ± 107	38.6 ± 26
14	11.6 ± 1.0	19.9 ± 7.6	198.6 ± 108	50.8 ± 29
21	11.2 ± 1.0	20.1 ± 7.1	176.7 ± 102	32.7 ± 28
29	11.3 ± 0.9	18.9 ± 6.9	182.9 ± 117	37.8 ± 25

The increase in hemoglobin and ferritin was statistically significant (< 0.02). Thus, in the presence of Epoetin alfa therapy, 1) ferritin and hemoglobin rise quickly after IV iron dextran, and 2) an early rise in transferrin saturation is transient, due to early incorporation of iron into hemoglobin and iron stores, 3) which is, in the first four weeks, highly variable and predictably incomplete. Accordingly, decisions to repeat iron dextran therapy based on low transferrin saturation should be weighed against the observation that, within the first month after IV administration, most of the original iron dose remains physiologically unavailable.

Based on the foregoing discussion and experimental data, one skilled in the art would readily be able to modify the production processes in order to optimize reaction and administration conditions for particular compositions of iron dextran. Thus, the following claims should be considered as defining our invention, rather than the foregoing specific examples. All articles and patent references are hereby incorporated by reference in their entireties.

Claims

What we claim is:

1. An iron-dextran composition for treating iron deficiency comprising an aqueous colloidal suspension or solution of a ferric oxyhydroxide-dextran complex in a physiologically acceptable carrier, said complex having a beta-FeO(OH) core and an average molecular weight range of about 100,000 to 600,000 daltons and a substantially uniform size distribution, said complex further having been treated under alkaline conditions with a low molecular weight stabilizing agent and having an increased plasma residence time as compared with iron-dextran compositions that have not been so treated.

2. The composition of claim 1, wherein said low molecular weight stabilizing agent is an oxidized low molecular weight carbohydrate.

3. The composition of claim 1, wherein said average molecular weight is about 150,000 to 350,000 daltons.

4. The composition of claim 1, wherein said average molecular weight is about 250,000 to 300,000 daltons.

5. The composition of claim 4, wherein said complex has the shape of an ellipsoid.

6. The composition of claim 5, wherein said ellipsoid has an average length of about 25 to 45 nanometers and a width of about 3.5 to 5.5 nanometers.

7. The composition of claim 6, wherein said ellipsoid has an average length of about 31.5 to 36.5 nanometers and a width of about 4 to 5 nanometers.

8. The composition of claim 1, wherein the iron component of said complex is contributed by an initial iron dextran preparation having particles with a molecular weight ranging from about 100,000 to 600,000 daltons and the low molecular weight stabilizing agent component of said complex is contributed by an oxidized dextran of low molecular weight ranging from about 1,000 to 15,000 daltons.

9. The composition of claim 8, wherein said oxidized dextran has a molecular weight of about 6,000 daltons.

10. The composition of claim 8, wherein the pH is adjusted to about 5.2 to 6.5.

13. The composition of claim 11, wherein said core is formed during the neutralization of an acidic ferric chloride/dextran solution with an alkali.

14. A method for making an iron dextran composition for treating iron deficiency, comprising the steps of:

preparing an iron dextran suspension, said suspension comprised of iron dextran particles having a beta-FeO(OH) core;

purifying said composition by the removal of contaminants and by-products inconsistent with administration to mammalian patients;

reacting said iron dextran complex under alkaline conditions with an oxidized low molecular weight carbohydrate stabilizing agent; and

purifying the iron dextran composition in the form of iron-dextran complexes, said complexes having an increased plasma residence time as compared with iron-dextran compositions that have not been so treated.

15. A method for reducing anemia in a human or animal subject comprising the administration of a pharmacetucially acceptable dose of the composition of claim 1.

16. A method for reducing anemia in a human or animal subject comprising the administration of a pharmacetucially acceptable dose of the composition of claim 31.

17. A stable injectable iron dextran solution prepared by the method of claim 14.

18. The method of claim 14, wherein said stabilizing agent is selected from the group consisting of mannitol, sorbitol, glycerol, inositol, ascorbate, dextrin, cellulose, carboxymethyl cellulose, starch, hydroxyethylstarch, heparin, dextran, dextran sulfate, carboxylmethylated dextran and dextran 1 (Pharmacia, Inc.).

19. The method of claim 18, wherein said stabilizing agent is dextran.

20. The method of claim 19, wherein said dextran has an average molecular weight in the range from about 1,000 to 15,000 daltons.

21. The method of claim 20, wherein said dextran has an average molecular weight of about 6,000 daltons.

22. The method of claim 14, wherein the pH of the composition is adjusted to about 5.2 to 6.5.

23. The method of claim 14, wherein said complexes have an average molecular weight in the range from about 150,000 to 350,000 daltons.

24. The method of claim 23 wherein said average molecular weight is about 250,000 to 300,000 daltons.

25. The method of claim 18, wherein said complexes have the shape of an ellipsoid.

26. The method of claim 25, wherein said ellipsoid has an average length of about 25 to 45 nanometers and a width of about 3.5 to 5.5 nanometers.

27. The method of claim 26, wherein said ellipsoid has an average length of about 31.5 to 36.5 nanometers and a width of about 4 to 5 nanometers.

28. An iron-dextran composition produced by the process of claim 14.

29. The composition of claim 28, wherein said composition is formulated for parenteral human administration in a physiologically acceptable carrier.

30. The composition of claim 1, wherein said stabilizing agent is selected from the group consisting of mannitol, sorbitol, glycerol, inositol, ascorbate, dextrin, cellulose, carboxymethyl cellulose, starch, hydroxyethylstarch, heparin, dextran, dextran sulfate, carboxylmethylated dextran and dextran 1 (Pharmacia, Inc.).

31. The composition of claim 30, wherein said stabilizing agent is dextran.

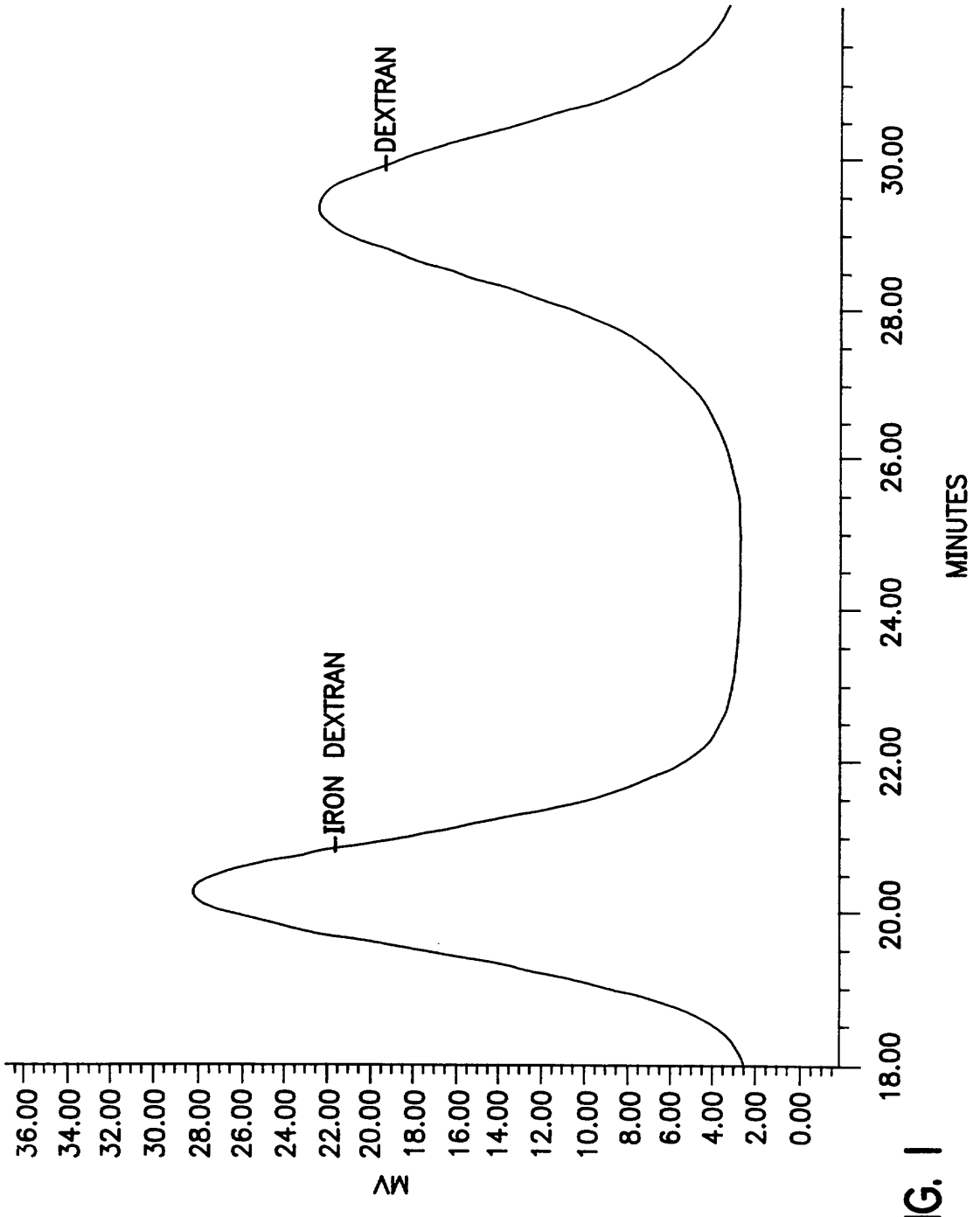


FIG. 1

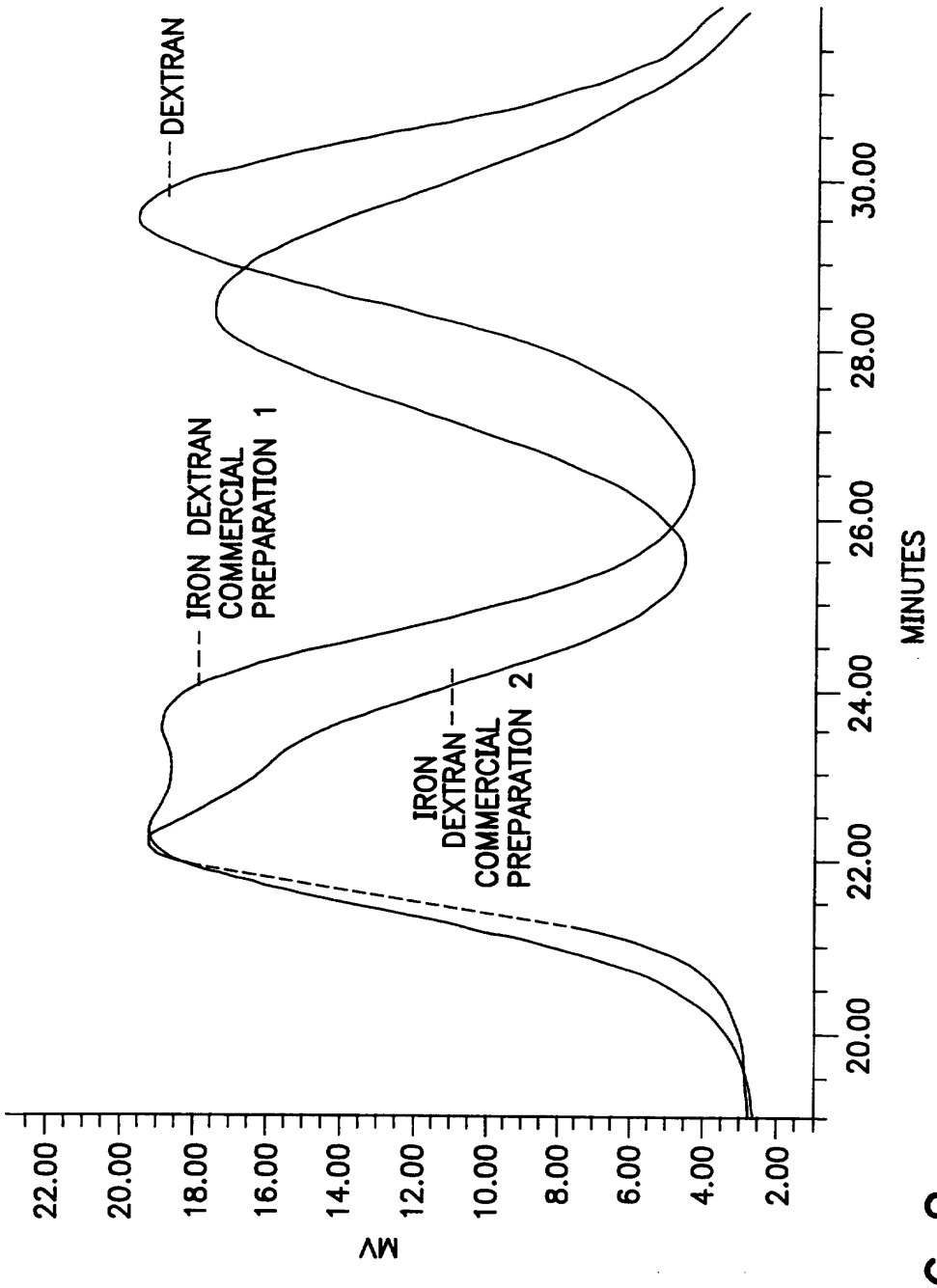


FIG. 2

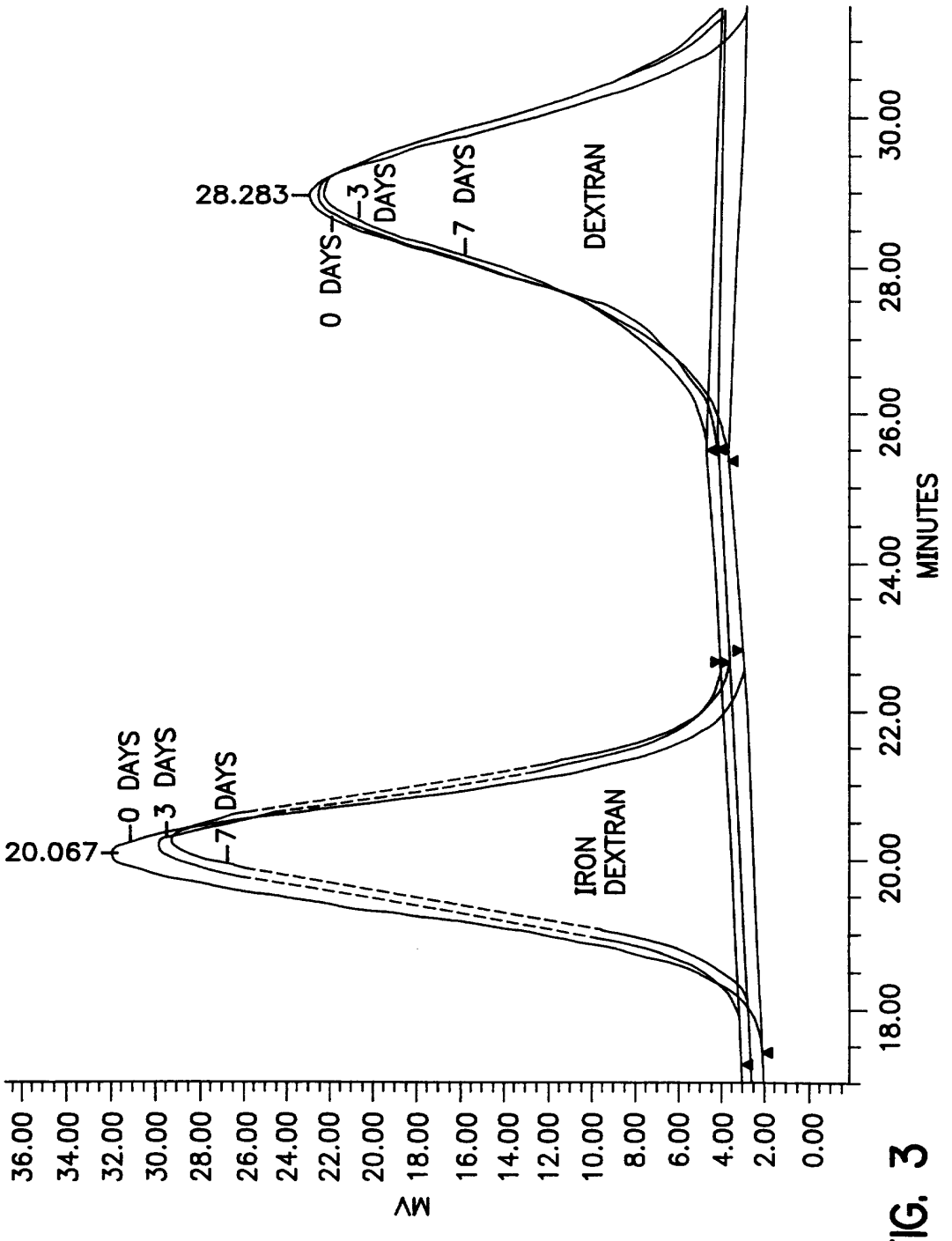


FIG. 3

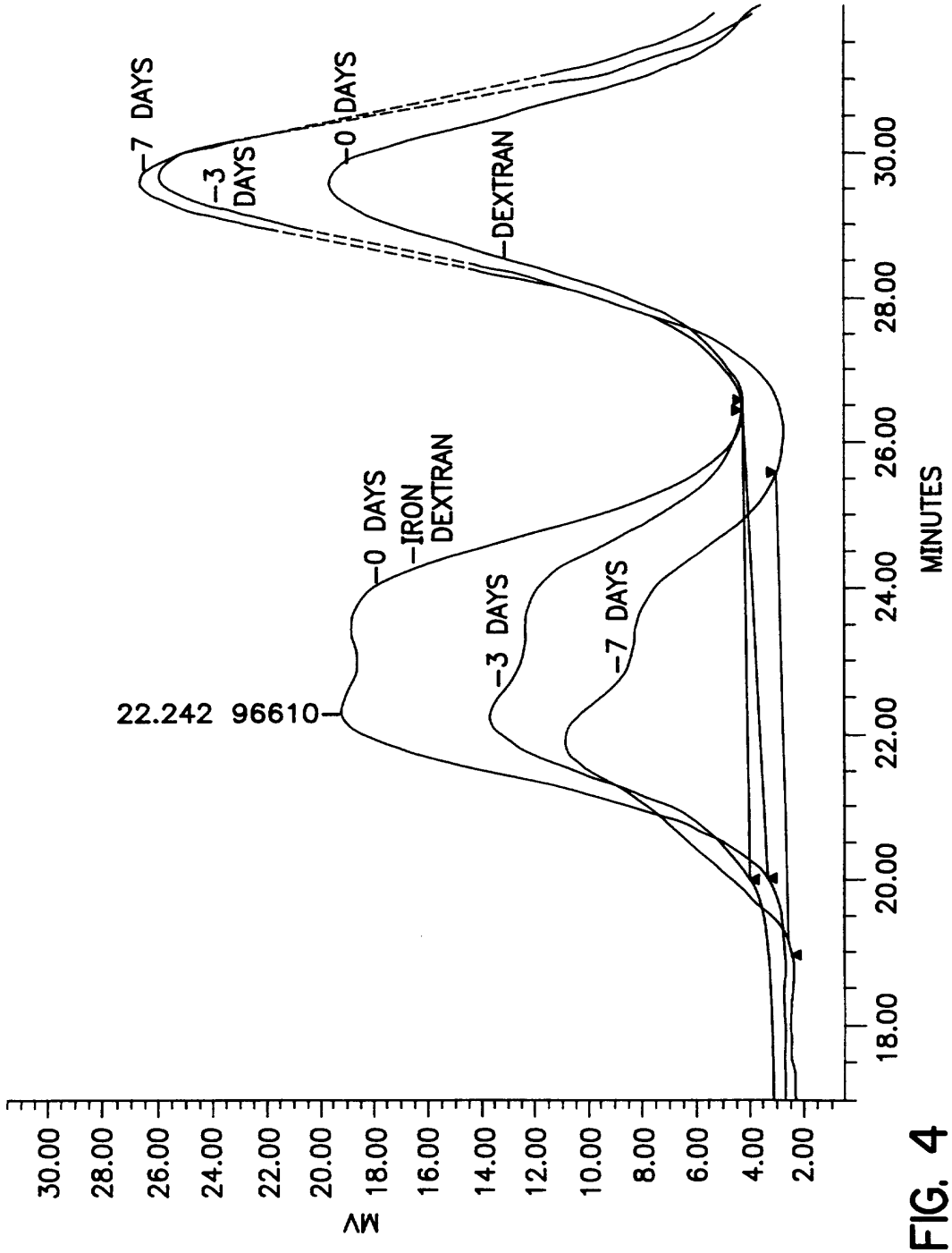


FIG. 4

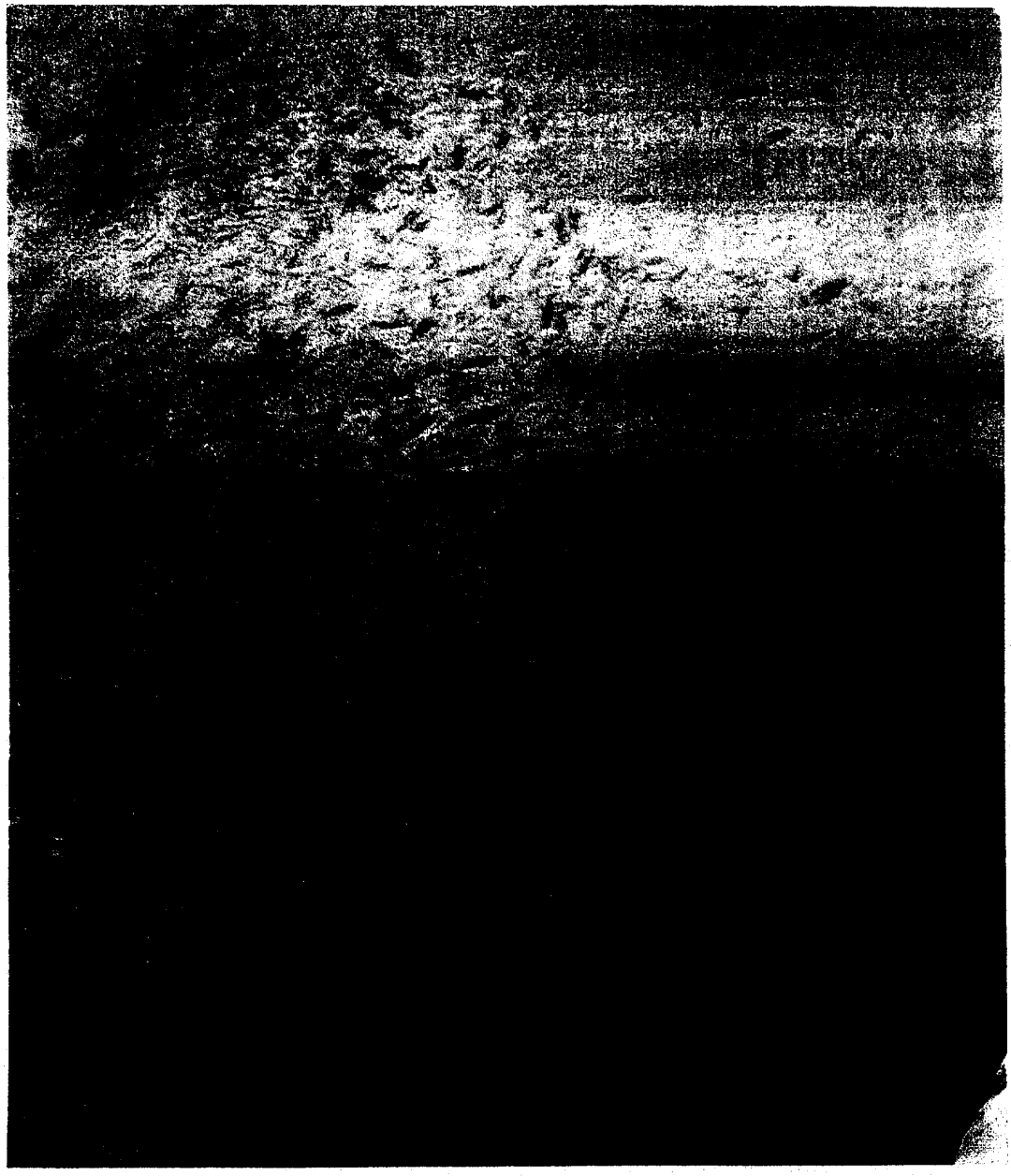


FIG. 5

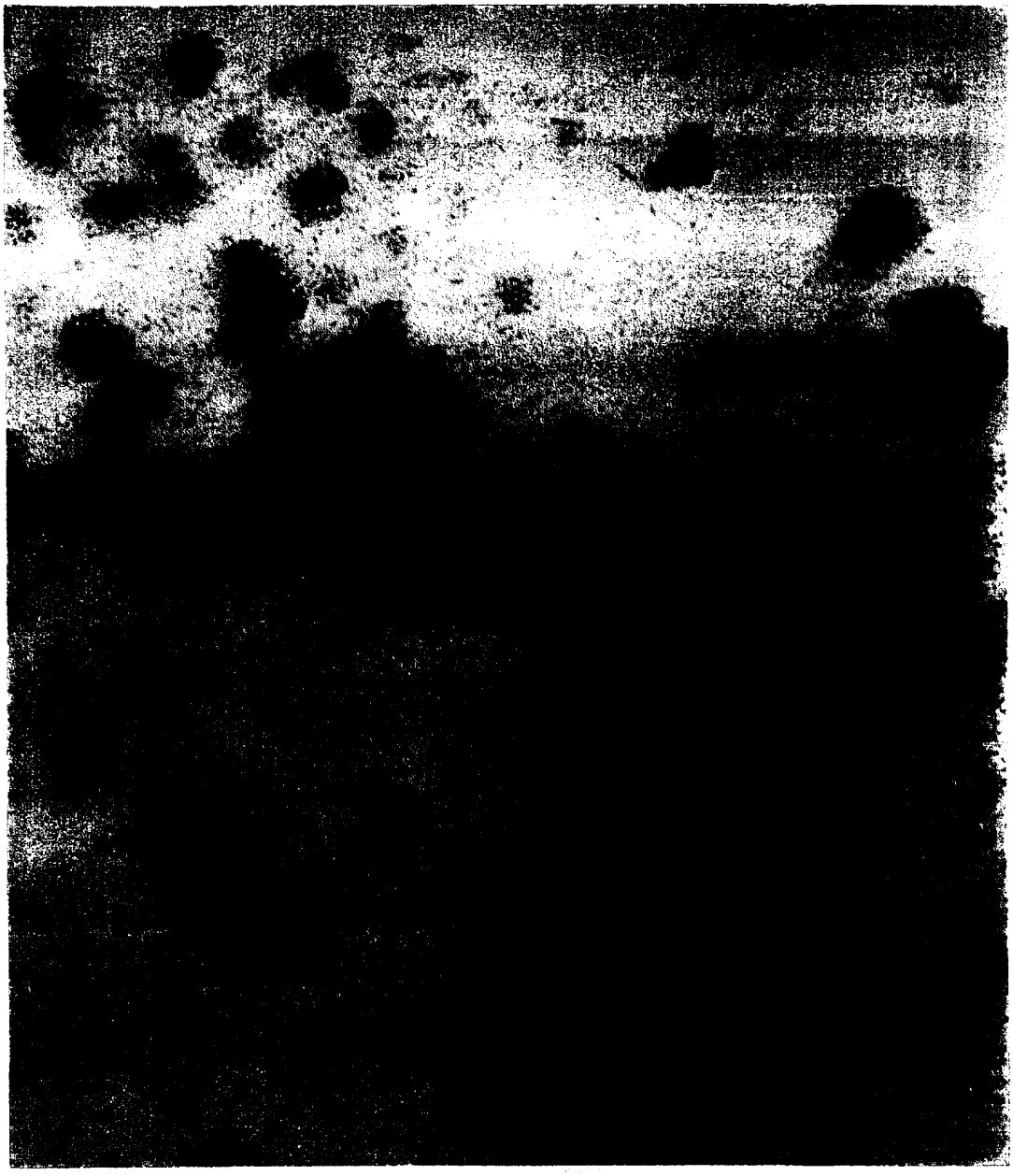


FIG. 6

INTERNATIONAL SEARCH REPORT

Int[illegible]ional application No.
PCT/US96/14153

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 33/26, 9/10
US CL :424/494, 547, 548
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/ 547, 548

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US RE 24,642 E (LONDON ET AL) 28 April 1959, see Examples 1-3.	1-10, 14, 15, 17-31
Y	US 3,908,004 A (KITCHING) 23 September 1975, see entire document.	1-10, 14, 15, 17-31
Y	US 3,686,397 A (MULLER) 22 August 1972, see entire document.	1-10, 14, 15, 17-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
24 OCTOBER 1996

Date of mailing of the international search report
03 JAN 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
IW for
PETER KULKOSKY
Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/14153

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 16
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
6. Mai 2004 (06.05.2004)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2004/037865 A1

(51) Internationale Patentklassifikation[7]: C08B 31/18, 30/18, A61K 33/26, 47/48, 31/295

(21) Internationales Aktenzeichen: PCT/EP2003/011596

(22) Internationales Anmeldedatum:
20. Oktober 2003 (20.10.2003)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
102 49 552.1 23. Oktober 2002 (23.10.2002) DE

(71) Anmelder *(für alle Bestimmungsstaaten mit Ausnahme von US)*: **VIFOR (INTERNATIONAL) AG** [CH/CH]; Rechenstrasse 37, CH-9001 St. Gallen (CH).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: **GEISSER, Peter** [CH/CH]; Marweesstrasse 8, CH-9014 St. Gallen (CH). **PHILIPP, Erik** [CH/CH]; Grüntalstr. 8, CH-9303 Wittenbach (CH).

(74) Anwalt: **GILLE HRABAL STRUCK NEIDLEIN PROP ROOS**; Brucknerstr. 20, 40593 Düsseldorf (DE).

(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *mit internationalem Recherchenbericht*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** WATER-SOLUBLE IRON-CARBOHYDRATE COMPLEXES, PRODUCTION THEREOF, AND MEDICAMENTS CONTAINING SAID COMPLEXES

(54) **Bezeichnung:** WASSERLÖSLICHE EISEN-KOHLENHYDRAT-KOMPLEXE, DEREN HERSTELLUNG UND DIESE ENTHALTENDE ARZNEIMITTEL

(57) **Abstract:** Disclosed is a water-soluble iron-carbohydrate complex obtained from an aqueous iron(III)-salt solution and an aqueous solution of the product obtained by oxidizing one or several maltodextrins with an aqueous hypochlorite solution at an alkaline pH value. The dextrose equivalent of the maltodextrin ranges from 5 to 20 if a single maltodextrin is used while the dextrose equivalent of the mixture of several maltodextrins ranges from 5 to 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture ranges from 2 to 40 if a mixture of several maltodextrins is used. Also disclosed are a method for the production of said complex and medicaments for the treatment and prophylaxis of iron deficiencies.

(57) **Zusammenfassung:** Wasserlöslicher Eisen-Kohlenhydrat-Komplex, erhältlich aus einer wässrigen Eisen(III)-Salzlösung und einer wässrigen Lösung des Produktes der Oxidation von einem oder mehreren Maltodextrinen mit einer wässrigen Hypochloritlösung bei alkalischem pH-Wert, wobei beim Einsatz von einem Maltodetrin dessen Dextrose-Äquivalent bei 5 bis 20 und beim Einsatz eines Gemisches aus mehreren Maltodextrinen das Dextrose-Äquivalent des Gemisches bei 5 bis 20 und das Dextrose-Äquivalent jedes am Gemisch beteiligten einzelnen Maltodextrins bei 2 bis 40 liegt, Verfahren zu dessen Herstellung und Arzneimittel zur Behandlung und Prophylaxe von Eisenmangelzuständen.

WO 2004/037865 A1

Wasserlösliche Eisen-Kohlenhydrat-Komplexe, deren Herstellung und diese enthaltende Arzneimittel

Gegenstand der vorliegenden Erfindung sind wasserlösliche Eisen-Kohlenhydrat-Komplexe, die zur Therapie von Eisenmangelanämien geeignet sind, sowie deren Herstellung, diese enthaltende Arzneimittel und deren Verwendung bei der Prophylaxe oder Therapie von Eisenmangelanämien. Die Arzneimittel sind insbesondere zur parenteralen Anwendung geeignet.

Durch Eisenmangel bedingte Anämien können durch Verabreichung von eisenhaltigen Arzneimitteln therapiert oder prophylaktisch behandelt werden. Hierzu ist der Einsatz von Eisen-Kohlenhydrat-Komplexen bekannt. Ein in der Praxis häufig erfolgreich angewandtes Präparat basiert auf einem wasserlöslichen Eisen(III)-Hydroxid-Saccharose-Komplex (Danielson, Salmonson, Derendorf, Geisser, Drug Res., Vol. 46 : 615 – 621, 1996). Im Stand der Technik werden zur parenteralen Verabreichung auch Eisen-Dextran-Komplexe sowie Komplexe auf der Basis schwer zugänglicher Pullulane (WO 02/46241), die unter Druck bei hohen Temperaturen und unter Einbeziehung von Hydrierschritten hergestellt werden müssen, beschrieben. Weitere Eisen-Kohlenhydrat-Komplexe sind zur oralen Verabreichung geläufig.

Die vorliegende Erfindung hat sich die Aufgabe gestellt, ein bevorzugt parenteral verabreichbares Eisenpräparat zur Verfügung zu stellen, das sich vergleichsweise einfach sterilisieren lässt; die bisherigen auf Saccharose bzw. Dextran basierenden parenteral verabreichbaren Präparate waren nämlich nur bei Temperaturen bis zu 100°C stabil, wodurch die Sterilisation erschwert wurde. Darüber hinaus soll das erfindungsgemäß bereitzustellende Präparat eine verringerte Toxizität aufweisen und die gefährlichen durch Dextran induzierbaren anaphylaktischen Schocks vermeiden. Auch soll das bereitzustellende

Präparat eine hohe Komplexstabilität aufweisen, so dass eine hohe Applikationsdosis bzw. eine hohe Applikationsgeschwindigkeit ermöglicht werden. Auch soll das Eisenpräparat aus einfach erhältlichen Ausgangsprodukten ohne besonderen Aufwand herstellbar sein.

Es hat sich gezeigt, dass diese Aufgabe gelöst wird, durch Eisen(III)-Kohlenhydrat-Komplexe auf der Basis der Oxidationsprodukte von Maltodextrinen. Einen Gegenstand der Erfindung bilden daher wasserlösliche Eisen-Kohlenhydrat-Komplexe, die erhältlich sind aus einer wässrigen Eisen(III)-Salzlösung und einer wässrigen Lösung des Produktes der Oxidation von einem oder mehreren Maltodextrinen mit einer wässrigen Hypochloritlösung bei einem alkalischen pH-Wert von z.B. 8 bis 12, wobei beim Einsatz von einem Maltodetrin dessen Dextrose-Äquivalent bei 5 bis 20 und beim Einsatz eines Gemisches aus mehreren Maltodextrinen das Dextrose-Äquivalent des Gemisches bei 5 bis 20 und das Dextrose-Äquivalent der am Gemisch beteiligten einzelnen Maltodextrine bei 2 bis 40 liegt.

Einen weiteren Gegenstand der Erfindung bildet ein Verfahren zur Herstellung der erfindungsgemäßen Eisen-Kohlenhydrat-Komplexe, bei dem man ein oder mehrere Maltodextrine in wässriger Lösung bei einem alkalischen pH-Wert von z.B. 8 bis 12 mit einer wässrigen Hypochloritlösung oxidiert und die erhaltene Lösung mit der wässrigen Lösung eines Eisen(III)-Salzes umsetzt, wobei beim Einsatz von einem Maltodextrin dessen Dextrose-Äquivalent bei 5 bis 20 und beim Einsatz eines Gemisches aus mehreren Maltodextrinen das Dextrose-Äquivalent des Gemisches bei 5 bis 20 und das Dextrose-Äquivalent der am Gemisch beteiligten einzelnen Maltodextrine bei 2 bis 40 liegt.

Die verwendbaren Maltodextrine sind leicht zugängliche Ausgangsprodukte, die im Handel erhältlich sind.

Zur Herstellung der Liganden der erfindungsgemäßen Komplexe werden die Maltodextrine in wässriger Lösung mit Hypochloritlösung oxidiert.

Geeignet sind beispielsweise Lösungen von Alkalihypochloriten, wie Natriumhypochloritlösung. Es können handelsübliche Lösungen eingesetzt werden. Die Konzentrationen der Hypochlorit-Lösungen liegen beispielsweise bei mindestens 13 Gew.-%, bevorzugt in der Größenordnung von 13 bis 16 Gew.-% jeweils berechnet als aktives Chlor. Die Lösungen werden bevorzugt in einer derartigen Menge eingesetzt, dass etwa 80 bis 100 %, bevorzugt etwa 90 % einer Aldehydgruppe pro Maltodextrinmolekül oxidiert werden. Auf diese Weise wird das durch die Glucoseanteile der Maltodextrinmoleküle bedingte Reduktionsvermögen auf etwa 20 % oder darunter, bevorzugt 10 % oder darunter verringert.

Die Oxidation erfolgt in alkalischer Lösung, beispielsweise bei pH-Werten von 8 bis 12, z.B. 9 bis 11. Zur Oxidation kann beispielsweise bei Temperaturen in der Größenordnung von 15 bis 40°C, bevorzugt 25 bis 35°C gearbeitet werden. Die Reaktionszeiten liegen beispielsweise in der Größenordnung von 10 Minuten bis 4 Stunden, z.B. 1 bis 1,5 Stunden.

Durch die beschriebene Verfahrensweise wird der Grad der Depolymerisation der eingesetzten Maltodextrine auf einem Minimum gehalten. Ohne eine bindende Theorie abzugeben, wird angenommen, dass die Oxidation vorwiegend an der endständigen Aldehydgruppe (bzw. Acetal- oder Halbacetalgruppe) der Maltodextrinmoleküle erfolgt.

Es ist auch möglich, die Oxidationsreaktion der Maltodextrine zu katalysieren. Geeignet hierzu ist der Zusatz von Bromidionen, z.B. in der Form von Alkalibromiden, beispielsweise Natriumbromid. Die zugesetzte Menge an Bromid ist nicht kritisch. Sie wird möglichst gering gehalten, um ein möglichst leicht zu reinigendes Endprodukt (Fe-Komplex) zu erhalten. Es genügen katalytische Mengen. Wie erwähnt, ist der Zusatz von Bromid zwar möglich, aber nicht erforderlich.

Darüber hinaus ist es beispielsweise auch möglich, das bekannte ternäre Oxidationssystem Hypochlorit/Alkalibomid/2,2,6,6-Tetramethylpiperidin-1-oxyl (TEMPO) zur Oxidation der Maltodextrine zu verwenden. Die

Verfahrensweise Maltodextrine unter Katalyse von Alkalibromiden bzw. mit dem ternären TEMPO-System zu oxidieren, wird beispielsweise von Thaburet et al. in Carbohydrate Research 330 (2001) 21 – 29 beschrieben; die dort beschriebene Verfahrensweise ist erfindungsgemäß anwendbar.

Zur Herstellung der erfindungsgemäßen Komplexe werden die erhaltenen oxidierten Maltodextrine in wässriger Lösung mit einem Eisen(III)-Salz umgesetzt. Hierzu können die oxidierten Maltodextrine isoliert und erneut gelöst werden; die erhaltenen wässrigen Lösungen der oxidierten Maltodextrine können jedoch auch direkt zur Weiterverarbeitung mit wässrigen Eisen(III)-Lösungen verwendet werden.

Als Eisen(III)-Salze können wasserlösliche Salze anorganischer oder organischer Säuren oder Mischungen davon verwendet werden, wie Halogenide, z.B. Chlorid und Bromid, oder Sulfate. Bevorzugt werden physiologisch unbedenkliche Salze verwendet. Besonders bevorzugt wird eine wässrige Lösung von Eisen(III)-Chlorid verwendet.

Es hat sich gezeigt, dass sich die Anwesenheit von Chloridionen günstig auf die Komplexbildung auswirkt. Letztere können beispielsweise in der Form von wasserlöslichen Chloriden, wie Alkalimetallchloriden, z.B. Natriumchlorid, Kaliumchlorid oder Ammoniumchlorid, zugesetzt werden. Bevorzugt wird, wie erwähnt, das Eisen(III) in der Form des Chlorids eingesetzt.

Zur Umsetzung kann beispielsweise die wässrige Lösung des oxidierten Maltodextrins mit einer wässrigen Lösung des Eisen(III)-Salzes vermischt werden. Dabei wird bevorzugt so gearbeitet, dass der pH-Wert des Gemisches aus oxidiertem Maltodextrin und Eisen(III)-Salz beim und unmittelbar nach dem Vermischen zunächst stark sauer ist, bzw. so niedrig ist, dass keine Hydrolyse des Eisen(III)-Salzes auftritt, z.B. 2 oder darunter beträgt, um eine unerwünschte Ausfällung von Eisenhydroxiden zu vermeiden. Beim Einsatz von Eisen(III)-Chlorid ist im allgemeinen kein Säurezusatz erforderlich, da wässrige Lösungen von Eisen(III)-Chlorid selbst ausreichend sauer sein können. Nach dem erfolgten Vermischen

kann der pH-Wert beispielsweise auf Werte in der Größenordnung von gleich oder größer als 5, beispielsweise bis zu 11, 12, 13 oder 14 angehoben werden. Das Anheben des pH-Wertes erfolgt bevorzugt langsam bzw. allmählich, was beispielsweise dadurch erfolgen kann, dass zunächst eine schwache Base zugesetzt wird, beispielsweise bis zu einem pH von etwa 3; anschließend kann dann mit einer stärkeren Base weiter neutralisiert werden. Als schwache Base kommen beispielsweise Alkali- oder Erdalkalicarbonate, -bicarbonate, wie Natrium- und Kaliumcarbonat oder –bicarbonat oder Ammoniak infrage. Starke Basen sind beispielsweise Alkali- oder Erdalkalihydroxide, wie Natrium-, Kalium-, Calcium- oder Magnesiumhydroxid.

Die Umsetzung kann durch Erwärmen begünstigt werden. Beispielsweise können Temperaturen in der Größenordnung von 15°C bis zur Siedetemperatur angewendet werden. Es ist bevorzugt, die Temperatur allmählich zu steigern. So kann beispielsweise zunächst auf etwa 15 bis 70°C erwärmt und allmählich bis zum Sieden gesteigert werden.

Die Reaktionszeiten liegen beispielsweise in der Größenordnung von 15 Minuten bis zu mehreren Stunden, z.B. 20 Minuten bis 4 Stunden, beispielsweise bei 25 bis 70 Minuten, z.B. 30 bis 60 Minuten.

Die Umsetzung kann im schwach sauren Bereich, beispielsweise bei pH-Werten in der Größenordnung von 5 bis 6, erfolgen. Es hat sich aber gezeigt, dass es zweckmäßig, wenn auch nicht erforderlich ist, den pH-Wert im Verlauf der Komplexbildung auf höhere Werte, bis zu 11, 12, 13 oder 14 anzuheben. Zur Fertigstellung der Reaktion kann der pH-Wert dann durch Säurezusatz weiter gesenkt werden, beispielsweise auf die genannte Größenordnung von 5 bis 6. Als Säuren können anorganische oder organische Säuren oder Gemische davon, insbesondere Halogenwasserstoffsäuren, wie Chlorwasserstoff bzw. wässrige Salzsäure eingesetzt werden.

Wie erwähnt, wird die Komplexbildung im allgemeinen durch Erwärmen begünstigt. Beispielsweise kann bei der bevorzugten Ausführungsform, bei

der der pH-Wert im Verlauf der Umsetzung auf Bereiche von über 5 hinaus bis zu 11 oder 14 gesteigert wird, zunächst bei niedrigen Temperaturen in der Größenordnung von 15 bis 70°C, z.B. 40 bis 60°C, z.B. etwa 50°C gearbeitet werden, worauf nach erneuter Verringerung des pH-Wertes beispielsweise auf Werte in der Größenordnung von mindestens 5, allmählich auf Temperaturen über 50°C bis zur Siedetemperatur erwärmt wird.

Die Reaktionszeiten liegen in der Größenordnung von 15 Minuten bis zu mehreren Stunden und können je nach Reaktionstemperatur variieren. Bei der Durchführung des Verfahrens unter zwischenzeitlicher Anwendung von pH-Werten, die über 5 liegen, kann beispielsweise 15 bis 70 Minuten, z.B. 30 bis 60 Minuten bei dem erhöhten pH-Wert, beispielsweise bei Temperaturen bis zu 70°C gearbeitet werden, worauf die Reaktion nach Absenken des pH-Wertes auf den Größenordnungsbereich von mindestens 5, weitere 15 bis 70 Minuten, z.B. 30 bis 60 Minuten bei Temperaturen bis zu beispielsweise 70°C und gegebenenfalls weitere 15 bis 70 Minuten, z.B. 30 bis 60 Minuten bei höheren Temperaturen bis zum Siedepunkt durchgeführt werden kann.

Nach erfolgter Umsetzung kann die erhaltene Lösung beispielsweise auf Raumtemperatur abgekühlt und gegebenenfalls verdünnt und gegebenenfalls filtriert werden. Nach dem Abkühlen kann der pH-Wert durch Zugabe von Säure oder Base auf den Neutralpunkt oder leicht darunter, beispielsweise auf Werte von 5 bis 7 eingestellt werden. Als Säuren oder Basen können beispielsweise die vorstehend zur Umsetzung genannten verwendet werden. Die erhaltenen Lösungen werden gereinigt und können direkt zur Herstellung von Arzneimitteln verwendet werden. Es ist aber auch möglich, die Eisen(III)-Komplexe aus der Lösung zu isolieren, beispielsweise durch Ausfällen mit einem Alkohol, wie einem Alkanol, beispielsweise Ethanol. Die Isolierung kann auch durch Sprühtrocknung erfolgen. Die Reinigung kann in üblicher Weise erfolgen, insbesondere zur Entfernung von Salzen. Dies kann z.B. durch Umkehrosmose erfolgen, wobei eine derartige Umkehrosmose z.B. vor der

Sprühtrocknung oder vor dem direkten Einsatz in Arzneimitteln durchgeführt werden kann.

Die erhaltenen Eisen(III)-Kohlenhydrat-Komplexe weisen beispielsweise einen Eisengehalt von 10 bis 40 % Gew./Gew., insbesondere 20 bis 35 % Gew./Gew. auf. Sie sind gut wasserlöslich. Man kann daraus neutrale wässrige Lösungen mit beispielsweise 1 % Gew./Vol. bis 20 % Gew./Vol. Eisengehalt herstellen. Diese Lösungen lassen sich thermisch sterilisieren. Das gewichtsmittlere Molekulargewicht Mw der so erhaltenen Komplexe beträgt beispielsweise 80 kDa bis 400 kDa, bevorzugt 80 bis 350 kDa, besonders bevorzugt bis zu 300 kDa (bestimmt mittels Gelpermeationschromatographie, beispielsweise wie von Geisser et al. in Arzneim. Forsch/Drug Res. 42(II), 12, 1439 – 1452 (1992), Absatz 2.2.5. beschrieben).

Wie erwähnt, lassen sich aus den erfindungsgemäßen Komplexen wässrige Lösungen erstellen. Diese sind insbesondere zur parenteralen Applikation geeignet. Sie können jedoch auch oral oder topisch angewendet werden. Im Gegensatz zu bisher üblichen parenteral verabreichbaren Eisenpräparaten können sie bei hohen Temperaturen, z. B. bei 121°C und darüber sterilisiert werden, bei kurzen Kontaktzeiten von beispielsweise etwa 15 Minuten unter Erreichen von $F_o \geq 15$. Bei höheren Temperaturen sind die Kontaktzeiten entsprechend kürzer. Bisher bekannte Präparate mussten bei Raumtemperatur steril filtriert und teilweise mit Konservierungsmitteln, wie Benzylalkohol oder Phenol versetzt werden. Derartige Zusätze sind erfindungsgemäß nicht nötig. Es ist möglich, die Lösungen der Komplexe beispielsweise in Ampullen abzufüllen. Beispielsweise lassen sich Lösungen von 1 bis 20 Gew.-%, beispielsweise 5 Gew.-% in Behälter, wie Ampullen oder Stechampullen (Vials) von beispielsweise 2 bis 100 ml, beispielsweise bis zu 50 ml abfüllen. Die Herstellung der parenteral verabreichbaren Lösungen kann in üblicher Weise, gegebenenfalls unter Mitverwendung von für parenterale Lösungen üblichen Zusätzen, erfolgen. Die Lösungen können so formuliert werden, dass sie als solche durch Injektion oder als Infusion, z.B. in Kochsalzlösung, verabreicht werden können. Zur oralen oder

topischen Verabreichung können Präparate mit entsprechenden üblichen Exzipienten und Hilfsmitteln formuliert werden.

Einen weiteren Gegenstand der Erfindung bilden daher wässrige Arzneimittel, die insbesondere zur parenteralen, intravenösen, aber auch intramuskulären Verabreichung, sowie zur oralen oder topischen Verabreichung, geeignet sind und insbesondere für die Behandlung von Eisenmangelanämien Verwendung finden können. Ein weiterer Gegenstand der Erfindung betrifft daher auch die Verwendung der erfindungsgemäßen Eisen(III)-Kohlenhydrat-Komplexe zur Behandlung und Prophylaxe von Eisenmangelanämien bzw. zur Herstellung von Arzneimitteln zur insbesondere parenteralen Behandlung von Eisenmangelanämien. Die Arzneimittel sind zum Einsatz in der Human- und der Veterinärmedizin geeignet.

Vorteile, die sich durch die erfindungsgemäßen Eisen-Kohlenhydrat-Komplexe ergeben, sind die bereits vorstehend erwähnten hohen Sterilisierungstemperaturen, die mit einer geringen Toxizität sowie einer verringerten Gefahr anaphylaktischer Schocks einhergehen. Die Toxizität der erfindungsgemäßen Komplexe ist sehr gering. Die LD_{50} liegt bei über 2000 mg Fe/Kg im Vergleich mit der LD_{50} der bekannten Pullulankomplexe, die bei 1400 mg Fe/Kg liegt. Durch die große Stabilität der erfindungsgemäß bereitgestellten Komplexe wird es möglich, die Applikationsgeschwindigkeiten sowie auch die Dosierungen zu erhöhen. Auf diese Weise wird es möglich, die erfindungsgemäßen Arzneimittel parenteral als Einmaldosis zu applizieren. Eine derartige Einmaldosis kann beispielsweise 500 bis 1000 mg Eisen betragen; sie kann beispielsweise im Verlauf von 1 Stunde appliziert werden. Ein weiterer Vorteil liegt in der leichten Verfügbarkeit der als Ausgangsprodukte verwendeten Maltodextrine, bei denen es sich z. B. um handelsübliche Zusätze der Nahrungsmittelindustrie handelt.

In der vorliegenden Beschreibung und den nachstehenden Beispielen werden die Dextrose-Äquivalente gravimetrisch bestimmt. Hierzu werden die Maltodextrine in wässriger Lösung mit Fehling'scher Lösung unter

Sieden umgesetzt. Die Umsetzung erfolgt quantitativ, d.h. bis keine Entfärbung der Fehling'schen Lösung mehr auftritt. Das ausgefällte Kupfer(I)-Oxid wird bei 105°C bis zur Gewichtskonstanz getrocknet und gravimetrisch bestimmt. Aus den erhaltenen Werten wird der Glucosegehalt (Dextrose-Äquivalent) als % Gew./Gew. der Maltodextrin-Trockensubstanz berechnet. Es kann beispielsweise mit folgenden Lösungen gearbeitet werden: 25 ml Fehling'sche Lösung I, vermischt mit 25 ml Fehling'scher Lösung II; 10 ml wässrige Maltodextrinlösung (10 % Mol/Vol) (Fehling'sche Lösung I: 34,6 g Kupfer(II)-Sulfat gelöst in 500 ml Wasser; Fehling'sche Lösung II: 173 g Kaliumnatriumtartrat und 50 g Natriumhydroxid, gelöst in 400 ml Wasser).

Beispiel 1

100 g Maltodextrin (9,6 Dextrose-Äquivalente, gravimetrisch bestimmt) werden bei 25°C unter Rühren in 300 ml Wasser gelöst und durch Zugabe von 30 g Natriumhypochloritlösung (13 bis 16 Gew.-% aktives Chlor) bei pH 10 oxidiert.

Zu 352 g Eisen(III)-Chloridlösung (12 % Gew./Gew. Fe) werden unter Rühren (Flügelrührer) bei Raumtemperatur zunächst die oxidierte Maltodextrinlösung und dann 554 g Natriumcarbonatlösung (17,3 % Gew./Gew.) zugegeben.

Danach wird durch Zugabe von Natronlauge ein pH von 11 eingestellt, die Lösung wird auf 50°C erwärmt und 30 Minuten bei 50°C gehalten. Danach wird durch Zugabe von Salzsäure auf einen pH von 5 bis 6 angesäuert, die Lösung weitere 30 Minuten bei 50°C gehalten und danach auf 97 – 98°C erhitzt und 30 Minuten bei dieser Temperatur gehalten. Nach Abkühlen der Lösung auf Raumtemperatur wird der pH-Wert durch Zusatz von Natronlauge auf 6 - 7 eingestellt.

Die Lösung wird sodann über einen Sterilfilter filtriert und auf Sedimente geprüft. Danach wird der Komplex durch Ausfällen mit Ethanol im Verhältnis 1 : 0,85 isoliert und im Vakuum bei 50°C getrocknet.

Man erhält 125 g (entsprechend 87 % d. Th.) eines braunen, amorphen Pulvers mit einem Eisengehalt von 29,3 % Gew./Gew. (komplexometrisch ermittelt).

Molekulargewicht Mw 271 kDa

Beispiel 2

200 g Maltodextrin (9,6 Dextrose-Äquivalente, gravimetrisch bestimmt) werden bei 25°C unter Rühren in 300 ml Wasser gelöst und durch Zugabe von 30 g Natriumhypochloritlösung (13 bis 16 Gew.-% aktives Chlor) bei pH 10 oxidiert.

Zu 352 g Eisen(III)-Chloridlösung (12 % Gew./Gew. Fe) werden unter Rühren (Flügelrührer) bei Raumtemperatur zunächst die oxidierte Maltrodextrinlösung und dann 554 g Natriumcarbonatlösung (17,3 % Gew./Gew.) zugegeben.

Danach wird durch Zugabe von Natronlauge ein pH von 11 eingestellt, die Lösung wird auf 50°C erwärmt und 30 Minuten bei 50°C gehalten. Danach wird durch Zugabe von Salzsäure auf einen pH von 5 bis 6 angesäuert, die Lösung weitere 30 Minuten bei 50°C gehalten und danach auf 97 – 98°C erhitzt und 30 Minuten bei dieser Temperatur gehalten. Nach Abkühlen der Lösung auf Raumtemperatur wird der pH-Wert durch Zusatz von Natronlauge auf 6 - 7 eingestellt.

Die Lösung wird sodann über einen Sterilfilter filtriert und auf Sedimente geprüft. Danach wird der Komplex durch Ausfällen mit Ethanol im Verhältnis 1 : 0,85 isoliert und im Vakuum bei 50°C getrocknet.

Man erhält 123 g (entsprechend 65 % d. Th.) eines braunen, amorphen Pulvers mit einem Eisengehalt von 22,5 % Gew./Gew. (komplexometrisch ermittelt).

Molekulargewicht Mw 141 kDa

Beispiel 3

100 g Maltodextrin (9,6 Dextrose-Äquivalente, gravimetrisch bestimmt) werden bei 25°C unter Rühren in 300 ml Wasser gelöst und durch Zugabe von 30 g Natriumhypochloritlösung (13 bis 16 Gew.-% aktives Chlor) und 0,7 g Natriumbromid bei pH 10 oxidiert.

Zu 352 g Eisen(III)-Chloridlösung (12 % Gew./Gew. Fe) werden unter Rühren (Flügelrührer) bei Raumtemperatur zunächst die oxidierte Maltrodextrinlösung und dann 554 g Natriumcarbonatlösung (17,3 % Gew./Gew.) zugegeben.

Danach wird durch Zugabe von Natronlauge ein pH von 6,5 eingestellt, die Lösung wird auf 50°C erwärmt und 60 Minuten bei 50°C gehalten. Danach wird durch Zugabe von Salzsäure auf einen pH von 5 bis 6 angesäuert, die Lösung weitere 30 Minuten bei 50°C gehalten und danach auf 97 – 98°C erhitzt und 30 Minuten bei dieser Temperatur gehalten. Nach Abkühlen der Lösung auf Raumtemperatur wird der pH-Wert durch Zusatz von Natronlauge auf 6 – 7 eingestellt.

Die Lösung wird sodann über einen Sterilfilter filtriert und auf Sedimente geprüft. Danach wird der Komplex durch Ausfällen mit Ethanol im Verhältnis 1 : 0,85 isoliert und im Vakuum bei 50°C getrocknet.

Man erhält 139 g (entsprechend 88 % d. Th.) eines braunen, amorphen Pulvers mit einem Eisengehalt von 26,8 % Gew./Gew. (komplexometrisch ermittelt).

Molekulargewicht Mw 140 kDa

Beispiel 4

Eine Mischung aus 45 g Maltodextrin (6,6 Dextrose-Äquivalente, gravimetrisch bestimmt) und 45 g Maltodextrin (14,0 Dextrose-Äquivalente, gravimetrisch bestimmt) wird bei 25°C unter Rühren in 300 ml Wasser gelöst und durch Zugabe von 25 g Natriumhypochloritlösung (13 bis 16 Gew.-% aktives Chlor) und 0,6 g Natriumbromid bei pH 10 oxidiert.

Zu 352 g Eisen(III)-Chloridlösung (12 % Gew./Gew. Fe) werden unter Rühren (Flügelrührer) bei Raumtemperatur zunächst die oxidierte Maltrinlösung und dann 554 g Natriumcarbonatlösung (17,3 % Gew./Gew.) zugegeben.

Danach wird durch Zugabe von Natronlauge ein pH von 11 eingestellt, die Lösung wird auf 50°C erwärmt und 30 Minuten bei 50°C gehalten. Danach wird durch Zugabe von Salzsäure auf einen pH von 5 bis 6 angesäuert, die Lösung weitere 30 Minuten bei 50°C gehalten und danach auf 97 bis 98°C erhitzt und 30 Minuten bei dieser Temperatur gehalten. Nach Abkühlen der Lösung auf Raumtemperatur wird der pH-Wert durch Zusatz von Natronlauge auf 6 bis 7 eingestellt.

Die Lösung wird sodann über einen Sterilfilter filtriert und auf Sedimente geprüft. Danach wird der Komplex durch Ausfällen mit Ethanol im Verhältnis 1 : 0,85 isoliert und im Vakuum bei 50°C getrocknet.

Man erhält 143 g (entsprechend 90 % d. Th.) eines braunen, amorphen Pulvers mit einem Eisengehalt von 26,5 % Gew./Gew. (komplexometrisch ermittelt).

Molekulargewicht Mw 189 kDa

Beispiel 5

90 g Maltodextrin (14,0 Dextrose-Äquivalente, gravimetrisch bestimmt) wird bei 25°C unter Rühren in 300 ml Wasser gelöst und durch Zugabe von 35 g Natriumhypochloritlösung (13 bis 16 Gew.-% aktives Chlor) und 0,6 g Natriumbromid bei pH 10 oxidiert.

Zu 352 g Eisen(III)-Chloridlösung (12 % Gew./Gew. Fe) werden unter Rühren (Flügelrührer) bei Raumtemperatur zunächst die oxidierte Maltrinlösung und dann 554 g Natriumcarbonatlösung (17,3 % Gew./Gew.) zugegeben.

Danach wird durch Zugabe von Natronlauge ein pH von 11 eingestellt, die Lösung wird auf 50°C erwärmt und 30 Minuten bei 50°C gehalten. Danach wird durch Zugabe von Salzsäure auf einen pH von 5 bis 6 angesäuert, die Lösung weitere 30 Minuten bei 50°C gehalten und danach auf 97 bis 98°C erhitzt und 30 Minuten bei dieser Temperatur gehalten. Nach Abkühlen der Lösung auf Raumtemperatur wird der pH-Wert durch Zusatz von Natronlauge auf 6 bis 7 eingestellt.

Die Lösung wird sodann über einen Sterilfilter filtriert und auf Sedimente geprüft. Danach wird der Komplex durch Ausfällen mit Ethanol im Verhältnis 1 : 0,85 isoliert und im Vakuum bei 50°C getrocknet.

Man erhält 131 g (entsprechend 93 % d. Th.) eines braunen, amorphen Pulvers mit einem Eisengehalt von 29,9 % Gew./Gew. (komplexometrisch ermittelt).

Molekulargewicht Mw 118 kDa

Beispiel 6

Eine Mischung aus 45 g Maltodextrin (5,4 Dextrose-Äquivalente, gravimetrisch bestimmt) und 45 g Maltodextrin (18,1 Dextrose-Äquivalente, gravimetrisch bestimmt) wird bei 25°C unter Rühren in 300

ml Wasser gelöst und durch Zugabe von 31 g Natriumhypochloritlösung (13 bis 16 Gew.-% aktives Chlor) und 0,7 g Natriumbromid bei pH 10 oxidiert.

Zu 352 g Eisen(III)-Chloridlösung (12 % Gew./Gew. Fe) werden unter Rühren (Flügelrührer) bei Raumtemperatur zunächst die oxidierte Maltrinlösung und dann 554 g Natriumcarbonatlösung (17,3 % Gew./Gew.) zugegeben.

Danach wird durch Zugabe von Natronlauge ein pH von 11 eingestellt, die Lösung wird auf 50°C erwärmt und 30 Minuten bei 50°C gehalten. Danach wird durch Zugabe von Salzsäure auf einen pH von 5 bis 6 angesäuert, die Lösung weitere 30 Minuten bei 50°C gehalten und danach auf 97 bis 98°C erhitzt und 30 Minuten bei dieser Temperatur gehalten. Nach Abkühlen der Lösung auf Raumtemperatur wird der pH-Wert durch Zusatz von Natronlauge auf 6 bis 7 eingestellt.

Die Lösung wird sodann über einen Sterilfilter filtriert und auf Sedimente geprüft. Danach wird der Komplex durch Ausfällen mit Ethanol im Verhältnis 1 : 0,85 isoliert und im Vakuum bei 50°C getrocknet.

Man erhält 134 g (entsprechend 88 % d. Th.) eines braunen, amorphen Pulvers mit einem Eisengehalt von 27,9 % Gew./Gew. (komplexometrisch ermittelt).

Molekulargewicht Mw 178 kDa

Beispiel 7

100 g Maltodextrin (9,6 Dextrose-Äquivalente, gravimetrisch bestimmt) werden bei 25°C unter Rühren in 300 ml Wasser gelöst und durch Zugabe von 29 g Natriumhypochloritlösung (13 bis 16 Gew.-% aktives Chlor) und 0,7 g Natriumbromid bei pH 10 oxidiert.

Zu 352 g Eisen(III)-Chloridlösung (12 % Gew./Gew. Fe) werden unter Rühren (Flügelrührer) bei Raumtemperatur zunächst die oxidierte Maltrinlösung und dann 554 g Natriumcarbonatlösung (17,3 % Gew./Gew.) zugegeben.

Danach wird durch Zugabe von Natronlauge ein pH von 11 eingestellt, die Lösung wird auf 50°C erwärmt und 30 Minuten bei 50°C gehalten. Danach wird durch Zugabe von Salzsäure auf einen pH von 5 bis 6 angesäuert, die Lösung weitere 70 Minuten bei 50°C gehalten. Nach Abkühlen der Lösung auf Raumtemperatur wird der pH-Wert durch Zusatz von Natronlauge auf 6 bis 7 eingestellt.

Die Lösung wird sodann über einen Sterilfilter filtriert und auf Sedimente geprüft. Danach wird der Komplex durch Ausfällen mit Ethanol im Verhältnis 1 : 0,85 isoliert und im Vakuum bei 50°C getrocknet.

Man erhält 155 g (entsprechend 90 % d. Th.) eines braunen, amorphen Pulvers mit einem Eisengehalt von 24,5 % Gew./Gew. (komplexometrisch ermittelt).

Molekulargewicht Mw 137 kDa

Beispiel 8

126 g Maltodextrin (6,6 Dextrose-Äquivalente, gravimetrisch bestimmt) werden bei 25°C unter Rühren in 300 ml Wasser gelöst und durch Zugabe von 24 g Natriumhypochloritlösung (13 bis 16 Gew.-% aktives Chlor) und 0,7 g Natriumbromid bei pH 10 oxidiert.

Zu 352 g Eisen(III)-Chloridlösung (12 % Gew./Gew. Fe) werden unter Rühren (Flügelrührer) bei Raumtemperatur zunächst die oxidierte Maltrinlösung und dann 554 g Natriumcarbonatlösung (17,3 % Gew./Gew.) zugegeben.

Danach wird durch Zugabe von Natronlauge ein pH von 11 eingestellt, die Lösung wird auf 50°C erwärmt und 30 Minuten bei 50°C gehalten. Danach wird durch Zugabe von Salzsäure auf einen pH von 5 bis 6 angesäuert, die Lösung weitere 70 Minuten bei 50°C gehalten. Nach Abkühlen der Lösung auf Raumtemperatur wird der pH-Wert durch Zusatz von Natronlauge auf 6 bis 7 eingestellt.
Die Lösung wird sodann über einen Sterilfilter filtriert und auf Sedimente geprüft. Danach wird der Komplex durch Ausfällen mit Ethanol im Verhältnis 1 : 0,85 isoliert und im Vakuum bei 50°C getrocknet.

Man erhält 171 g (entsprechend 86 % d. Th.) eines braunen, amorphen Pulvers mit einem Eisengehalt von 21,35 % Gew./Gew. (komplexometrisch ermittelt).

Molekulargewicht Mw 170 kDa

Vergleich

Im folgenden Vergleich werden die Eigenschaften von erfindungsgemäßen Eisen-Kohlenhydrat-Komplexen einem handelsüblichen Eisen-Saccharose-Komplex gegenübergestellt. Es ist ersichtlich, dass ein erhöhter Eisengehalt möglich ist, eine Thermobehandlung bei höheren Temperaturen durchführbar ist und die Toxizität erfindungsgemäß verringert wird (LD_{50}).

	erfindungsgemäß	Eisenhydroxid/Saccharose-Komplex
Fe-Gehalt [%]	5,0	2,0
PH	5 – 7	10,5 – 11,0
Mw [kDa][1)]	80 – 350	34 – 54
Thermobehandlung	121°C/15'	100°C/35'
LD_{50} i.v., w.m. [mg Fe/kg Körpergew.]	> 2000	> 200

Patentansprüche:

1. Wasserlöslicher Eisen-Kohlenhydrat-Komplex, erhältlich aus einer wässrigen Eisen(III)-Salzlösung und einer wässrigen Lösung des Produktes der Oxidation von einem oder mehreren Maltodextrinen mit einer wässrigen Hypochloritlösung bei einem pH-Wert im alkalischen Bereich, wobei beim Einsatz von einem Maltodextrin dessen Dextrose-Äquivalent bei 5 bis 20 und beim Einsatz eines Gemisches aus mehreren Maltodextrinen das Dextrose-Äquivalent des Gemisches bei 5 bis 20 und das Dextrose Äquivalent der am Gemisch beteiligten einzelnen Maltodextrine bei 2 bis 40 liegt.

2. Verfahren zur Herstellung eines Eisen-Kohlenhydrat-Komplexes nach Anspruch 1, dadurch gekennzeichnet, dass man ein oder mehrere Maltodextrine in wässriger Lösung bei einem alkalischen pH-Wert mit einer wässrigen Hypochloritlösung oxidiert und die erhaltene Lösung mit der wässrigen Lösung eines Eisen(III)-Salzes umsetzt, wobei beim Einsatz von einem Maltodextrin dessen Dextrose-Äquivalent bei 5 bis 20 und beim Einsatz eines Gemisches aus mehreren Maltodextrinen das Dextrose-Äquivalent des Gemisches bei 5 bis 20 und das Dextrose Äquivalent der am Gemisch beteiligten einzelnen Maltodextrine bei 2 bis 40 liegt.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, dass die Oxidation des Maltodextrins bzw. der Maltodextrine in Gegenwart von Bromidionen durchgeführt wird.

4. Verfahren nach Anspruch 2 oder 3, dadurch gekennzeichnet, dass als Eisen(III)-Salz Eisen(III)-Chlorid verwendet wird.

5. Verfahren nach Anspruch 2, 3 oder 4, dadurch gekennzeichnet, dass oxidiertes Maltodextrin und Eisen(III)-Salz zu einer wässrigen Lösung

mit einem pH-Wert der so niedrig ist, dass keine Hydrolyse des Eisen(III)-Salzes auftritt gemischt werden, worauf der pH-Wert durch Zusatz von Base auf 5 bis 12 angehoben wird.

6. Verfahren nach einem der Ansprüche 3 bis 5, dadurch gekennzeichnet, dass man die Umsetzung 15 Minuten bis zu mehreren Stunden bei einer Temperatur von 15°C bis zum Siedepunkt durchführt.

7. Arzneimittel, enthaltend die wässrige Lösung eines Eisen-Kohlenhydrat-Komplexes gemäß Anspruch 1 oder 2, oder erhalten gemäß einem der Ansprüche 3 bis 6.

8. Arzneimittel gemäß Anspruch 7, dadurch gekennzeichnet, dass es zur parenteralen oder oralen Verabreichung formuliert ist.

9. Verwendung der Eisen-Kohlenhydrat-Komplexe von Anspruch 1 oder erhalten gemäß einem der Ansprüche 2 bis 6, zur Behandlung oder Prophylaxe von Eisenmangelzuständen.

10. Verwendung der Eisen-Kohlenhydrat-Komplexe von Anspruch 1 oder erhalten gemäß einem der Ansprüche 2 bis 6, zur Herstellung eines Arzneimittels zur Behandlung oder Prophylaxe von Eisenmangelzuständen.

11. Wasserlöslicher Eisen-Kohlenhydrat-Komplex gemäß Anspruch 1 für die Behandlung oder Prophylaxe von Eisenmangelzuständen.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 03/11596

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08B31/18 C08B30/18 A61K33/26 A61K47/48 A61K31/295

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1 111 929 A (BAYER AG) 1 May 1968 (1968-05-01) page 1, line 9 - line 19 page 1, line 35 -page 2, line 43 examples 1,6,7	1-11
A	DE 34 43 251 A (SCHERING AG) 28 May 1986 (1986-05-28) examples 2,4	1
A	FR 1 451 203 A (ROCADOR SA) 7 January 1966 (1966-01-07) the whole document	1
A	US 3 821 192 A (JHAVERI C ET AL) 28 June 1974 (1974-06-28) the whole document	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2004	23/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mazet, J-F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/11596

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 086 009 A (FRED ZUSCHEK ET AL) 16 April 1963 (1963-04-16) the whole document	1
A	WO 02 46241 A (CAKIC MILORAD ;ILIC LJUBOMIR (YU); NIKOLIC GORAN (YU); RISTIC SUZA) 13 June 2002 (2002-06-13) cited in the application	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/11596

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1111929 A	01-05-1968	BE 689779 A	16-05-1967
		DE 1617463 A1	08-04-1971
		FR 1501352 A	10-11-1967
		NL 6616205 A	22-05-1967
DE 3443251 A	28-05-1986	DE 3443251 A1	28-05-1986
		AT 56880 T	15-10-1990
		AU 583070 B2	20-04-1989
		AU 5022585 A	29-05-1986
		CA 1252950 A1	18-04-1989
		DE 3579899 D1	31-10-1990
		DK 541785 A	24-05-1986
		EP 0186616 A1	02-07-1986
		ES 8703153 A1	16-04-1987
		ES 8704352 A1	16-06-1987
		GR 852815 A1	21-03-1986
		IE 58324 B1	08-09-1993
		JP 2740782 B2	15-04-1998
		JP 61171434 A	02-08-1986
		NO 854679 A ,B,	26-05-1986
		NZ 214228 A	26-04-1990
		PT 81498 A ,B	01-12-1985
		US 2002136693 A1	26-09-2002
		US 5746999 A	05-05-1998
		US 2002064502 A1	30-05-2002
		ZA 8508973 A	30-07-1986
FR 1451203 A	07-01-1966	CH 423744 A	15-11-1966
US 3821192 A	28-06-1974	AU 463243 B2	17-07-1975
		AU 4575772 A	21-02-1974
		BE 787662 A1	18-12-1972
		CA 982121 A1	20-01-1976
		DE 2240782 A1	01-03-1973
		ES 405961 A1	01-05-1976
		FR 2150794 A1	13-04-1973
		GB 1377006 A	11-12-1974
		JP 48028615 A	16-04-1973
		NL 7211158 A	20-02-1973
		PH 11363 A	02-11-1977
		ZA 7205556 A	30-05-1973
US 3086009 A	16-04-1963	NONE	
WO 0246241 A	13-06-2002	AU 2028002 A	18-06-2002
		EP 1363951 A2	26-11-2003
		WO 0246241 A2	13-06-2002

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONALER RECHERCHENBERICHT

Internales Aktenzeichen
PCT/EP 03/11596

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 C08B31/18 C08B30/18 A61K33/26 A61K47/48 A61K31/295

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 C08B

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
CHEM ABS Data, EPO-Internal

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	GB 1 111 929 A (BAYER AG) 1. Mai 1968 (1968-05-01) Seite 1, Zeile 9 - Zeile 19 Seite 1, Zeile 35 -Seite 2, Zeile 43 Beispiele 1,6,7	1-11
A	DE 34 43 251 A (SCHERING AG) 28. Mai 1986 (1986-05-28) Beispiele 2,4	1
A	FR 1 451 203 A (ROCADOR SA) 7. Januar 1966 (1966-01-07) das ganze Dokument	1
A	US 3 821 192 A (JHAVERI C ET AL) 28. Juni 1974 (1974-06-28) das ganze Dokument	1

-/--

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist
"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist
"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist
"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
14. Januar 2004	23/01/2004

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Mazet, J-F

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 03/11596

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	US 3 086 009 A (FRED ZUSCHEK ET AL) 16. April 1963 (1963-04-16) das ganze Dokument	1
A	WO 02 46241 A (CAKIC MILORAD ;ILIC LJUBOMIR (YU); NIKOLIC GORAN (YU); RISTIC SUZA) 13. Juni 2002 (2002-06-13) in der Anmeldung erwähnt	

Formblatt PCT/ISA/210 (Fortsetzung von Blatt 2) (Juli 1992)

INTERNATIONALER RECHERCHENBERICHT

Internales Aktenzeichen
PCT/EP 03/11596

Im Recherchenbericht angeführtes Patentdokument		Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
GB 1111929	A	01-05-1968	BE	689779 A	16-05-1967
			DE	1617463 A1	08-04-1971
			FR	1501352 A	10-11-1967
			NL	6616205 A	22-05-1967
DE 3443251	A	28-05-1986	DE	3443251 A1	28-05-1986
			AT	56880 T	15-10-1990
			AU	583070 B2	20-04-1989
			AU	5022585 A	29-05-1986
			CA	1252950 A1	18-04-1989
			DE	3579899 D1	31-10-1990
			DK	541785 A	24-05-1986
			EP	0186616 A1	02-07-1986
			ES	8703153 A1	16-04-1987
			ES	8704352 A1	16-06-1987
			GR	852815 A1	21-03-1986
			IE	58324 B1	08-09-1993
			JP	2740782 B2	15-04-1998
			JP	61171434 A	02-08-1986
			NO	854679 A ,B,	26-05-1986
			NZ	214228 A	26-04-1990
			PT	81498 A ,B	01-12-1985
			US	2002136693 A1	26-09-2002
			US	5746999 A	05-05-1998
			US	2002064502 A1	30-05-2002
			ZA	8508973 A	30-07-1986
FR 1451203	A	07-01-1966	CH	423744 A	15-11-1966
US 3821192	A	28-06-1974	AU	463243 B2	17-07-1975
			AU	4575772 A	21-02-1974
			BE	787662 A1	18-12-1972
			CA	982121 A1	20-01-1976
			DE	2240782 A1	01-03-1973
			ES	405961 A1	01-05-1976
			FR	2150794 A1	13-04-1973
			GB	1377006 A	11-12-1974
			JP	48028615 A	16-04-1973
			NL	7211158 A	20-02-1973
			PH	11363 A	02-11-1977
			ZA	7205556 A	30-05-1973
US 3086009	A	16-04-1963	KEINE		
WO 0246241	A	13-06-2002	AU	2028002 A	18-06-2002
			EP	1363951 A2	26-11-2003
			WO	0246241 A2	13-06-2002

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
1. März 2007 (01.03.2007)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2007/023154 A2

(51) Internationale Patentklassifikation:
A61K 33/26 (2006.01) *A61P 7/06* (2006.01)
A61K 31/715 (2006.01)

(21) Internationales Aktenzeichen: PCT/EP2006/065532

(22) Internationales Anmeldedatum:
22. August 2006 (22.08.2006)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
05107790.7 25. August 2005 (25.08.2005) EP

(71) Anmelder *(für alle Bestimmungsstaaten mit Ausnahme von US)*: **VIFOR (INTERNATIONAL) AG** [CH/CH]; Rechenstrasse 37, CH-9001 St. Gallen (CH).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: **ERICHSEN, Kari** [NO/NO]; Kronstadveien 23B, N-5053 Bergen (NO). **DANIELSON, Bo** [SE/CH]; Pilatusstrasse 46, CH-6052 Hergiswil (CH).

(74) Anwalt: **GILLE HRABAL STRUCK NEIDLEIN PROP ROOS**; Brucknerstr. 20, 40593 Düsseldorf (DE).

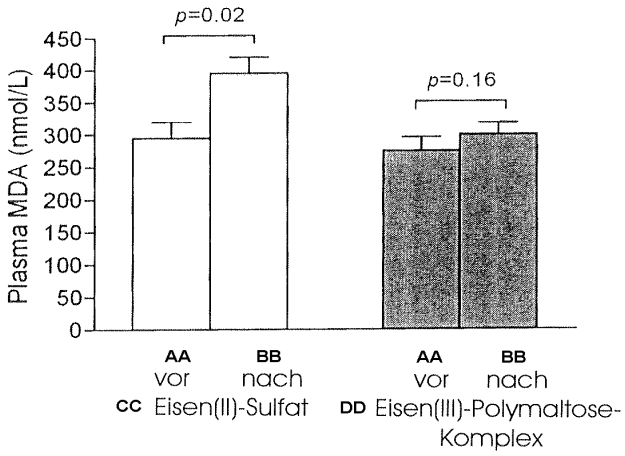
(81) Bestimmungsstaaten *(soweit nicht anders angegeben, für jede verfügbare nationale Schutzrechtsart)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Bestimmungsstaaten *(soweit nicht anders angegeben, für jede verfügbare regionale Schutzrechtsart)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Fortsetzung auf der nächsten Seite]

(54) **Title:** USE OF IRON (III) COMPLEX COMPOUNDS FOR PRODUCING A MEDICAMENT FOR THE ORAL TREATMENT OF CONDITIONS CAUSED BY AN IRON DEFICIENCY IN PATIENTS WITH CHRONIC INFLAMMATORY INTESTINAL DISEASES

(54) **Bezeichnung:** VERWENDUNG VON EISEN (III)-KOMPLEXVERBINDUNGEN ZUR HERSTELLUNG EINES ARZNEIMITTELS ZUR ORALEN BEHANDLUNG VON EISENMANGEL-ZUSTÄNDEN BEI PATIENTEN MIT CHRONISCH-ENTZÜNDLICHER DARMERKRANKUNG



AA ... BEFORE
BB ... AFTER
CC ... IRON (II) SULFATE
DD ... IRON (III) POLYMALTOSE COMPLEX

(57) **Abstract:** The invention relates to the use of iron (III) complex compounds comprising carbohydrates or derivatives of the latter for producing a medicament for the oral treatment of conditions caused by an iron deficiency in patients with chronic inflammatory intestinal diseases, in particular Crohn's disease and ulcerative colitis.

(57) **Zusammenfassung:** Es wird die Verwendung von Eisen(lll)-Komplexverbindungen mit Kohlenhydraten oder Derivaten davon zur Herstellung eines Arzneimittels zur oralen Behandlung von Eisenmangel-Zustanden bei Patienten mit chronisch entzündlicher Darmerkrankung offenbart, insbesondere Morbus Crohn und Colitis ulcerosa.

WO 2007/023154 A2

Veröffentlicht:
— *ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

VERWENDUNG VON EISEN(III)-KOMPLEXVERBINDUNGEN ZUR HERSTELLUNG EINES ARZNEIMITTELS ZUR ORALEN BEHANDLUNG VON EISENMANGEL-ZUSTÄNDEN BEI PATIENTEN MIT CHRONISCH-ENTZÜNDLICHER DARMERKRANKUNG

BESCHREIBUNG:

Die vorliegenden Erfindung betrifft neue therapeutische Anwendungen von Eisen(III)-Komplexverbindungen mit Kohlehydraten oder Derivaten davon, insbesondere mit Dextrinen oder Oxidationsprodukten von Dextrinen, nämlich zur Herstellung von Arzneimitteln zur oralen Behandlung von Eisenmangel-Zuständen bei Patienten mit chronisch entzündlichen Darmerkrankungen, insbesondere Morbus Crohn und/oder Colitis ulcerosa.

Eisenmangel ist der häufigste Spurenelementmangel weltweit. Ca. 2 Milliarden Menschen weltweit leiden an Eisenmangel oder Eisenmangel-Anämie (E.M. DeMaeyer, „Preventing and controlling iron deficiency anaemia through primary health care", World Health Organization, Genf, 1989, ISBN 92 4 154249 7).

Aus der WO 95/35113 ist die Verwendung von Eisen(III)-oxid als Wirkstoff zur Behandlung von Immunschwächerkrankungen, insbesondere AIDS, bekannt.

Aus der DE 1467980 sind therapeutisch verwendbare Eiseninjektionspräparate und Verfahren zu Ihrer Herstellung bekannt.

Aus der US 3076798 sind Verfahren zur Herstellung von Eisen(III)-Polymaltose-Komplexverbindungen bekannt, die zur parenteralen Verabreichung geeignet sind.

Aus der WO 04/037865 ist die Verwendung von Eisen-Kohlenhydrat-Komplexen zur Behandlung oder Prophylaxe von Eisenmangelzuständen bekannt.

Aus der WO 03/087164 sind Eisen-Komplexverbindungen mit hydrierten Dextrinen zur Behandlung oder Prophylaxe von Eisenmangelzuständen bekannt.

Aus der WO 02/46241 sind Eisen(III)-Pullulan-Komplexverbindungen und ihre Verwendung zur Behandlung oder Prophylaxe von Eisenmangelzuständen bekannt.

WO 99/48533 offenbart Eisen-Dextran-Verbindungen zur Behandlung von Eisenmangelanämie, die hydriertes Dextran mit einem bestimmten Molekulargewicht von ca. 1000 Dalton umfassen.

I. Maslovski, American Journal of Hematology, Apr. 2005, Bd. 78, Nr. 4, S. 261-264 offenbart die Aktivität von Ferrlecit®, einem Eisen(III)-Gluconatkomplex in Sucrose mit einem Molekulargewicht von 350000, oder Venofer®, einem Eisen(III)-Sucrosekomplex, zur intravenösen Behandlung von anämischen Patienten, die an chronisch entzündlicher Darmerkrankung leiden.

G. Bodemar et al., Scandinavian Journal of Gastroenterology, Mai 2004, Bd. 39, S. 454-458, beschreibt Eisen(III)-Sucroseverbindungen zur intravenösen Behandlung von Anämie bei Patienten mit Morbus Crohn und ulcerativer Colitis.

DE-A-102 49 552beschreibt Eisen(III)-Komplexverbindungen mit Maltodextrinen und deren (besonders bevorzugt parenterale) Verwendung zur Behandlung von Anämie.

CH-A-694 197 beschreibt Eisen(III)-Polymaltoseverbindungen zur Behandlung von Anämie, ohne jedoch Hinweise auf Wirkungen im Magen-Darm-Trakt oder auf IBD oder Morbus Crohn zu geben.

Eisensulfat ist dafür bekannt, dass es relativ häufig unangenehme dosisabhängige Nebenreaktionen, wie gastrointestinale Störungen oder eine Verfärbung der Zähne hervorruft. Eisen aus Eisensalz-Verbindungen unterliegt der passiven Diffusion freier Eisenionen. Das Eisen kann in den Kreislauf eintreten und dadurch Nebenreaktionen oder eine Eisenvergiftung hervorrufen. Dementsprechend ist auch der LD50-Wert bei weißen Mäusen mit 230 mg Eisen/kg relativ niedrig.

In Oski et al. „Effect of Iron Therapy on Behavior Performance in Nonannemic, Iron-Deficient Infants", PEDIATRICS 1983; Band 71; 877-880 ist die Verwendung von Eisen-Dextran offenbart. Die parenterale Verwendung

von Eisen-Dextran ist nachteilig, weil ein Dextran-induzierter anaphylaktischer Schock auftreten kann.

Entzündliche Darmerkrankungen (inflammatory bowel disease, IBD) umfassen eine Gruppe von Erkrankungen des Gastrointestinaltrakts, die durch intestinale Entzündung und einen chronisch Verlauf mit ständigen Rückfällen gekennzeichnet sind.IBD wurde traditionell entweder als Colitis ulcerosa oder Morbus Crohn charakterisiert, basierend auf klinischen, radiologischen, endoskopischen und histologischen Kriterien. Obwohl die Ätiologie von IBD noch der Definition bedarf, legen neuere klinische und experimentelle Studien nahe, dass der Auslöser und die Pathogenese dieser Erkrankungen multifaktoriell sind und dass Wechselwirkungen zwischen genetischen, Umwelt- und Immunfaktoren involviert sind.

Entzündliche Darmerkrankungen sind weltweit nicht gleichmäßig verbreitet. Es besteht eine klare Tendenz zu einem vermehrten Auftreten in entwickelten Ländern verglichen mit weniger entwickelten Ländern. Das Vorkommen von IBD in Europa beträgt ca. 390 Fälle pro 100.000 Personen. Eine Extrapolation dieser Zahlen auf die europäische Population von ca. 580 Millionen ergibt eine geschätzte Zahl von 2,2 Millionen Personen, die von IBD betroffen sind (Loftus EV, Jr., Gastroenterolgy 2004, 126, 11504-1517). Colitis ulcerosa und Morbus Crohn werden am häufigsten bei älteren Heranwachsenden und jungen Erwachsenen diagnostiziert, können aber in jedem Lebensalter auftreten.

Colitis ulcerosa ist eine Schleimhauterkrankung, die üblicherweise das Rektum befällt und sich dann in die benachbarten Bereiche ausdehnt, so dass das Kolon ganz oder teilweise befallen wird. Die Ausbreitung erfolgt kontinuierlich, ohne dass Bereiche nicht betroffener Schleimhaut verbleiben. Die Hauptsymptome von Colitis ulcerosa sind heftiger Durchfall, rektale Blutungen, Schleimabgang und krampfartige Bauchschmerzen. Die Schwere der Symptome korreliert mit der Ausdehnung der Erkrankung.

Morbus Crohn kann jeden Bereich des Gastrointestinaltrakts vom Mund bis zum Anus befallen, betrifft aber am häufigsten den Dünndarm und/oder das Kolon. Die Entzündung ist transmural und segmental, wobei normale Bereiche zwischen Bereichen erkrankten Darms vorhanden sind. Folgen der Entzündung schließen Fistelbildung an anderen Darmschlingen, Harnblase, Vagina oder Perianalhaut, abdominale oder perianale Abszesse und intestinale Verengungen ein. Die Lokalisierung und der Verlauf der

Erkrankung beeinflussen die klinischen Manifestationen. Die häufigsten Symptome sind Durchfall, krampfartige Bauchschmerzen, Fieber, Anorexie und Gewichtsverlust.

Extraintestinale Manifestationen von Colitis ulcerosa und Morbus Crohn können multiple Organsysteme betreffen, wie Augen, Haut und Gelenke, genauso wie gastrointestinale Organe einschließlich Leber und Gallenblase.

Die Behandlung umfasst die Gabe antientzündlicher Mittel, u.U. von Antibiotika, und eine Ernährungsumstellung. Gelegentlich kann eine Operation erforderlich sein. Weiter erfolgt häufig eine Psychotherapie, einerseits zur Bewältigung von Stress, der mit als Auslöser gilt, andererseits zur Behandlung von Depressionen, die häufig als Folge der chronisch immer wiederkehrenden Beschwerden auftreten (s. z.B. Pschyrembel, Klinisches Wörterbuch, 256. Auflage, de Gruyter, S. 302/303, S. 443; http://familydoctor.org oder http://www.mayoclinic.com).

Eisenmangel tritt bei Patienten mit chronisch entzündlicher Darmerkrankung häufig als Komplikation auf. Chronische intestinale Blutungen können dazu führen, dass mehr Eisen verloren geht, als durch die Nahrung aufgenommen wird. Übliche orale Eisenpräparate, im allgemeinen Eisen(II)-Salze, verursachen häufig schwere gastrointestinale Nebenwirkungen, was zu einer schlechten Patienten-Copmpliance führt. Die orale Eisentherapie kann die Läsionen des intestinalen Gewebes durch die Katalyse der Bildung von reaktiven Sauerstoffspezies verstärken. Da freies Eisen ein starker Katalysator des Bildung von reaktiven Sauerstoffspezies ist, kann die orale Eisen(II)-Therapie für Patienten mit chronisch entzündlicher Darmerkrankung sogar schädlich sein. Orale Eisen(II)-Präparate werden schlecht absorbiert und führen zu hohen faecalen Eisenkonzentrationen, und ein signifikanter Anteil des faecalen Eisens ist für die katalytische Aktivität verfügbar. Wenn Eisen in Kontakt mit der entzündeten intestinalen Mucosa kommt, kann es die Produktion reaktiver Sauerstoffspezies erhöhen und dadurch Gewebeschädigungen verstärken. Daher ist es für Patienten mit chronischer entzündlicher Darmerkrankung besonders wichtig, gut verträgliche Eisenpräparate zur Verfügung zu haben.

Eisen(III)-Polymaltose-Komplex enthält Eisen in nicht-ionischer Form, die weniger toxisch ist. Es treten bei Gabe von Verbindungen dieses Typs weniger Nebenwirkungen auf, und die Patienten-Compliance ist gegenüber Eisen(II)-sulfat verbessert (Jacobs, P., Wood, L., Bird, AR., Hematol. 2000,

5:77-83). Es gibt jedoch noch keine Erfahrungen oder Berichte über die Anwendung von Eisen(III)-Polymaltose-Komplex bei Patienten mit chronisch-entzündlicher Darmerkrankung.

Die Erfinder stellten sich daher die Aufgabe, gut verträgliche Eisenverbindungen zu finden, die geeignet sind, die Eisenmangel-Zustände bei Patienten mit chronisch entzündlicher Darmerkrankung zu behandeln.

In einer Studie konnten sie nachweisen, dass Eisen(III)-Komplexverbindungen mit Kohlehydraten, insbesondere mit Polymaltose (Maltodextrin) besonders verträglich sind und eine hohe Patienten-Compliance besitzen. Überraschend war dabei, dass unter der Behandlung mit den Eisen(III)-Komplexen kein oxidativer Stress auftrat, im Gegensatz zur Behandlung mit Eisen(II)-sulfat, unter der eine signifikante Erhöhung von Plasma-Malondialdehyd (MDA), einem Marker der Lipid-Peroxidation, beobachtet wurde.

Oxidativer Stress, insbesondere die Lipidperoxidation, wird mit einem erhöhten Risiko, an Herzinfarkt, Krebs und Atherosklerose zu erkranken, in Verbindung gebracht. Die oxidative Modifizierung von Low-Density Lipoprotein (LDL) wird für die Atherogenese verantwortlich gemacht (s. in Tuomainen et al., Nutrition Research, Vol 19, No.8, pp. 1121-1132, 1999 angegebene Referenzen).

Eisen(III)-Polymaltose-Komplex-Verbindungen führen zwar nur zu einer langsamen Erhöhung des Ferritinspiegels, werden aber effizienter für die Hämoglobin-Synthese verwendet (T.-P. Tuomainen et al., aaO., p. 1127). Auf der Basis dieses Ergebnisses stellten die Erfinder die vorliegende Erfindung fertig.

Gegenstand der Erfindung ist daher die Verwendung von Eisen(III)-Komplexverbindungen mit Kohlehydraten oder Derivaten davon zur Herstellung eines Arzneimittels zur Behandlung von Eisenmangel-Zuständen bei Patienten mit chronisch entzündlicher Darmerkrankung.

Unter Eisenmangel-Zustand gemäß der Erfindung wird ein Zustand verstanden, bei dem Hämoglobin, Eisen und Ferritin im Plasma vermindert sind und Transferrin erhöht ist, was zu einer erniedrigten Transferrin-Sättigung führt.

Der erfindungsgemäß zu behandelnde Zustand umfasst Eisenmangelanämie und Eisenmangel ohne Anämie. Die Einteilung kann beispielsweise durch den Hämoglobinwert und den Wert für die

Transferrinsättigung (%) erfolgen. Referenzwerte für Hämoglobin, bestimmt durch Durchflusszytometrie oder die photometrische Cyanhämoglobinmethode, und Referenzwerte für Eisen, Ferritin und Transferrin sind beispielsweise gelistet in der Referenzdatenbank der Charité, Institut für Laboratoriumsmedizin und Pathobiochemie (http://www.charite.de/ilp/routine/parameter.html) und in Thomas, L. Labor und Diagnose, TH Book Verlagsgesellschaft, Frankfurt/Main 1998. Die Transferrinsättigung ist bei Patienten ohne Eisenmangel in der Regel >16 %. Die Normalwerte sind in der später folgenden Tabelle III angegeben.

Laut M. Wick, W. Pinggera, P. Lehmann, Eisenstoffwechsel – Diagnostik und Therapien der Anämien, 4., erw. Aufl. Springer Verlag Wien 1998 lassen sich alle Formen des Eisenmangels klinisch-chemisch nachweisen. Dabei geht im allgemeinen eine erniedrigte Ferritin-Konzentration mit kompensatorisch erhöhtem Transferrin und niedriger Transferrinsättigung einher.

Unter chronisch entzündlicher Darmerkrankung (inflammatory bowel disease, IBD) wird eine chronische Entzündung des Verdauungstrakts verstanden, insbesondere Morbus Crohn und Colitis ulcerosa.

Erfindungsgemäß anwendbare Eisen(III)-Komplexverbindungen mit Kohlehydraten schließen bevorzugt diejenigen ein, worin Kohlenhydrate aus der Gruppe ausgewählt werden, die aus Dextranen und Derivaten davon, Dextrinen und Derivaten davon sowie Pullulan, Oligomeren und/oder Derivaten davon besteht. Die genannten Derivate umfassen insbesondere die hydrierten Derivate. Besonders bevorzugt sind Eisen(III)-Komplexverbindungen mit Dextrinen oder Oxidationsprodukten davon. Beispiele der Herstellung der erfindungsgemäßen Eisen(III)-Komplexverbindungen finden sich beispielsweise in den eingangs erwähnten Patentschriften DE 14679800, WO 04037865 A1, US 3076798, WO 03/087164 sowie WO 02/46241, deren Offenbarungsgehalt insbesondere hinsichtlich der Herstellverfahren hier vollumfänglich eingeschlossen sein soll. Der Begriff der erfindungsgemäß bevorzugt verwendeten „Dextrine" ist eine *Sammelbezeichnung für verschiedene niedere und höhere Polymere aus* D-Glucose-Einheiten, die bei unvollständiger Hydrolyse von Stärke entstehen. Dextrine können ferner durch Polymerisation von Zuckern hergestellt werden (z.B. WO 02083739 A2, US 20030044513 A1, US 3766165). Zu den Dextrinen gehören die Maltodextrine bzw. Polymaltosen, die durch enzymatische

Spaltung von zum Beispiel Mais- oder Kartoffelstärke mit alpha-Amylase hergestellt werden und die durch den Hydrolysegrad ausgedrückt durch den DE-Wert (Dextrose-Äquivalent) charakterisiert werden. Polymaltose kann erfindungsgemäß auch durch saure Hydrolyse von Stärken, insbesondere von Dextrinen erhalten werden. Die Herstellung der erfindungsgemäß anwendbaren Eisen(III)-Komplexverbindungen erfolgt im allgemeinen durch Umsetzung von Eisen(II)- oder (III)-salzen, insbesondere Eisen(III)-chlorid, mit den Dextrinen, insbesondere Polymaltose, oder Oxidationsprodukten der Dextrine in wässriger alkalischer Lösung (pH > 7) und anschließender Aufarbeitung. Die Herstellung gelingt auch im schwach sauren pH-Bereich. Bevorzugt sind jedoch alkalische pH-Werte von beispielsweise >10.

Das Anheben des pH-Wertes erfolgt bevorzugt langsam bzw. allmählich, was beispielsweise dadurch erfolgen kann, dass zunächst eine schwache Base zugesetzt wird, beispielsweise bis zu einem pH von etwa 3; anschließend kann dann mit einer stärkeren Base weiter neutralisiert werden. Als schwache Base kommen beispielsweise Alkali-oder Erdalkalicarbonate, -bicarbonate, wie Natrium- und Kaliumcarbonat oder -bicarbonat oder Ammoniak infrage. Starke Basen sind beispielsweise Alkali- oder Erdalkalihydroxide, wie Natrium-, Kalium-, Calcium-oder Magnesiumhydroxid.

Die Umsetzung kann durch Erwärmen begünstigt werden. Beispielsweise können Temperaturen in der Größenordnung von 15°C bis zur Siedetemperatur angewendet werden. Es ist bevorzugt, die Temperatur allmählich zu steigern. So kann beispielsweise zunächst auf etwa 15 bis 70°C erwärmt und allmählich bis zum Sieden gesteigert werden.

Die Reaktionszeiten liegen beispielsweise in der Größenordnung von 15 Minuten bis zu mehreren Stunden, z.B. 20 Minuten bis 4 Stunden, beispielsweise bei 25 bis 70 Minuten, z. B. 30 bis 60 Minuten.

Nach erfolgter Umsetzung kann die erhaltene Lösung beispielsweise auf Raumtemperatur abgekühlt und gegebenenfalls verdünnt und gegebenenfalls filtriert werden. Nach dem Abkühlen kann der pH-Wert durch Zugabe von Säure oder Base auf den Neutralpunkt oder leicht darunter, beispielsweise auf Werte von 5 bis 7 eingestellt werden. Als Basen können beispielsweise die vorstehend zur Umsetzung genannten verwendet werden. Säuren schließen beispielsweise Salzsäure und Schwefelsäure ein. Die erhaltenen Lösungen werden gereinigt und können direkt zur Herstellung von Arzneimitteln verwendet werden. Es ist aber auch möglich, die Eisen(III)-

Komplexe aus der Lösung zu isolieren, beispielsweise durch Ausfällen mit einem Alkohol, wie einem Alkanol, beispielsweise Ethanol. Die Isolierung kann auch durch Sprühtrocknung erfolgen. Die Reinigung kann in üblicher Weise erfolgen, insbesondere zur Entfernung von Salzen, Dies kann z. B. durch Umkehrosmose erfolgen, wobei eine derartige Umkehrosmose z. B. vor der Sprühtrocknung oder vor dem direkten Einsatz in Arzneimitteln durchgeführt werden kann.

Die erhaltenen Eisen(III)-Komplexe weisen beispielsweise einen Eisengehalt von 10 bis 40 % Gew./Gew., insbesondere 20 bis 35% Gew./Gew. auf. Sie sind im allgemeinen gut wasserlöslich. Man kann daraus neutrale wässrige Lösungen mit beispielsweise 1 % Gew./Vol. bis 20 % Gew./Vol. Eisengehalt herstellen. Diese Lösungen lassen sich thermisch sterilisieren.

Bezüglich der Herstellung von Eisen(III)-Polymaltose-Komplexverbindungen kann auch auf die US 3076798 verwiesen werden.

In einer bevorzugten Ausführungsform der Erfindung wird eine Eisen(III)-hydroxid-Polymaltose-Komplexverbindung verwendet. Bevorzugt besitzt diese die Eisen(III)-Polymaltose-Komplexverbindung ein Molekulargewicht im Bereich von 20000 bis 500000, in einer bevorzugten Ausführungsform 30000 bis 80000 Dalton (bestimmt mittels Gelpermeationschromatographie, beispielsweise wie von Geisser et al. In Arzneim. Forsch/Drug Res. 42(11), 12,1439-1452 (1992), Absatz 2.2. 5. beschrieben). Eine besonders bevorzugte Eisen(III)-hydroxid-Polymaltose-Komplexverbindung ist das im Handel erhältlich Maltofer® der Firma Vifor AG, Schweiz. In einer weiteren bevorzugten Ausführungsform wird eine Eisen(III)-Komplexverbindung mit einem Oxidationsprodukt von einem oder mehreren Maltodextrinen verwendet. Diese ist beispielweise erhältlich aus einer wässrigen Eisen(III)-Salzlösung und einer wässrigen Lösung des Produktes der Oxidation von einem oder mehreren Maltodextrinen mit einer wässrigen Hypochloritlösung bei einem pH-Wert im alkalischen Bereich, wobei beim Einsatz von einem Maltodextrin dessen Dextrose-Äquivalent bei 5 bis 37 und beim Einsatz eines Gemisches aus mehreren Maltodextrinen das Dextrose-Äquivalent des Gemisches bei 5 bis 37 und das Dextrose Äquivalent der am Gemisch beteiligten einzelnen Maltodextrine bei 2 bis 40 liegt. Das gewichtsmittlere Molekulargewicht Mw der so erhaltenen Komplexe beträgt beispielsweise 30 kDa bis 500 kDa, bevorzugt 80 bis 350 kDa, besonders bevorzugt bis zu 300

kDa (bestimmt mittels Gelpermeationschromatographie, beispielsweise wie von Geisser et al. In Arzneim. Forsch/Drug Res. 42(11), 12,1439-1452 (1992), Absatz 2.2. 5. beschrieben). Diesbezüglich kann beispielsweise auf die WO 2004037865 A1 verwiesen werden, deren Offenbarungsgehalt vollumfänglich in vorliegender Anmeldung eingeschlossen sein soll.

Bezüglich der Herstellung von Eisen-Komplexverbindungen mit hydrierten Dextrinen kann auf die WO 03/087164 verwiesen werden.

Bezüglich der Herstellung von Eisen(III)-Pullulan-Komplexverbindungen kann auf die WO 02/46241 verwiesen werden.

Die erfindungsgemäß verwendeten Eisen(III)-hydroxid-Komplexverbindungen werden bevorzugt oral verabreicht. Prinzipiell können sie aber auch parenteral, wie intravenös, aber auch intramuskulär verabreicht werden. Die orale tägliche Dosis beträgt beispielsweise zwischen 10 und 500 mg Eisen/Tag der Anwendung. Die Verabreichung kann bedenkenlos über einen Zeitraum von mehreren Monaten bis zur Verbesserung des Eisenstatus, reflektiert durch den Hämoglobin-Wert, die Transferrin-Sättigung und den Ferritin-Wert, der Patienten eingenommen werden. Die orale Verabreichung erfolgt bevorzugt in Form einer Tablette, einer Kapsel, einer wässrigen Lösung oder Emulsion, als Granulat, Kapsel, Gel oder als Sachet. Die Anwendung von Lösungen oder Emulsionen ist besonders bei Kindern in der Form von Sirups bzw. Säften, Tropfen etc. bevorzugt. Dazu können die Eisen(III)-hydroxid-Dextrin-Komplex-Verbindungen mit üblichen pharmazeutischen Träger- bzw. Hilfsstoffen in die geeignete Verabreichungsform gebracht werden. Dazu können übliche Bindemittel bzw. Gleitmittel, Verdünnungsmittel, Desintegrationsmittel etc. verwendet werden.

Die erfindungsgemäße Verwendung kann bei Kindern, Jugendlichen und Erwachsenen erfolgen, welche an chronisch entzündlichen Darmerkrankungen leiden, bevorzugt bei Erwachsenen.

Die erfindungsgemäße Verwendung verläuft insbesondere mittels Verbesserung der Eisen-, Hämoglobin-, Ferritin- und Transferrinwerte, wobei die klinischen Erkrankungsaktivitätsindizes, der Darmzustand, Bauchschmerzen und Übelkeit durch die erfindungsgemäße Behandlung nicht verschlechtert werden.

Kurze Beschreibung der Figur

Figur 1 ist ein Diagramm, das die im Beispiel gemessenen Plasma-MDA-Spiegel vor und nach der Behandlung mit Eisen(II)-sulfat bzw. Eisen(III)-Polymaltose-Komplex zeigt. Der Effekt von Eisen(II)-Sulfat und Eisen(III)-Polymaltose-Komplex auf den Plasmaspiegel von Malondialdehyd (MDA) bei Patienten mit chronisch entzündlicher Darmerkrankung wird dargestellt. Die Ergebnisse sind als Mittelwert ± SEM angegeben. P-Werte sind für Paar-Vergleiche angegeben.

Die Erfindung wird in ihrer Wirkungsweise durch das folgende Beispiel erläutert und belegt.

BEISPIEL

Patienten

41 Patienten mit chronisch entzündlicher Darmerkrankung (Colitis ulcerosa oder Morbus Crohn im aktiven oder ruhenden Zustand) und Eisenmangel (definiert durch das mittlere corpusculäre Volumen (MCV) <80 fl oder S-Ferritin < 15 µg/l oder S-löslicher Transferrin-Rezeptor > 1.54 mg/l) wurden nach dem Zufallsprinzip in zwei Gruppen aufgeteilt. Patienten, die während 6 Wochen vor Durchführung der Studie eine Eisentherapie oder Bluttransfusionen, eine weniger als zwei Monate vor Beginn der Studie beginnende Azathioprin-Behandlung oder eine Infliximab-Behandlung erhalten hatten, an Cobalamin- oder Folsäuremangel, Krebs oder Nierenerkrankungen litten oder schwanger waren, wurden ausgeschlossen. Die Untersuchung von Blut, Urin und Stuhl sowie die klinische Beurteilung der Erkrankung erfolgten am Tag 1 und 15.

Medikation

Die Behandlung erfolgte in Gruppe 1 mit Eisen(II)-sulfat (Nycoplus Ferro-Retard®, Nycomed Pharma AS, Norwegen), mit einer Tablette (100 mg) (entspr. 100 mg Fe^{2+}) morgens und einer Tablette (100 mg) abends zwischen den Mahlzeiten während 14 Tagen und in Gruppe 2 mit Eisen(III)-Polymaltose-Komplex (Maltofer Filmtabletten®, Vifor International AG, Schweiz) mit zwei Tabletten (insges. 200 mg) (entspr. 200 mg Fe(III)) einmal täglich morgens während der Mahlzeit während 14 Tagen. Die Einnahme

erfolgte nach den Herstellerempfehlungen. Die Patienten-Compliance wurde definiert als Verbrauch der ausgegebenen Tabletten, wobei 80% als zufriedenstellend betrachtet wurde.

Laboruntersuchungen

Blutproben wurden nach Fasten während der Nacht am Morgen von Tag 1 und Tag 15 entnommen.

Plasma-Malondialdehyd (MDA), Plasmaaminothiophenole, Plasma-Vitamine A, E und C und Plasma-Betacarotin wurden durch Hochleistungsflüssigkeitschromatographie (HPLC) bestimmt wie in der Literatur beschrieben (Svardal, AM., Manssor, MA., Ueland, PM., Anal. Biochem. 1990; 184:338-346; Vaagenes, H., Muna, ZA., Madsen, L., Berge, RK., Lipids 1998; 33:1131-1137).

Routine-Laboruntersuchungen umfassten die Bestimmung von Blut-Hämoglobin, die Blut-Reticulocytenzählung, die Bestimmung des mittleren corpusculären Volumens (MCV), des mittleren corpusculären Hämoglobins (MCH), der mittleren corpusculären Hämoglobin-Konzentration (MCHC), eine Blut-Erythrocytenzählung, Blut-Leukocytenzählung, und Blut-Plättchenzählung, die Bestimmung des Reticulocyten-Hämoglobins (CHr), die Zählung der hypochromen roten Zellen (HYPO), die Bestimmung von Serum-Ferritin und Serum-Eisen, die Bestimmung der Serum-Eisen-Gesamtbindungskapazität, des Serum-löslichen Transferrin-Rezeptors, des Serum-C-reaktiven Proteins (S-CRP), die Messung der Blut-Erythrocyten-Sedimentationsgeschwindigkeit (B-ESR),die Bestimmung von Serum-Protein und Serum-Albumin.

Urinproben wurden am Morgen von Tag 1und Tag 15 genommen und auf Kreatinin untersucht. Butyl-hydroxy-toluol (BHT) wurde zu 2 ml Urin gegeben auf eine Endkonzentration von 20 mM. Die Proben wurden dann bis zur Analyse von Urin-8-isoprostaglandin $F_{2\alpha}$ (8-Iso-PG $F_{2\alpha}$) bei –80°C gelagert. Die Analyse erfolgte durch Gaschromatographie-Massenspektrometrie nach der Methode von Nourooz-Zadeh et al. (Nourooz-Zadeh J., Gopaul NK., Barrow S., Mallet AI., Anggard EE., J. Chromatogr. B. Biomed. Appl. 1995; 667:199-208), wurde aber hinsichtlich der Urinmatrix durch Weglassen des anfänglichen Hydrolyseschritts und Anwendung des Festphasenprotokolls von Lee et al. (Lee CY, Jenner AM., Halliwell B., Biochem. Biophys. Res. Commun. 2004; 320: 696-702) modifiziert.

Klinische Erkrankungsaktivität

Der Zustand der klinischen Erkrankung wurde vor (Tag 1) und nach (Tag 15) der Eisentherapie aufgenommen. Die klinische Erkrankungsaktivität wurde bei Patienten mit Morbus Crohn mit dem „Harvey-Bradshaw Simple Index of

Crohn's Disease Ativity" (Harvey, RF., Bradshaw, JM., Lancet, 1980; 1:514) bewertet. Der Harvey-Bradshaw Simple Index basiert auf 5 Parametern: allgemeines Wohlbefinden, Bauchschmerzen, Stuhlhäufigkeit, Abdominalmasse und extraintestinale Komplikationen. Der Maximalwert ist 25 und Werte von ≥5 zeigen aktiven Morbus Crohn an.

Bei Patienten mit Colitis ulcerosa wurde der „Simple Clinical Colitis Activity Index" aufgezeichnet (Walmsley, RS., Ayres, RC., Pounder, RE., Allan, RN., Gut 1998; 43; 29-32). Der Simple Clinical Colitis Activity Index basiert auf 6 Parametern: allgemeines Wohlbefinden, Stuhlhäufigkeit tags und nachts, Stuhldrang, Blut im Stuhl und extraintestinale Komplikationen. Der Maximalwert ist 20 und Werte von ≥ 4 zeigen aktive Colitis ulcerosa an.

Der Harvey-Bradshaw Simple Index und der Simple Clinical Colitis Activity Index sind gleich im Hinblick auf den Aufbau und die klinische Bedeutung einer gegebenen Änderung der Werte. Um die gemeinsame Berücksichtigung der Ergebnisse von Patienten mit Morbus Crohn und Colitis ulcerosa zu ermöglichen, wurden die Aktivitätswerte als tatsächlicher Wert dividiert durch den Maximalwert berechnet.

Alle Patienten führten die jeweilige Crohn Disease Activity Index (CDAI) Tagebuchkarte (Best, WR., Becktel, JM., Singleton, JW., Kern, F. Jr., Gastroenterology 1976; 70:439-444) in der Woche vor Beginn der Eisentherapie und während der zweiwöchigen Eisentherapie. Die CDAI-Tagebuchkarte beinhaltet die tägliche Aufzeichnung des allgemeinen Wohlbefindens, der Bauchschmerzen und der Anzahl der flüssigen oder sehr weichen Stühle. Die Summe von sieben täglichen Aufzeichnungen ergibt einen Wert für jedes Symptom. Je höher der Wert, desto mehr ist der Patient beeinträchtigt. Die Arzneimittelgabe während der Studie erfolgte während 14 Tagen und daher wird der Mittelwert für die zwei Wochen für die Analyse verwendet. Die Patienten dokumentierten auch das Auftreten von Übelkeit vor und während der Eisentherapie.

Patienten, die die Arzneimittelbehandlung wegen einer Verschlechterung der Symptome abbrachen, wurden in die Analyse der klinischen Erkankungsaktivität und der Symptomwerte einbezogen. Ihre Erkrankungsaktivitätswerte wurden um zwei Punkte erhöht, und die Symptomwerte wurden um einen Punkt pro Tag erhöht.

Ziel und Ergebnisse

Das primäre Ziel der Studie war ein Vergleich der Wirkung von oralem Eisen(II)-sulfat und oralem Eisen(III)-Polymaltose-Komplex auf Marker für oxidative Gewebeschäden. Die primären Ergebnisse waren Plasma-MDA und Urin-iso-$PGF_{2\alpha}$. Das zweite Ziel war der Vergleich der Wirkung der beiden Eisenformulierungen auf die klinische Erkrankungsaktivität und spezifische Symptome. Die Behandlungszeit war zu kurz für eine Studie der klinischen Wirksamkeit auf die Behebung des Eisenmangels.

Statistische Analyse

Die Differenzen innerhalb der und zwischen den Gruppen wurden mit dem gepaarten und ungepaarten Student t-Test beurteilt, und der Mittelwert der Differenzen und das 95%-Konfidenzintervall sind angegeben. Die Werte wurden unter Verwendung des Wilcoxon-Test für Paar-Differenzen analysiert, und es sind der Median und der Bereich angegeben. Der Vergleich von Verhältnissen wurde mit dem Fisher-Exakt-Test beurteilt. P-Werte von weniger als 0,05 werden als statistisch signifikant betrachtet. Die Daten wurden unter Verwendung des Statistik-Softwarepakets GraphPad Prism 4 for Windows (GraphPad Software, Inc., San Diego, USA) analysiert.

Ergebnisse

41 Patienten (Tabelle I) wurden zur Behandlung entweder mit Eisen(II)-sulfat (n=21) oder Eisen(III)-Polymaltose-Komplex (n=20) nach dem Zufallsprinzip aufgeteilt. 37 Patienten durchliefen den Versuch protokollgemäß. Bei diesen Patienten ergab die Zählung der Tabletten eine vergleichbare Compliance bei den mit Eisen(II)-sulfat (100% (82-100)) und mit Eisen(III)-Polymaltose-Komplex (100% (86-100)) behandelten Patienten. Drei Patienten (1 Morbus Crohn, 2 Colitis ulcerosa) brachen die Einnahme von Eisen(II)-sulfat nach 1, 4 bzw. 5 Tagen ab, und ein Patient (Morbus Crohn) brach die Behandlung mit Eisen(III)-Polymaltose-Komplex nach 1 Tag ab. Sie erlitten alle nicht tolerierbare Darmbewegungen, Bauchschmerzen und Übelkeit. Diese Patienten wurden von der Analyse der Laborwerte ausgeschlossen, sind in der Analyse der klinischen Erkrankungsaktivität und der Symptomwerte aber eingeschlossen.

Marker für oxidativen Stress

Die Behandlung mit Eisen(II)-sulfat erhöhte die Plasma-MDA-Werte deutlich um 95 nmol/l (CI 18 bis 171; p=0,018) (Figur 1) und erhöhte die Urin-Iso-$PGF_{2\alpha}$ -Werte um 194 pg/mg Kreatinin (CI-58 bis 447; p =0,12). Die Behandlung mit Eisen(III)-Polymaltose-Komplex veränderte Plasma-MDA (p=0,16) (Figur 1) oder Urin-Iso-$PGF_{2\alpha}$ (p=0,56) nicht signifikant (Tabelle II). Plasma-Vitamine A, C und E, Beta-Carotin, Glutathion, Cystein, Cysteinyl-Glycin und Homocystein waren nach beiden Behandlungen unverändert (Tabelle II). Beim Vergleich der Behandlung von Eisen(II)-sulfat und Eisen(III)-Polymaltose-Komplex unterschieden sich die Veränderungen (vorher-nachher) in Plasma-MDA (p=0,08) und Urin-Iso-$PGF_{2\alpha}$ (p=0,28) nicht signifikant. Die mittleren Plasma-MDA-Werte der beiden Gruppen waren aber nach der jeweiligen Behandlung signifikant unterschiedlich (p=0,007), wobei in der Eisen(II)-sulfat-Gruppe höhere MDA-Werte auftraten (Tabelle II). Keiner der Urin-oder Plasma-Parameter korrelierte mit den klinischen Aktivitäts-Indizes.

Klinische Erkrankungsaktivität und Symptome

Die Wertzahlen der klinischen Erkrankungsaktivität sind in Tabelle III angegeben. Weder die Behandlung mit Eisen(II)-sulfat (p=0,45) noch die Behandlung mit Eisen(III)-Polymaltosekomplex (p=0,80) veränderte die klinischen Erkrankungsaktivitäts-Indizes wesentlich, und die Veränderungen zwischen den Behandlungen unterschieden sich nicht (p=0,81), wobei sich während der Behandlung mit Eisen(II)-sulfat die Anzahl der Stuhlgänge (von 19 (7-106) auf 24 (7-55); p=0,0087) erhöhte, Eisen(III)-Polymaltosekomplex die Gesamtzahl der Stuhlgänge pro Woche jedoch nicht veränderte (von 17(7-46) auf 17 (6-66); p=0,25. Weder Eisen(II)-sulfat noch Eisen(III)-Polymaltose-Komplex hatte Einfluss auf das allgemeine Wohlbefinden oder auf die Bauchschmerzen-Wertzahl (Daten nicht angegeben). Vermehrte Übelkeit wurde von 9/21 Patienten bei Eisen(II)-sulfat und bei 7/20 Patienten beim Eisen(III)-Polymaltosekomplex angegeben (p=0,75).

Routine-Laboruntersuchungen

Die Routine-Laboruntersuchungen sind in Tabelle III angegeben. Weder Eisen(II)-sulfat noch Eisen(III)-Polymaltosekomplex erhöhte Blut-Hämoglobin. Nur Eisen(II)-sulfat hatte einen signifikanten Einfluss auf die biochemischen

Marker von Eisenmangel, mit einem Anstieg in Reticulocyten-Hämoglobin (1,9 pg mi CI 0,01 bis 3,8; p=0,049), S-Ferritin (12 µg/l mit CI 6 bis 17; p=0,0003) und Blut-Reticulozytenzahl (0,016 $x10^{12}$/l mit CI –0,004 bis 0,036; p=0,10), und einer Abnahme der hypochromen roten Zellen (-2,5% mit CI –4,6 bis –0,3; p=0,026), des Serum-löslichen Transferrin-Rezeptors (-0,21 mg/l mit CI –0,31 bis –0,11; p=0,0005) und der Serum-Gesamteisenbindungs-kapazität (-7 µmol/l mit CI –10 bis –4; p<0,0001). Eisen(III)-Polymaltose-Komplex erhöhte nur die Blut-Reticulozytenzahl (0,016x10^{12}/l mit CI ,001 bis 0,030; p=0,034).

Aus den Ergebnissen der Studie wird deutlich, dass bei Patienten mit chronisch entzündlichen Darmerkrankungen eine gute Verträglichkeit der Eisentherapie mit Eisen(III)-Polymaltosekomplex erreicht wird, wobei insbesondere die Stuhlfrequenz gegenüber Eisen(II)-sulfat erniedrigt war und weniger Patienten die Studie wegen Darmbeschwerden abbrachen. Darüber hinaus ist der oxidative Stress bei der erfindungsgemäßen Therapie deutlich geringer als mit Eisen(II)-sulfat.

Tabelle I. Patientencharakteristik. Median (Bereich) für Alter, Anzahl und weitere Parameter

	Eisen(II)-sulfat	Eisen(III)-Polymaltose-Komplex
M. Crohn/Colitis ulcerosa	13/8	11/9
Weiblich/männlich	13/8	12/8
Alter	41 (17-69)	31.5 (16-68)
Krankheitslokalisierung M. Crohn*		
terminales Ileum	2	2
Colon	4	1
Ileocolon	3	4
oberer GI	4	4
Krankheitslokalisierung UC		
distale Colitis	1	2
subtotale Colitis	3	3
Gesamt-Colitis	4	4
Gleichzeitige Medikation		
5-ASA	13	11
Sulphasalazin	1	2
Steroide	7	5
Azathioprin	6	5
Keine	1	5

*Krankheitslokalisierung für M. Crohn wie von der Wiener Klassifikation für M. Crohn definiert.
UC: Colitis ulcerosa

Tabelle II. Marker für oxidativen Stress. Mittelwert (SEM).

	Eisen(II)-sulfat		Eisen(III)-Polymaltose-Komplex	
Parameter	Vorher	Nachher	Vorher	Nachher
U-8-iso-$PGF_{2\alpha}$ (pg/mg Kreatinin)	417 (46)	629 (124)	396 (46)	434 (64)
P-Malondialdehyd (nmol/L)	294 (25)	395 (25) *	275 (21)	300 (19)
P-Vitamin A (µmol/L)	1.7 (0.2)	1.8 (0.2)	1.6 (0.1)	1.9 (0.3)
P-Vitamin C (µmol/L)	60.9 (6.0)	58.6 (5.4)	61.3 (5.1)	54.5 (5.5)
P-Vitamin E (µmol/L)	30.2 (1.8)	29.3 (1.5)	29.3 (1.6)	28.3 (1.7)
P-beta-Carotin (µmol/L)	0.67 (0.09)	0.67 (0.10)	0.59 (0.13)	0.57 (0.09)
P-Glutathion (µmol/L)	5.05 (0.48)	5.08 (0.54)	5.22 (0.30)	5.43 (0.43)
P-Cystein (µmol/L)	203 (11)	199 (13)	211 (11)	209 (11)
P-Cysteinylglycin (µmol/L)	16.7 (1.1)	16.6 (1.2)	18.7 (0.9)	18.5 (1.1)
P-Homocystein (µmol/L)	4.87 (0.59)	4.58 (0.47)	6.53 (1.16)	6.04 (0.94)

* Signifikant verschieden vom Spiegel vor der Behandlung ($p<0.05$). Daten von 4 Patienten, die die Behandlung abbrachen, sind nicht in der Tabelle enthalten.
P: Plasma; U: Urin

Tabelle III. Routine-Laboruntersuchungen. Mittelwert (SEM)

		Eisen(II)-sulfat		Eisen(III)-Polymaltose-Komplex	
Parameter	Normal	Vorher	Nachher	vorher	nachher
B-Hämoglobin (g/dL)	w 11.6-16.0 m 13.2-16.6	13.1 (0.4)	13.3 (0.3)	12.5 (0.3)	12.5 (0.3)
B-Hämatokrit (%)	w 36-46 m 37-49	41 (1)	42 (1)*	39 (1)	40 (1)
MCV (fL)	80-102	86 (1.6)	87 (1.3)*	84 (1.8)	85 (1.6)
MCH (pg)	27-35	27 (0.8)	28 (0.8)*#	27 (0.7)	27 (0.7)
MCHC (g/dL)	31.0-36.0	31.8 (0.4)	32.0 (0.3)	31.6 (0.3)	31.2 (0.3)
Reticulocyten-Hämoglobin (CHr) (pg)	>28	29.3 (0.8)	31.1(0.7)*	29.1 (0.8)	29.5 (0.7)
Hypochrome rote Zellen (HYPO) (%)	<5	10.4 (3.6)	8.8 (3.2)*	10.3 (3.0)	10.6 (2.8)
B-Erythrocytenzahl (10^{12}/L)	w 3.7-5.5 m 4.0-5.8	4.8 (0.1)	4.8 (0.1)	4.7 (0.1)	4.7 (0.1)
B-Reticulocytenzahl (10^{12}/L)	0.030-0.100	0.068 (0.006)	0.084 (0.007)	0.059 (0.006)	0.075 (0.008)*
B-Leucocytenzahl (10^9/L)	3.5-11.0	6.5 (0.5)	6.3 (0.4)	6.9 (0.6)	7.0 (0.7)
B-Plättchenzahl (10^9/L)	140-400	324 (23)	306 (21)	347 (18)	343 (21)
S-Gesamteisenbindungs-kapazität (µmol/L)	49-85	81 (2)	74 (2)*#	77 (2)	77 (2)
S-Eisen (µmol/L)	9.0-33.0	11.1 (2.0)	14.2 (2.2)	8.8 (0.8)	8.9 (1.5)
S-Ferritin (µg/L)	w 15-160 m 25-200	13 (2)	25 (3)*#	13 (2)	13 (2)
S-löslicher Transferrin-Rezeptor (mg/L)	0.84-1.54	1.95 (0.18)	1.77 (0.13)*	2.08 (0.24)	2.03 (0.21)
B-ESR (mm/h)	w <20 m <15	11 (2)	10 (2)	22 (3)	20 (3)*
S-CRP (mg/L)	<10	7 (2)	6 (2)	12 (3)	11 (2)

* Signifikant verschieden vom Spiegel vor der Behandlung ($p<0.05$).
# Signifikant unterschiedliche Änderung verglichen mit Eisen(III)-Polmaltose-Komplexp<0.05). Daten von vier Patienten, die die Behandlung abbrachen, sind nicht in der Tabelle enthalten.
w: weiblich
m: männlich
B: Blut
S: Serum

PATENTANSPRÜCHE:

1. Verwendung von Eisen(III)-Komplexverbindungen mit Kohlenhydraten zur Herstellung eines Arzneimittels zur oralen Behandlung von Eisenmangel-Zuständen bei Patienten mit chronisch entzündlicher Darmerkrankung.

2. Verwendung nach Anspruch 1, worin die Kohlenhydrate aus der Gruppe ausgewählt werden, die aus Dextranen und hydrierten Dextranen, Dextrinen und hydrierten oder oxidierten Dextrinen sowie Pullulan, Oligomeren davon und hydriertem Pullulan besteht.

3. Verwendung nach Anspruch 1 oder 2, worin die Kohlenhydrate aus oxidierten oder hydrierten Dextrinen ausgewählt werden.

4. Verwendung nach Anspruch 1 oder 2, worin die Eisen(III)-Komplexverbindung eine Eisen(III)-Polymaltose-Komplexverbindung ist.

5. Verwendung nach Anspruch 4, worin die Eisen(III)-Polymaltose-Komplexverbindung ein Molekulargewicht im Bereich von 20000 bis 500000 Dalton besitzt.

6. Verwendung nach einem der Ansprüche 1 bis 5, worin die Eisen(III)-Komplexverbindung eine Eisen(III)-Komplexverbindung mit einem Oxidationsprodukt von einem oder mehreren Maltodextrinen ist.

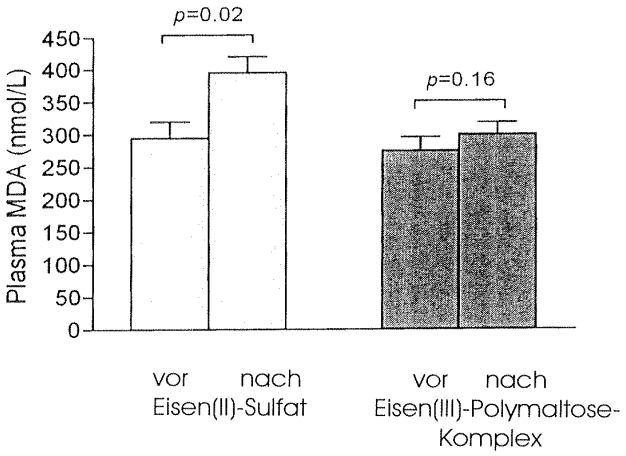
7. Verwendung nach Anspruch 6, worin die Eisen(III)-Komplexverbindung ein wasserlöslicher Eisen-Kohlenhydrat-Komplex ist, erhältlich aus einer wässrigen Eisen(III)-Salzlösung und einer wässrigen Lösung des Produktes der Oxidation von einem oder mehreren Maltodextrinen mit einer wässrigen Hypochloritlösung bei einem pH-Wert im

alkalischen Bereich, wobei beim Einsatz von einem Maltodextrin dessen Dextrose-Äquivalent bei 5 bis 37 und beim Einsatz eines Gemisches aus mehreren Maltodextrinen das Dextrose-Äquivalent des Gemisches bei 5 bis 37 und das Dextrose Äquivalent der am Gemisch beteiligten einzelnen Maltodextrine bei 2 bis 40 liegt.

8. Verwendung nach einem der Ansprüche 1 bis 7, worin das Arzneimittel in der Form einer Tablette, einer wässrigen Lösung oder Emulsion, als Granulat, Kapsel, Gel oder als Sachet vorliegt.

9. Verwendung nach einem der Ansprüche 1 bis 8, wobei die chronisch entzündliche Darmerkrankung Morbus Crohn und/oder Colitis ulcerosa ist.

Figur 1


p=0.02
p=0.16
Plasma MDA (nmol/L)
450
400
350
300
250
200
150
100
50
0
vor
nach
Eisen(II)-Sulfat
vor
nach
Eisen(III)-Polymaltose-Komplex

Electronic Acknowledgement Receipt

EFS ID:	6848230
Application Number:	11620986
International Application Number:	
Confirmation Number:	1325
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	George H. Blosser/Elizabeth Holtmann
Filer Authorized By:	George H. Blosser
Attorney Docket Number:	30015730-0043
Receipt Date:	20-JAN-2010
Filing Date:	08-JAN-2007
Time Stamp:	16:58:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_Transmittal_Luitpold_0043.pdf	98036 8f9aa8cca5ee875b71907557b4e591b52e7d0cff	no	2
Warnings:					
Information:					

2	Information Disclosure Statement (IDS) Filed (SB/08)	US_IDS_Form__SB_08_From_ESR.pdf	771009 2762eb75cced215590b6c1af7111aec913fb94ed	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Foreign Reference	WO1997011711.pdf	1581882 aa76527dce8a53db57a88761ed8503b499d2ce65	no	38
Warnings:					
Information:					
4	Foreign Reference	WO2004037865.pdf	1184350 3d9c452d5c29a879995fba0e234cce100b20d11f	no	25
Warnings:					
Information:					
5	Foreign Reference	WO2007023154.pdf	1333685 696dc7502b72cff045aa18946d02d494d2d8bcda	no	24
Warnings:					
Information:					
			Total Files Size (in bytes):	4968962	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **11/620,986**	Examiner: **LAU, Jonathan S.**
Applicant: **HELENEK, Mary Jane**	Group Art Unit: **1623**
Filed: **08 January 2007**	Confirmation No.: **1325**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	Customer No.: **26263**
Docket No.: **30015730-0043**	

January 20, 2010

FILED ELECTRONICALLY VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT

UNDER 37 C.F.R. 1.97(c)

Sir:

In accordance with the provisions of 37 C.F.R. § 1.56, Applicants request citation and examination of the references identified on the attached PTO-SB08A and PTO-SB08B forms, in accordance with 37 C.F.R. §1.98, be made during the course of examination of the above-referenced application for United States Letters Patent.

Under 37 C.F.R. § 1.97(c), the information disclosure statement transmitted herewith is being filed ***after*** : (1) three months of the filing date of a national application other than a continued prosecution application under § 1.53(d); (2) three months of the date of entry of the national stage as set forth in § 1.491 in an international application; (3) the mailing of a first Office action on the merits; or (4) the mailing of a first Office action after the filing of a request for continued examination under § 1.114; but ***before*** the mailing date of any of a final action under § 1.113, a notice of allowance under § 1.311, or an action that otherwise closes prosecution in the application, whichever occurs first. 37 C.F.R. § 1.97(c).

Pursuant to 37 C.F.R. § 1.97(e)(2), no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application and to the knowledge of the person signing the statement after making

reasonable inquiry, was known to any individual designated in Section 1.56(c) more than three months prior to the filing of the information disclosure statement.

The filing of this information disclosure statement shall not be construed as a representation that a search has been made, an admission that the information cited is, or is considered to be, material to patentability, or that no other material information exists (*see* 37 C.F.R. § 1.97(g)). The filing of this information disclosure statement shall not be construed as an admission against interest in any manner. Notice of January 9, 1992, 1135 O.G. 13-25, at 25.

Applicants believe that no fee is due at this time. However, the Commissioner is hereby authorized to charge any required fees to Deposit Account No. 19-3140.

Respectfully submitted,

SONNENSCHEIN NATH & ROSENTHAL LLP

/G. Harley Blosser/
By: _____
G. Harley Blosser
Reg. No. 33,650
Telephone No. 314-259-5806

ATTORNEYS FOR APPLICANT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **11/620,986**	Examiner: **LAU, Jonathan S**
Applicant: **HELENEK, MARY JANE**	Group Art Unit: **1623**
Filed: **January 1, 2007**	Confirmation No.: **1325**
Title: **30015730-0043**	Customer No.: **26263**
Docket No.: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	

January 8, 2010

FILED ELECTRONICALLY VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO OFFICE ACTION

UNDER 37 C.F.R. § 1.111

Sir:

In response to the Office Action of December 15, 2009, Applicants request the Office consider the following amendments and remarks.

IN THE CLAIMS

1. (**currently amended**) A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism **resulting in reduced bioavailability of dietary iron**, comprising

administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron;

wherein

the iron carbohydrate complex is selected from the group consisting of an iron carboxymaltose complex, an iron mannitol complex, ~~**an iron polyisomaltose complex,**~~ an iron polymaltose complex, an iron gluconate complex, **and** an iron sorbitol complex~~**, and an iron hydrogenated dextran complex**~~; and

the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component and substantially no cross reactivity with anti-dextran antibodies.

2. (original) The method of claim 1 wherein the disease, disorder, or condition is anemia.

3. (original) The method of claim 2 wherein the anemia is iron deficiency anemia.

4. (original) The method of claim 3 wherein the iron deficiency anemia is associated with chronic blood loss; acute blood loss; pregnancy; childbirth; childhood development; psychomotor and cognitive development in children; breath holding spells; heavy uterine bleeding; menstruation; chronic recurrent hemoptysis; idiopathic pulmonary siderosis; chronic internal bleeding; gastrointestinal bleeding; parasitic infections; chronic kidney disease; dialysis; surgery or acute trauma; and chronic ingestion of alcohol, chronic ingestion of salicylates, chronic ingestion of steroids; chronic ingestion of non-steroidial anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents.

5. (original) The method of claim 2 wherein the anemia is anemia of chronic disease.

6. (original) The method of claim 5 wherein the chronic disease is selected from the group consisting of rheumatoid arthritis; cancer; Hodgkins leukemia; non-Hodgkins leukemia; cancer chemotherapy; inflammatory bowel disease; ulcerative colitis thyroiditis; hepatitis; systemic lupus erythematosus; polymyalgia rheumatica; scleroderma; mixed connective tissue disease; Sojgren's syndrome; congestive heart failure / cardiomyopathy; and idiopathic geriatric anemia.

7. (original) The method of claim 2 wherein the anemia is due to impaired iron absorption or poor nutrition.

8. (original) The method of claim 7, wherein the anemia is associated with Crohn's Disease; gastric surgery; ingestion of drug products that inhibit iron absorption; or chronic use of calcium.

9. (**currently amended**) The method of claim 1 wherein the disease, disorder, or condition is selected from the group consisting of restless leg syndrome; blood donation; ~~**Parkinson's disease;**~~ hair loss; and attention deficit disorder.

10. (original) The method of claim 1 wherein the single dosage unit of elemental iron is at least about 0.7 grams.

11. (original) The method of claim 10 wherein the single dosage unit of elemental iron is at least about 0.8 grams.

12. (original) The method of claim 11 wherein the single dosage unit of elemental iron is at least about 0.9 grams.

13. (original) The method of claim 12 wherein the single dosage unit of elemental iron is at least about 1.0 grams.

14. (original) The method of claim 13 wherein the single dosage unit of elemental iron is at least about 1.5 grams.

15. (original) The method of claim 14 wherein the single dosage unit is at least about 2.0 grams.

16. (original) The method of claim 15 wherein the single dosage unit of elemental iron is at least about 2.5 grams.

17. (original) The method of claim 1 wherein the single dosage unit of elemental iron is administered in about 15 minutes or less.

18. (original) The method of claim 17 wherein the single dosage unit of elemental iron is administered in about 10 minutes or less.

19. (original) The method of claim 18, wherein the single dosage unit of elemental iron is administered in about 5 minutes or less.

20. (original) The method of claim 19, wherein the single dosage unit of elemental iron is administered in about 2 minutes or less.

21. (**canceled**)

22. (original) The method of claim 1 wherein the iron carbohydrate complex has a pH between about 5.0 to about 7.0; physiological osmolarity; an iron core size no

greater than about 9 nm; a mean diameter particle size no greater than about 35 nm; and a blood half-life of between about 10 hours to about 20 hours.

23. (original) The method of claim 1 wherein the iron carbohydrate complex contains about 24% to about 32% elemental iron; contains about 25% to about 50% carbohydrate; and has a molecular weight of about 90,000 daltons to about 800,000 daltons.

24-25. (canceled)

26. (previously presented) The method of claim 1 wherein the iron carbohydrate complex is an iron carboxymaltose complex.

27. (original) The method of claim 26 wherein the iron carboxymaltose complex contains about 24% to about 32% elemental iron, about 25% to about 50% carbohydrate, and is about 100,000 daltons to about 350,000 daltons.

28. (original) The method of claim 26 wherein the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between about 5 and about 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between about 5 and about 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between about 2 and about 20.

29. (original) The method of claim 26 wherein:

the iron carboxymaltose complex has a chemical formula of $[FeO_x(OH)_y(H_2O)_z]_n$ $[\{(C_6H_{10}O_5)_m(C_6H_{12}O_7)\}_l]_k$, where n is about 103, m is about 8, l is about 11, and k is about 4;

contains about 28% elemental iron; and

has a molecular weight of about 150,000 Da.

30. (original) The method of claim 26 wherein the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

31. (original) The method of claim 25 wherein the iron carbohydrate complex is an iron polyglucose sorbitol carboxymethyl ether complex.

32. (original) The method of claim 31 wherein the iron polyglucose sorbitol carboxymethyl ether complex is a polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite complex.

33. (original) The method of any one of claims 1 wherein the iron carbohydrate complex comprises an iron core with a mean iron core size of no greater than about 9 nm.

34. (original) The method of claim 33 wherein the mean iron core size is at least about 1 nm but no greater than about 9 nm.

35. (original) The method of claim 34 wherein the mean iron core size is at least about 3 nm but no greater than about 7 nm.

36. (original) The method of claim 35 wherein the mean iron core size is at least about 4 nm but not greater than about 5 nm.

37. (original) The method of claim 1 wherein mean size of a particle of the iron carbohydrate complex is no greater than about 35 nm.

38. (original) The method of claim 37 wherein the particle mean size is no greater than about 30 nm.

39. (original) The method of claim 38 wherein the particle mean size is no greater than about 25 nm.

40. (original) The method of claim 39 wherein the particle mean size is no greater than about 20 nm.

41. (original) The method of claim 40 wherein the particle mean size is no greater than about 15 nm.

42. (original) The method of claim 41 wherein the particle mean size is no greater than about 10 nm.

43. (original) The method of claim 42 wherein the particle mean size is at least 6 nm but no greater than about 7 nm.

44. (original) The method of claim 1 wherein the iron carbohydrate complex is administered parenterally.

45. (original) The method of claim 44 wherein the iron carbohydrate complex is administered intravenously.

46. (original) The method of claim 45 wherein the iron carbohydrate complex is intravenously infused.

47. (original) The method of claim 46 wherein the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent.

48. (original) The method of claim 47 wherein the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 250 ml of diluent.

49. (original) The method of claim 47 wherein the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 215 ml of diluent.

50. (original) The method of claim 45 wherein the iron carbohydrate complex is intravenously injected as a bolus.

51. (original) The method of claim 50 wherein the single unit dose of iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent.

52. (original) The method of claim 51 wherein the single unit dose of iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 250 ml of diluent.

53. (original) The method of claim 51 wherein the single unit dose of iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 215 ml of diluent.

54. (original) The method of claim 44 wherein the iron carbohydrate complex is administered intramuscularly.

55. (original) The method of claim 54 wherein the iron carbohydrate complex is intramuscularly injected at a concentration of about 500 mg elemental iron in less than about 10 ml diluent.

56. (original) The method of claim 1 further comprising a second administration of said iron carbohydrate complex upon recurrence of at least one symptom of the disease, disorder, or condition.

57. (original) The method of claim 1 further comprising a second administration of said iron carbohydrate complex after 1 day to 12 months after the first administration.

58. (**currently amended**) A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism **resulting in reduced bioavailability of dietary iron**, comprising:

intravenously administering to a subject in need thereof an iron carboxymaltose complex in a single dosage unit of at least about 1000 mg of elemental iron in about 200 ml to about 300 ml of diluent in about 5 minutes or less;

wherein the iron carboxymaltose complex comprises an iron core with a mean iron core size of at least about 1 nm but no greater than about 9 nm;

wherein mean size of a particle of the iron carboxymaltose complex is no greater than about 35 nm;

wherein the iron carboxymaltose complex is administered intravenously infused or intravenously injected at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent.

59. (original) The method of claim 58 wherein the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between about 5 and about 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between about 5 and about 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between about 2 and about 20.

60. (original) The method of claim 58 wherein the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

REMARKS

Upon entry of this amendment, claims 1-20, 22-23, and 26-60 are pending. Claims 1 and 58 have been amended. No claims have been added. No claims are presently withdrawn. Claims 21 and 24-25 have been canceled.

Support for the amendment to claim 1 appears at least at claim 1 and at p. 15, ¶0052. Support for the amendment to claim 58 appears at least at p. 15, ¶0052.

No new matter has been added by way of this response.

Election/Restrictions

Applicants acknowledge withdrawal of the species election requirement of the Action of Feb. 23, 2009. Applicants acknowledge rejoinder of previously withdrawn claims 6-9, 31, 32, 44, and 50-55.

The Office is presently examining the full scope of claims 1-23 and 26-60.

Allowable Subject Matter

The Office acknowledges the following as allowable subject matter (at Action, p. 13-14):

> … treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism resulting in reduced bioavailability of dietary iron comprising administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron wherein the iron carbohydrate complex is selected from the group consisting of an iron carboxymaltose complex, iron mannitol complex, iron polymaltose complex, iron gluconate complex, iron sorbitol complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies.

Withdrawn Rejections

Applicants acknowledge withdrawal of the rejection of claims 1-5, 10-24, 33-43, 45-49, and 56-57 under 35 U.S.C. §112, ¶2 as being indefinite.

Applicants acknowledge withdrawal of the rejection of claims 1-5, 10-30, 33-43, 45-49, and 56-60 under 35 U.S.C. §103(a) as being unpatentable over Lawrence et al., US 5,624,668, in view of Helenek et al., US 2004/0180849 issued as US 6,960,571.

Claim Rejections under 35 U.S.C. § 112, ¶1 : Enablement

Applicants respectfully traverse and, for the following reasons, request reconsideration and withdrawal of the rejection of claims 1-23 and 26-60 under 35 U.S.C. §112, ¶1 as failing to comply with the enablement requirement. Claim 21 has been canceled making the above rejection moot as to this claim.

The Office acknowledges that the specification is enabling for "treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism resulting in reduced bioavailability of dietary iron" (Action, p. 5).

First, the Office asserts that the specification does not reasonably provide enablement for "treating a disease, disorder, or condition characterized by dysfunctional iron metabolism resulting in an increased iron content (instant claims 1 and 58), such as Parkinson's disease (instant claim 9)". In the interest of furthering prosecution, claims 1, 9 and 58 have been amended in accordance with the Office's acknowledgment of allowable subject matter.

Second, the Office asserts that the specification does not reasonably provide enablement for "iron polyisomaltose complex or iron hydrogenated dextran complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies (instant claim I)". In the interest of furthering prosecution, claim 1 has been amended in accordance with the Office's acknowledgment of allowable subject matter.

Third, the Office asserts that the specification does not reasonably provide enablement for "the method wherein the subject does not experience a significant adverse reaction to the single dosage unit administration of at least about 0.6 grams of elemental iron (instant claim 21)". In the interest of furthering prosecution, claim 21 has been canceled.

Thus, Applicants believe all concerns of the Office to be addressed with respect to the above rejection.

CONCLUSION

Applicants respectfully request withdrawal of the rejections and believe that the claims as presented represent allowable subject matter. If the Examiner desires, Applicants welcome a telephone interview to expedite prosecution. Applicants believe there are no fees due at this time. The Commissioner is hereby authorized to deduct any deficiency or credit any overpayment with respect to this response to Deposit Account No. 19-3140.

Respectfully submitted,

By: /G. Harley Blosser/ (Reg. 33,650)
G. Harley Blosser
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. Box 061080
Wacker Drive Station, Sears Tower
Chicago, IL 60606-1080
Telephone: 314/259-5806
Fax: 312/876-7934

ATTORNEYS FOR APPLICANT

Electronic Acknowledgement Receipt

EFS ID:	6778783
Application Number:	11620986
International Application Number:	
Confirmation Number:	1325
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	George H. Blosser/Dennis Harney
Filer Authorized By:	George H. Blosser
Attorney Docket Number:	30015730-0043
Receipt Date:	08-JAN-2010
Filing Date:	08-JAN-2007
Time Stamp:	17:15:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	ROA_30015730-0043_Jan8_2010.pdf	96155 d444046b66d6bc2c208651b33d1df4c40e05523d	no	13

Warnings:	
Information:	

Total Files Size (in bytes):	96155

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/620,986	Filing Date 01/08/2007	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	01/08/2010	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 57	Minus	** 60	= 0	X $26 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $110 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/Renee Collins/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043	1325

26263 7590 12/15/2009

SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, WILLIS TOWER
CHICAGO, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
12/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No.	Applicant(s)	
	11/620,986	HELENEK ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 26-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 26-60* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office is responsive to Applicant's Amendment and Remarks, filed 26 Aug 2009, in which claim 1 is amended to change the scope and breadth of the claim, claim 58 is amended to correct a minor informality, claim 26 is amended to change dependency, and claims 24-25 are canceled.

The declaration of Richard P. Lawrence (inventor), submitted by Applicants on 26 Aug 2009 under 37 CFR § 1.132, is acknowledged and will be further discussed below.

This application is a domestic application, filed 08 Jan 2007; and claims benefit of provisional application 60/757,119, filed 06 Jan 2006.

Claims 1-23 and 26-60 are pending in the current application. Claims 6-9, 31, 32, 44 and 50-55, drawn to non-elected species, are rejoined herein. Claims 1-23 and 26-60 are examined on the merits herein.

Election/Restrictions

The election of species requirement detailed in the Office Action mailed 23 Feb 2009 is **withdrawn**.

Claims 6-9, 31, 32, 44 and 50-55, drawn to non-elected species, are rejoined herein. The full scope of claims 1-23 and 26-60 are examined on the merits herein.

Rejections Withdrawn

Applicant's Amendment, filed 26 Aug 2009, with respect to claims 1-5, 10-24, 33-43, 45-49 and 56-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite has been fully considered and is persuasive, as amended claim 1 recites the structural features of said iron carbohydrate complex necessary for the recited function.

This rejection has been **withdrawn**.

Applicant's Remarks, filed 26 Aug 2009, and the declaration of Richard P. Lawrence (inventor), submitted by Applicants on 26 Aug 2009 under 37 CFR § 1.132, with respect to claims 1-5, 10-30, 33-43, 45-49 and 56-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawrence et al. (US Patent 5,624,668, issued 29 Apr 1997, of record) in view of Helenek et al. (US Patent Application Publication 2004/0180849, published 16 Sep 2004, of record, issued as US Patent 6,960,571, provided by Applicant in IDS mailed 24 Jan 2008) has been fully considered and is persuasive, as Applicant's Remarks in view of the declaration of Richard P. Lawrence (inventor) under 37 CFR § 1.132 are persuasive that the teaching of Helenek et al. is drawn to the properties of the specific iron carbohydrate complexes taught by Helenek et al. such as release rate and dosage and the declaration of Richard P. Lawrence (inventor) is persuasive that the teaching of Helenek et al. are therefore not combinable with the teaching of Lawrence et al. with a reasonable expectation of success; Applicant's Remarks in view of the declaration of Richard P. Lawrence (inventor) under

37 CFR § 1.132 are persuasive that the combination of Lawrence et al. in view of Helenek et al. does not teach the instant invention as claimed; and the ordinary level of skill taught by the state of the art teaches away from high dose iron carbohydrate complexes are provided by Applicant at page 18 of Remarks filed 26 Aug 2009 and as further detailed below.

This rejection has been **withdrawn**.

Claim Objections

Amended Claim 1 is objected to because of the following informalities: at lines 14-17, claim 1 appears to repeat the text of canceled claim 25. Appropriate correction is required.

The following are new grounds of rejection in view of the withdrawal of the election of species requirement and the expansion of examination to the full scope of claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended Claims 1-23 and 26-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism

resulting in reduced bioavailability of dietary iron (specification page 15, paragraph 52), does not reasonably provide enablement for:

- treating a disease, disorder, or condition characterized by dysfunctional iron metabolism resulting in an increased iron content (instant claims 1 and 58), such as Parkinson's disease (instant claim 9),
- iron polyisomaltose complex or iron hydrogenated dextran complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies (instant claim 1),
- the method wherein the subject does not experience a significant adverse reaction to the single dosage unit administration of at least about 0.6 grams of elemental iron (instant claim 21).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism comprising administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron wherein the iron carbohydrate complex is selected from the group consisting of an iron carboxymaltose complex, iron mannitol complex, iron polyisomaltose complex, iron polymaltose complex, iron gluconate complex, iron sorbitol complex and iron hydrogenated dextran complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies.

The state of the prior art:

- treating a disease, disorder, or condition characterized by dysfunctional iron metabolism resulting in an increased iron content

Sofic et al. (J. Neural Transm, 1988, 74, p199-205, cited in PTO-892) discloses that there is an increase in the levels of total iron in the port morten substantia nigra of Parkinson's disease compared to controls and concludes changes in total iron are likely to be involved in the pathphysiology and treatment of this disorder (anstract). Sofic et al. discloses that a special ferric-ferrous complex has therapeutic effect (page 200, paragraph 1) increased availability of non-reactive iron may be an additional factor of enhanced vulnerability of substantia nigra towards neurotoxic events (page 200, paragraph 2). Sofic et al. discloses a significant increase in the concentration of total iron and iron (III) found in the substantia nigra of Parkinson's disease (page 202, paragraph 1). Sofic et al. discloses that it is known that there is a dependence of

severity and increase of iron in substantia nigra and that the distribution of iron might contribute to increase the vulnerability of the nigrostriatial system to neurotoxins (page 202, section Discussion).

Sipe et al. (Brain Iron Metabolism and Neurodegenerative Disorders, 2002, 24(2-3), p188-196, cited in PTO-892) discloses that iron has frequently been found to accumulate in brain regions that undergo degeneration in neurological diseases and that neurodegenerative disorders are associated with iron overload (abstract). Sipe et al. discloses that dysfunctional iron metabolism can lead to iron accumulation in distinctive brain regions (page 190, right column, paragraph 2). Sipe et al teaches increased total brain iron content is associated with diseases such as Alzheimer disease and Parkinson's disease (page 191). Sipe et al. concludes that iron excess in the nervous system may result in neurodegenerative disorders (page 193, right column, paragraph 3).

- iron polyisomaltose complex or iron hydrogenated dextran complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies

Cisar et al. (Journal of Experimental Medicine, 1975, 142, p435-459, cited in PTO-892) discloses that while dextrans are branched polymers, anti-dextran antibodies recognize both terminal and non-terminal α(1-6) chains of dextran binding to a trisaccharide to hexasaccharide sized site (page 436, paragraphs 2-3). Cisar et al. discloses an antibody that binds to dextran binding with synthetic dextran that reacts as a completely linear molecule (paragraph spanning bottom of page 436 and top of page

437), or polyisomaltose. Therefore one of skill in the art would expect anti-dextran antibodies to cross react with polyisomaltose, which is a linear α(1-6) chain of dextran, and hydrogenated dextran, which is a dextran of lower molecular weight.

- the method wherein the subject does not experience a significant adverse reaction to the single dosage unit administration of at least about 0.6 grams of elemental iron

Macdougall (Nephrol. Dial. Transplant, 2000, 15, p1743-1745, cited in PTO-892) discloses that the maximum dose of iron gluconate is 125 mg, and if the maximum dose is exceeded it may result in "free iron" reactions which are anaphylactoid in nature (page 1743, right column, paragraph 1), which are adverse events. Macdougall suggests the maximum dose of iron sucrose is 500 mg, teaching that it is known that other iron carbohydrate complexes also have a maximum dose above which there are adverse events.

Andersson (British Medical Journal, 1961, p275-279, cited in PTO-892) discloses adminstration of iron sorbitol complex at a dosage of 100 mg of elemental iron caused no significant adverse reaction (page 277, left column, paragraph 2), however administration at 250 mg of elemental iron were reported to cause systemic side effects (page 278, paragraph spanning bottom of left column and top of right column). Andersson suggests that the absence of systemic side effects was due to the lower dosage of iron sorbitol complex, implying the subject would experience a significant adverse reaction if the dosage were increased.

Fielding (British Medical Journal, 1961, p279-283, cited in PTO-892) discloses administration of iron dextrin complex, or iron polymaltose complex, at a dosage of 100 mg (page 280, right column, paragraphs 1-2). Fielding teaches the risk of severe local inflammation and general toxic reactions, or significant adverse reaction, are minimized with iron-dextrin at the 100 mg dose level (page 283, left column, paragraph 4), implying that increasing the dose would result in significant adverse reaction.

Intervening art Newnham et al. (Internal Medicine Journal, 2006, 36(10), p672-674, published online 4 Sep 2006, cited in PTO-892) discloses infusion of a mean dose of 1338 mg iron polymaltose resulting in adverse reactions in 5.7% of patients, and in 6 patients reaction was significant enough to warrant cessation of infusion (page 673, right column, paragraphs 2-3).

Post art Haines et al. (Internal Medicine Journal, 2009, 39, p252-255, cited in PTO-892) discloses high single doses of iron polymaltose may cause significant adverse reaction (page 252, right column, paragraph 2). Haines et al. discloses the dose administered was weight-based (page 253, left column, paragraph 5) resulting in a total of 32 adverse reactions by 13/50 patients (page 253, right column, paragraph 1). Haines et al. discloses the dose received within the high single dose regime had no impact on the rate of adverse events (page 253, right column, paragraph 2).

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The sheer number of diseases, disorders, or conditions characterized by iron deficiency or dysfunctional iron metabolism and subject in need of treatment thereof means that one skilled in the art

cannot predict the usefulness for all possible method of treating said disease, disorder, or condition in said subject. Absent specific guidance it is unpredictable how dysfunctional iron metabolism that results in an increased iron content can be treated by administration of an iron complex, which would be predicted to further increase iron content. Therefore the claimed invention is unpredictable.

The Breadth of the claims: The scope of the claims implicitly includes treating a disease, disorder, or condition characterized by dysfunctional iron metabolism resulting in an increased iron content (instant claims 1 and 58), such as explicitly Parkinson's disease (instant claim 9); explicitly iron polyisomaltose complex or iron hydrogenated dextran complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies (instant claim 1); and explicitly the method wherein the subject does not experience a significant adverse reaction to the single dosage unit administration of at least about 0.6 grams of elemental iron (instant claim 21).

The amount of direction or guidance presented: The specification speaks generally about treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism leading to iron deficiency at page 1 of the specification. It is suggested that treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism leading to iron deficiency is generally known in the art at page 8 of the specification, especially paragraph 26. It is suggested that states characterized by dysfunctional iron metabolism and treatable by dosage with iron carbohydrate complexes include

Parkinson's disease at page 9, paragraph 30. However, guidance is not given for treating dysfunctional iron metabolism resulting in iron overload, such as Parkinson's disease, by administration of an iron complex. Page 16, paragraph 56 provides guidance for iron therapy that avoids iron overload, but does not provides guidance for treating iron overload by administering an iron complex.

The presence or absence of working examples: The only working examples provided are for treating a disease, disorder, or condition characterized by iron deficiency by treating patients with iron-deficiency anemia, renal anemia, postpartum anemia, hemodialysis-associated anemia, gastrointestinal disorder-associate anemia and anemia due to blood loss at pages 29-40 of the specification.

No working example is provided of an iron polyisomaltose complex or iron hydrogenated dextran complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies.

The specification at page 39, paragraphs 125-126 discloses the method as claimed results in 6.8% of patients, encompassed within the full scope of the invention as claimed, reporting adverse events upon treatment with iron carboxymaltose complex by the single dosage unit administration of at least about 0.6 grams of elemental iron.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as treating dysfunctional iron metabolism resulting in an increased iron content by administration of an iron complex or methods wherein the subject does not experience a significant adverse reaction to the single dosage unit administration. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the invention with the full range of all possible methods of administration beyond those known in the art, (such as those causing significant adverse reaction or cross reactivity with anti-dextran antibodies) one skilled in the art would undertake a novel and extensive research program into methods of treating all diseases, disorders, or conditions characterized by iron deficiency or dysfunctional iron metabolism and all subjects in need of treatment. Because this research would have to be exhaustive, and because it would involve such a wide and unpredictable scope of diseases, disorders, or conditions and patient populations, it would constitute an undue and unpredictable experimental burden.

> *Genentech*, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims, Applicants fail to provide information sufficient to practice the claimed invention for the full scope of the claim such as methods of treating a disease, disorder, or condition characterized by dysfunctional iron metabolism resulting in an increased iron content (instant claims 1 and 58), such as explicitly Parkinson's disease (instant claim 9); explicitly iron polyisomaltose complex or iron hydrogenated dextran complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies (instant claim 1); and explicitly the method wherein the subject does not experience a significant adverse reaction to the

single dosage unit administration of at least about 0.6 grams of elemental iron (instant claim 21).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites "significant adverse reaction". This term renders the claim indefinite because it is unclear what standard is used to decide if an adverse reaction is significant or not, and therefore it is unclear which adverse reactions are significant and which are not. The specification at page 39, paragraphs 125-126 provides a measure of adverse reactions in a patient population in terms of statistical significance, but does not provide a standard for determining which adverse reactions are considered significant and which might not be. Absent clear guidance as to determining what adverse reactions are considered significant, all adverse reactions significant enough to merit reporting are interpreted as "significant adverse reactions".

Allowable Subject Matter

As indicated above, the instant invention as claimed is enabled for treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism resulting in reduced bioavailability of dietary iron comprising administering

to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron wherein the iron carbohydrate complex is selected from the group consisting of an iron carboxymaltose complex, iron mannitol complex, iron polymaltose complex, iron gluconate complex, iron sorbitol complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies.

The following is a statement of reasons for the indication of allowable subject matter: Macdougall (Nephrol. Dial. Transplant, 2000, 15, p1743-1745, cited in PTO-892), Andersson (British Medical Journal, 1961, p275-279, cited in PTO-892), and Fielding (British Medical Journal, 1961, p279-283, cited in PTO-892) teach as above with regard to optimizing a lower unit dosage of an iron carbohydrate complex to minimize adverse events.

Nissenson et al. (Kidney International, 2003, 64(Supplement 87), pS64–S71, cited in PTO-892) teaches optimizing the maximum amount of iron carbohydrate complex to minimize adverse events (page S67). Nissenson et al. teaches experience with high doses of iron sucrose and iron gluconate are limited for safety reasons, that doses of iron sucrose between 200 and 400 mg may be safely infused over 120 minutes whereas doses of 400 to 500 mg are best infused over 240 minutes, and infusions of 312.5 to 500 mg iron gluconate have been safely administered but slower infusion rates may be preferable (page S67, right column, paragraph 2).

The instant invention would not have been obvious to one of ordinary skill in the art at the time of the invention because Nissenson et al. in view of the level of skill in the art teaches optimizing the maximum amount of iron carbohydrate complex to minimize adverse events and experience with high doses of iron sucrose and iron gluconate are limited for safety reasons. Therefore it would not have been obvious to one of ordinary skill in the art to increase the dosage because the reasonable expectation of increased adverse events caused by increased dosage constitutes a teaching away from increasing the dosage. It is noted that, regarding patentable utility and safety and efficacy consideration, MPEP 2107.03 V provides, "The Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs."

Intervening art Newnham et al. (Internal Medicine Journal, 2006, 36(10), p672-674, published online 4 Sep 2006, cited in PTO-892) discloses infusion of a mean dose of 1338 mg iron polymaltose to treat a disease, disorder, or condition characterized by iron deficiency such as anemia (page 673, right column, paragraph 2). However, Newnham et al. was published **after** the filing date of parent provisional application 60/757,119, filed 06 Jan 2006.

Therefore the instant invention is not suggested or fairly taught by the prior art of record.

Conclusion

No claim is found to be allowable.

This Office Action details new grounds of rejection not necessitated by Applicant's Amendment. Accordingly, this Office Action is Non-Final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623

Notice of References Cited	Application/Control No. 11/620,986	Applicant(s)/Patent Under Reexamination HELENEK ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 1 of 3

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Sofic et al. J. Neural Transm, 1988, 74, p199-205.
	V	Sipe et al. Brain Iron Metabolism and Neurodegenerative Disorders, 2002, 24(2-3), p188-196.
	W	Cisar et al. Journal of Experimental Medicine, 1975, 142, p435-459.
	X	Macdougall. Nephrol. Dial. Transplant, 2000, 15, p1743-1745.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 11/620,986	Applicant(s)/Patent Under Reexamination HELENEK ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 2 of 3

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Andersson, NSE. British Medical Journal, 1961, p275-279.
	V	Fielding, J. British Medical Journal, 1961, p279-283.
	W	Newnham et al. Internal Medicine Journal, 2006, 36(10), p672-674
	X	Haines et al. Internal Medicine Journal, 2009, 39, p252-255.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 11/620,986	Applicant(s)/Patent Under Reexamination HELENEK ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 3 of 3

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Nissenson et al. Kidney International, 2003, 64(Supplement 87), pS64–S71.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Google scholar iron sorbitol OR mannitol OR gluconate OR pol Search Advanced Scholar Search Scholar Preferences

Scholar Articles and patents anytime include citations Results **1** - **10** of about **36,600**. (**0.05** sec)

… efficacy and safety of **iron** sucrose (Venofer (R)) vs **iron gluconate** (Ferrlecit (R)) in …- •**oxfordjournals.org**
M Kosch, U Bahner, H Bettger, F Matzkies, M … - Nephrology Dialysis …, 2001 - ERA-EDTA
Results. Efficacy parameters: Haemoglobin levels could be maintained from baseline to endpoint in both groups. There were, however, more patients in the **iron** sucrose group than in the **iron gluconate** group for whom treatment was discontinued because their haemoglobin values **...**
Cited by 52 - Related articles - BL Direct - All 5 versions

… of methods used to measure serum **iron** in the presence of **iron gluconate** or **iron** …- •**clinchem.org** [PDF]
PA Seligman, RB Schleicher - Clinical Chemistry, 1999 - Am Assoc Clin Chem
References 1. Feverey J. Pathogenesis of Gilbert syndrome. Eur J Clin Investig 1981;11: 417–8. 2. Watson KJR, Gollan JL. Gilbert's syndrome. Baillie`re's Clin Gastroenterol 1989;3:337–55. 3. De Morais SMF, Uetrecht JP, Wells PG. Decreased glucuronidation **...**
Cited by 36 - Related articles - BL Direct - All 3 versions

Studies on a new intramuscular haematinic, **iron-sorbitol**- •**nih.gov** [PDF]
S Lindvall, NSE Andersson - British Journal of Pharmacology …, 1961 - pubmedcentral.nih.gov
A new **iron** preparation for intramuscular use is described. It contains a complex of **iron**, **sorbitol** and citric acid. Its properties in comparison with several other complexes, particularly **iron**-dextran, have been studied. The preparation is stable in serum, is hypertonic, does **...**
Cited by 30 - Related articles - All 3 versions

[PDF] •Better tolerance of **iron polymaltose** complex compared with ferrous sulphate in the …
P Jacobs, L Wood, AR Bird - Hematology, 2000 - awgla.com
... Printed in Malaysia. Erythrocytes Better Tolerance of **Iron Polymaltose** Complex Compared with Ferrous Sulphate in the Treatment of Anaemia **...** An alter- native formulation is an **iron polymaltose** complex where animal data supported a promoting effect of glycerophosphate. **...**
Cited by 25 - Related articles - View as HTML - All 3 versions

… subjects, comparative absorption between ferrous salts and **iron polymaltose**.
P Jacobs, G Johnson, L Wood - Journal of medicine, 1984 - ncbi.nlm.nih.gov
Iron absorption was directly compared between equivalent doses of ferrous salts and a **polymaltose** complex using a twin-isotope technique in which each individual acts as his own control. In the first study, bioavailability of **iron** from ferrous sulfate and the complex was defined at **...**
Cited by 17 - Related articles - All 2 versions

… with ferrous sulfate but not with non-ionic **iron polymaltose** complex increases the …
TP Tuomainen, K Nyyssönen, E Porkkala-Sarataho, R … - Nutrition Research, 1999 - Elsevier
Iron deficiency anemia is customarily treated by **iron** supplementation. However, **iron** can act as a catalyst of lipid peroxidation in vitro, and high intake of heme **iron** has been associated with an increased risk of myocardial infarction in some, but not in all epidemiologic studies. **...**
Cited by 21 - Related articles - BL Direct - All 9 versions

Effects of ferrous sulphate and non-ionic **iron-polymaltose** complex on markers of …
K Erichsen, RJ Ulvik, T Grimstad, A … - Alimentary …, 2005 - interscience.wiley.com
It is also possible that your web browser is not configured or not able to display style sheets. In this case, although the visual presentation will be degraded, the site should continue to be functional. We recommend using the latest version of Microsoft or Mozilla web browser to **...**
Cited by 15 - Related articles - BL Direct - All 4 versions

[PDF] •A comparison between intravenous **iron polymaltose** complex (Ferrum Hausmann) …
K Singh, YF Fong, P Kuperan - Eur J Haematol, 1998 - awgla.com
Eur J Haematol 1998:60:119-124 Printed in UK - all rights reserved Copyright © Munksgaard 1998 EUROPEAN %- - JOURNAL OF H A E M A T OIII C X^ з Ю и З ISSN 0902-4441 /^ A comparison between intravenous **iron polymaltose** complex (Ferrum Hausmann®) and oral ferrous **...**
Cited by 20 - Related articles - BL Direct - All 6 versions

[CITATION] 59Fe **iron sorbitol** citric-acid complex in **iron**-deficiency anaemia.
A Pringle, GA GOLDBER, E Macdonald, S Johnston - Lancet, 1962 - ncbi.nlm.nih.gov
1: Lancet. 1962 Oct 13;2(7259):749-52. 59Fe **iron sorbitol** citric-acid complex in **iron**-deficiency anaemia. **...** Mesh Terms: Anemia, Hypochromic*; Citrates*; **Iron** Isotopes*; **Iron**-Dextran Complex*; **Sorbitol***. Substances: Citrates; **Iron** Isotopes; **Sorbitol**; **Iron**-Dextran Complex. **...**
Cited by 16 - Related articles

Urinary White-cell Excretion After **Iron-sorbitol**–Citric-acid- •**nih.gov** **[PDF]**
JD Briggs, AC Kennedy, A Goldberg - British Medical Journal, 1963 - pubmedcentral.nih.gov
REFERENCES Avila, R., Pugh, DG, Slocumb, CH, and Winkelmann, RK (1960). Radiology, 75, 691. Baer, RL, and Witten, VH (1962). The Year Book of Dermato- logy, 1961-62, p. 222. Year Book Publishers, Chicago. Baker, H., Golding, DN, and Thompson, M. (1963). Ann. **...**
Cited by 17 - Related articles - All 2 versions

Gooooooooogle ▶
Result Page: **1** 2 3 4 5 6 7 8 9 10 **Next**

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

SEARCHED			
Class	**Subclass**	**Date**	**Examiner**

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
EAST - see attached notes	5/22/2009	JSL
Google Scholar - see attached notes	5/22/2009	JSL
EAST - inventor name search (Mary Helenek; Marc Tokars; Richard Lawrence)	5/22/2009	JSL
Google Scholar - see attached notes	12/8/2009	JSL
EAST - see attached notes	12/8/2009	JSL

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/17/2008	02/12/2009	05/22/2009	12/08/2009					
	1	÷	÷	✓	✓					
	2	÷	÷	✓	✓					
	3	÷	÷	✓	✓					
	4	÷	÷	✓	✓					
	5	÷	÷	✓	✓					
	6	÷	÷	N	✓					
	7	÷	÷	N	✓					
	8	÷	÷	N	✓					
	9	÷	÷	N	✓					
	10	÷	÷	✓	✓					
	11	÷	÷	✓	✓					
	12	÷	÷	✓	✓					
	13	÷	÷	✓	✓					
	14	÷	÷	✓	✓					
	15	÷	÷	✓	✓					
	16	÷	÷	✓	✓					
	17	÷	÷	✓	✓					
	18	÷	÷	✓	✓					
	19	÷	÷	✓	✓					
	20	÷	÷	✓	✓					
	21	÷	÷	✓	✓					
	22	÷	÷	✓	✓					
	23	÷	÷	✓	✓					
	24	÷	÷	✓	-					
	25	÷	÷	✓	-					
	26	÷	÷	✓	✓					
	27	÷	÷	✓	✓					
	28	÷	÷	✓	✓					
	29	÷	÷	✓	✓					
	30	÷	÷	✓	✓					
	31	÷	÷	N	✓					
	32	÷	÷	N	✓					
	33	÷	÷	✓	✓					
	34	÷	÷	✓	✓					
	35	÷	÷	✓	✓					
	36	÷	÷	✓	✓					

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/17/2008	02/12/2009	05/22/2009	12/08/2009					
	37	÷	÷	✓	✓					
	38	÷	÷	✓	✓					
	39	÷	÷	✓	✓					
	40	÷	÷	✓	✓					
	41	÷	÷	✓	✓					
	42	÷	÷	✓	✓					
	43	÷	÷	✓	✓					
	44	÷	÷	N	✓					
	45	÷	÷	✓	✓					
	46	÷	÷	✓	✓					
	47	÷	÷	✓	✓					
	48	÷	÷	✓	✓					
	49	÷	÷	✓	✓					
	50	÷	÷	N	✓					
	51	÷	÷	N	✓					
	52	÷	÷	N	✓					
	53	÷	÷	N	✓					
	54	÷	÷	N	✓					
	55	÷	÷	N	✓					
	56	÷	÷	✓	✓					
	57	÷	÷	✓	✓					
	58	÷	÷	✓	✓					
	59	÷	÷	✓	✓					
	60	÷	÷	✓	✓					

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S4	3	iron and carboxymaltose	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/07 15:49
S5	1	iron and carboxymaltose	EPO; DERWENT	ADJ	ON	2009/12/07 15:50
S6	1	2007-687415.NRAN.	DERWENT	ADJ	ON	2009/12/07 15:50
S7	2	"3022221".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/07 17:46
S8	2	"2807610".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/07 17:46
S9	5	((MARC) near2 (TOKARS)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/08 15:10
S10	398	((RICHARD) near2 (LAWRENCE)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/08 15:10
S11	9	((MARY) near2 (HELENEK)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/08 15:10
S12	36	(S10 or S11 or S9) and iron	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/08 15:10
S13	1	((iron near9 (sorbitol OR mannitol OR gluconate OR polymaltose or carboxymaltose or gluconate)) or (iron same (sorbitol OR mannitol OR gluconate OR polymaltose or carboxymaltose or gluconate))) and (total dose)	EPO; DERWENT	ADJ	ON	2009/12/08 15:18
S14	95	((iron near9 (sorbitol OR mannitol OR gluconate OR polymaltose or carboxymaltose or gluconate)) or (iron same (sorbitol OR mannitol OR gluconate OR polymaltose or carboxymaltose or gluconate))) and (total dose)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/08 15:18
S15	55	S14 and @ad<="20060106"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/08 15:19

S16	3	((iron near9 (sorbitol OR mannitol OR gluconate OR polymaltose or carboxymaltose or gluconate)) or (iron same (sorbitol OR mannitol OR gluconate OR polymaltose or carboxymaltose or gluconate))) and (high single dose)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/08 15:23
S17	2	S16 and @ad<="20060106"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/12/08 15:23

EAST Search History (Interference)

<This search history is empty>

12/8/2009 3:25:02 PM
C:\Documents and Settings\jlau1\My Documents\EAST\Workspaces\11620986 - iron carboxymaltose.wsp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **11/620,986**	Examiner: **LAU, Jonathan S**
Applicant: **HELENEK, MARY JANE**	Group Art Unit: **1623**
Filed: **January 1, 2007**	Confirmation No.: **1325**
Title: **30015730-0043**	Customer No.: **26263**
Docket No.: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	

August 26, 2009

FILED ELECTRONICALLY VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO OFFICE ACTION

UNDER 37 C.F.R. § 1.111

Sir:

In response to the Office Action of May 29, 2009, Applicants request the Office consider the following amendments and remarks.

IN THE CLAIMS

1. (**currently amended**) A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism, comprising

administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron**; [[,]]**

wherein

the iron carbohydrate complex is selected from the group consisting of an iron carboxymaltose complex, an iron mannitol complex, an iron polyisomaltose complex, an iron polymaltose complex, an iron gluconate complex, an iron sorbitol complex, and an iron hydrogenated dextran complex; and

the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component and substantially no cross reactivity with anti-dextran antibodies.

The method of claim 1 wherein the iron carbohydrate complex is an iron carboxymaltose complex, iron mannitol complex, iron polyisomaltose complex, iron polymaltose complex, iron gluconate complex, iron sorbitol complex, or an iron hydrogenated dextran complex.

2. (original) The method of claim 1 wherein the disease, disorder, or condition is anemia.

3. (original) The method of claim 2 wherein the anemia is iron deficiency anemia.

4. (original) The method of claim 3 wherein the iron deficiency anemia is associated with chronic blood loss; acute blood loss; pregnancy; childbirth; childhood development; psychomotor and cognitive development in children; breath holding spells; heavy uterine bleeding; menstruation; chronic recurrent hemoptysis; idiopathic

pulmonary siderosis; chronic internal bleeding; gastrointestinal bleeding; parasitic infections; chronic kidney disease; dialysis; surgery or acute trauma; and chronic ingestion of alcohol, chronic ingestion of salicylates, chronic ingestion of steroids; chronic ingestion of non-steroidial anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents.

5. (original) The method of claim 2 wherein the anemia is anemia of chronic disease.

6. (withdrawn) The method of claim 5 wherein the chronic disease is selected from the group consisting of rheumatoid arthritis; cancer; Hodgkins leukemia; non-Hodgkins leukemia; cancer chemotherapy; inflammatory bowel disease; ulcerative colitis thyroiditis; hepatitis; systemic lupus erythematosus; polymyalgia rheumatica; scleroderma; mixed connective tissue disease; Sojgren's syndrome; congestive heart failure / cardiomyopathy; and idiopathic geriatric anemia.

7. (withdrawn) The method of claim 2 wherein the anemia is due to impaired iron absorption or poor nutrition.

8. (withdrawn) The method of claim 7, wherein the anemia is associated with Crohn's Disease; gastric surgery; ingestion of drug products that inhibit iron absorption; or chronic use of calcium.

9. (withdrawn) The method of claim 1 wherein the disease, disorder, or condition is selected from the group consisting of restless leg syndrome; blood donation; Parkinson's disease; hair loss; and attention deficit disorder.

10. (original) The method of claim 1 wherein the single dosage unit of elemental iron is at least about 0.7 grams.

11. (original) The method of claim 10 wherein the single dosage unit of elemental iron is at least about 0.8 grams.

12. (original) The method of claim 11 wherein the single dosage unit of elemental iron is at least about 0.9 grams.

13. (original) The method of claim 12 wherein the single dosage unit of elemental iron is at least about 1.0 grams.

14. (original) The method of claim 13 wherein the single dosage unit of elemental iron is at least about 1.5 grams.

15. (original) The method of claim 14 wherein the single dosage unit is at least about 2.0 grams.

16. (original) The method of claim 15 wherein the single dosage unit of elemental iron is at least about 2.5 grams.

17. (original) The method of claim 1 wherein the single dosage unit of elemental iron is administered in about 15 minutes or less.

18. (original) The method of claim 17 wherein the single dosage unit of elemental iron is administered in about 10 minutes or less.

19. (original) The method of claim 18, wherein the single dosage unit of elemental iron is administered in about 5 minutes or less.

20. (original) The method of claim 19, wherein the single dosage unit of elemental iron is administered in about 2 minutes or less.

21. (original) The method of claim 1 wherein the subject does not experience a significant adverse reaction to the single dosage unit administration.

22. (original) The method of claim 1 wherein the iron carbohydrate complex has a pH between about 5.0 to about 7.0; physiological osmolarity; an iron core size no greater than about 9 nm; a mean diameter particle size no greater than about 35 nm; and a blood half-life of between about 10 hours to about 20 hours.

23. (original) The method of claim 1 wherein the iron carbohydrate complex contains about 24% to about 32% elemental iron; contains about 25% to about 50% carbohydrate; and has a molecular weight of about 90,000 daltons to about 800,000 daltons.

24. (**canceled**)

25. (**canceled**)

26. (**currently amended**) The method of claim **1** ~~**25**~~ wherein the iron carbohydrate complex is an iron carboxymaltose complex.

27. (original) The method of claim 26 wherein the iron carboxymaltose complex contains about 24% to about 32% elemental iron, about 25% to about 50% carbohydrate, and is about 100,000 daltons to about 350,000 daltons.

28. (original) The method of claim 26 wherein the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between about 5 and about 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between about 5 and about 20 and

the dextrose equivalent of each individual maltodextrin contained in the mixture lies between about 2 and about 20.

29. (original) The method of claim 26 wherein:

the iron carboxymaltose complex has a chemical formula of $[FeO_x(OH)_y(H_2O)_z]_n$ $[\{(C_6H_{10}O_5)_m(C_6H_{12}O_7)\}_l]_k$, where n is about 103, m is about 8, l is about 11, and k is about 4;

contains about 28% elemental iron; and

has a molecular weight of about 150,000 Da.

30. (original) The method of claim 26 wherein the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

31. (withdrawn) The method of claim 25 wherein the iron carbohydrate complex is an iron polyglucose sorbitol carboxymethyl ether complex.

32. (withdrawn) The method of claim 31 wherein the iron polyglucose sorbitol carboxymethyl ether complex is a polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite complex.

33. (original) The method of any one of claims 1 wherein the iron carbohydrate complex comprises an iron core with a mean iron core size of no greater than about 9 nm.

34. (original) The method of claim 33 wherein the mean iron core size is at least about 1 nm but no greater than about 9 nm.

35. (original) The method of claim 34 wherein the mean iron core size is at least about 3 nm but no greater than about 7 nm.

36. (original) The method of claim 35 wherein the mean iron core size is at least about 4 nm but not greater than about 5 nm.

37. (original) The method of claim 1 wherein mean size of a particle of the iron carbohydrate complex is no greater than about 35 nm.

38. (original) The method of claim 37 wherein the particle mean size is no greater than about 30 nm.

39. (original) The method of claim 38 wherein the particle mean size is no greater than about 25 nm.

40. (original) The method of claim 39 wherein the particle mean size is no greater than about 20 nm.

41. (original) The method of claim 40 wherein the particle mean size is no greater than about 15 nm.

42. (original) The method of claim 41 wherein the particle mean size is no greater than about 10 nm.

43. (original) The method of claim 42 wherein the particle mean size is at least 6 nm but no greater than about 7 nm.

44. (original) The method of claim 1 wherein the iron carbohydrate complex is administered parenterally.

45. (original) The method of claim 44 wherein the iron carbohydrate complex is administered intravenously.

46. (original) The method of claim 45 wherein the iron carbohydrate complex is intravenously infused.

47. (original) The method of claim 46 wherein the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent.

48. (original) The method of claim 47 wherein the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 250 ml of diluent.

49. (original) The method of claim 47 wherein the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 215 ml of diluent.

50. (withdrawn) The method of claim 45 wherein the iron carbohydrate complex is intravenously injected as a bolus.

51. (withdrawn) The method of claim 50 wherein the single unit dose of iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent.

52. (withdrawn) The method of claim 51 wherein the single unit dose of iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 250 ml of diluent.

53. (withdrawn) The method of claim 51 wherein the single unit dose of iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 215 ml of diluent.

54. (withdrawn) The method of claim 44 wherein the iron carbohydrate complex is administered intramuscularly.

55. (withdrawn) The method of claim 54 wherein the iron carbohydrate complex is intramuscularly injected at a concentration of about 500 mg elemental iron in less than about 10 ml diluent.

56. (original) The method of claim 1 further comprising a second administration of said iron carbohydrate complex upon recurrence of at least one symptom of the disease, disorder, or condition.

57. (original) The method of claim 1 further comprising a second administration of said iron carbohydrate complex after 1 day to 12 months after the first administration.

58. (**currently amended**) A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism, comprising:

intravenously administering to a subject in need thereof an iron carboxymaltose complex in a single dosage unit of at least about 1000 mg of elemental iron in about 200 ml to about 300 ml of diluent in about 5 minutes or less;

wherein the iron carboxymaltose complex comprises an iron core with a mean iron core size of at least about 1 nm but no greater than about 9 nm;

wherein mean size of a particle of the iron carboxymaltose complex is no greater than about 35 nm;

wherein the iron carboxymaltose complex is administered intravenously infused or intravenously injected at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent.

59. (original) The method of claim 58 wherein the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the

oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between about 5 and about 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between about 5 and about 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between about 2 and about 20.

60. (original) The method of claim 58 wherein the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

REMARKS

Upon entry of this amendment, claims 1-23 and 26-60 are pending. Claims 1, 26, and 58 have been amended. No claims have been added. Claims 6-9, 31, 32, and 50-55 have been presently withdrawn but are maintained in the application for rejoinder. Claims 24, 25 have been canceled.

Support for the amendment to claim 1 appears at least at claim 25. Support for the amendment to claim 26 appears at least at claim 1 and canceled claim 25. Claim 58 was amended to correct a punctuation error.

No new matter has been added by way of this response.

Species Election

The Office is presently examining a first species of iron deficiency anemia associated with chronic blood loss; a second species of iron carboxymaltose complex; and a third species of intravenous infusion. The Office maintains that claims 6-9, 31, 32, 44, and 50-55 are withdrawn as being drawn to non-elected species.

Applicants note that claim 44 recites "administered parenterally". Intravenous infusion is a species of parenteral administration. In fact, Applicants clarified this very point with the Office in the first Response to Restriction filed November 21, 2008 (see p. 2), which resulted in the Office withdrawing the first and issuing a second Restriction Requirement dated February 23, 2009. Because claim 44 is generic to elected species of intravenous infusion, contrary to the assertions of the Office, claim 44 is under examination and is not withdrawn.

Applicants reserve the right to request REJOINDER, under MPEP § 821.04, and examination of the non-elected species upon allowance of any claims generic to the non-elected species.

Claim Rejections under 35 U.S.C. § 1112, ¶2 : Indefiniteness

Applicants respectfully traverse and, for the following reasons, request reconsideration and withdrawal of the rejection of claims 1-5, 10-24, 33-43, 45-49, and 56-57 under 35 U.S.C. §112, ¶2 as being indefinite. The Office asserts that the claims

do not particularly point out any structural component of the iron carbohydrate complex. It is noted that claim 25 is not rejected as indefinite.

In the interest of furthering prosecution, claim 1 has been amended to recite all features of claim 25. Because claim 25 is not rejected as indefinite, Applicants assert that claim 1, and claims dependent thereon, satisfy the requirements of 35 U.S.C. § 1112, ¶2.

Claim Rejections under 35 U.S.C. §103(a)

Applicants respectfully traverse and, for the following reasons, request reconsideration and withdrawal of the rejection of claims 1-5, 10-30, 33-43, 45-49, and 56-60 under 35 U.S.C. §103(a) as being unpatentable over Lawrence et al., US 5,624,668 ("Lawrence"), in view of Helenek et al., US 2004/0180849 ("Helenek") issued as US 6,960,571.

First, Applicants note the Office recites the "Landry et al." reference on pages 5-7 of the Action. "Landry et al." is not a reference of record in the above rejection. Applicants assume that the Office intended to recite "Lawrence et al." rather than "Landry et al." If such assumption is incorrect, Applicants respectfully request the Office to correct the rejection of record. In such case, where the Office would add a "Landry et al." reference to the rejection of record, the next Office Action should be a non-final Office Action (see (MPEP § 706.07(a) (finality of an Office Action is not proper where the Office introduces a new ground of rejection that is neither necessitated by Applicants' amendment of the claims nor based on information submitted in a later filed information disclosure statement)). The balance of remarks are based upon the assumption that "Lawrence et al." was intended where "Landry et al." was recited by the Office.

To establish obviousness of a claim, the prior art must disclose or suggest each element of the claim; there must be some reason that would have prompted one of ordinary skill in the art to combine the elements and/or modify a reference(s) so as to reach the requirements of the claim; and there must have been a reasonable expectation of success of the combination and/or modification. MPEP § 2143; *KSR Int'l*

Co. v. Teleflex Inc., 550 U.S. __, Slip Op No. 04-1350, 119 Fed. Appx. 282 (April 30, 2007).

Species Restriction Establishes Nonobviousness of Iron Carboxymaltose Complex

The Office has acknowledged that the elected species of iron carboxymaltose complex is patently distinct and nonobvious over other species of the genus of iron carbohydrate complex. For a species election requirement to be proper, the species must be patentably distinct (MPEP 806.04; 37 CFR 1.146). By the Office's required species election among the various iron carbohydrate complexes (*see* Restriction Requirement of February 23, 2009), the Office acknowledges that each species, such as elected species of iron carboxymaltose complex, is independent, distinct, and nonobvious over other species of the genus of iron carbohydrate complex.

Neither Lawrence nor Helenek disclose use of an iron carboxymaltose complex, the elected species under examination. As shown above, use of an iron carboxymaltose complex according to claim 1 is patentably distinct and nonobvious over use of other non-elected species, such as those recited in Lawrence or Helenek. **For at least this reason, claim 1 with respect to the elected species, iron carboxymaltose complex, has not been shown to be *prima facie* obvious**.

Furthermore, because iron carboxymaltose complex has not been shown as *prima facie* obvious, and because the Office recites additional non-elected species in the rejection (see e.g., iron polymaltose, Action, p. 6, ln. 8-9), **Applicants understand the non-elected species of iron carbohydrate complexes to be rejoined and under examination**. If such is not the case, Applicants respectfully request the Office to clarify the present scope of examination.

References do not Teach or Suggest Every Feature

Neither Lawrence nor Helenek teach or suggest all features of the claims.

Lawrence is directed to treatment of iron deficiency anemia with a ferric oxyhydroxide-dextran composition. The Office acknowledges that Lawrence fails to teach or suggest administration of a single dosage unit of at least 0.6 mg of elemental

iron in a substantially non-immunogenic iron carbohydrate complex having substantially no cross reactivity with anti-dextran antibodies. The maximum disclosed single unit dosage in Lawrence is 100 mg (see col. 10., ln. 27-31; col. 12, ln. 33-36). The Office also acknowledges that Lawrence fails to teach or suggest iron carbohydrate complexes recited in claim 1 (formerly in claim 25).

Helenek is directed to treatment of Restless Leg Syndrome (RLS) with an iron complex having an iron release rate greater than iron dextran (IDI). Specifically, Helenek focuses on treatment of RLS with iron sucrose compositions having an iron release rate greater than IDI, as quantified by at least 115 µg/dl at a concentration of at least 2,000 µg/dl (see Helenek, p. 3, ¶0026).

The Office asserts that Helenek discloses (i) administration of iron polymaltose, citing p. 3, ¶00210; and (ii) optimization of the amount of elemental iron per dose up to 2.0 g/dose, citing p. 5, ¶0051.

First, Helenek recites iron polymaltose and other iron carbohydrate complexes in a generic listing of examples of iron carbohydrate complexes. Immediately thereafter, Helenek makes clear that in the disclosed methods of that invention, "the iron complex must have a release rate of at least 115 µg/dl at a concentration of at least 2,000 µg/dl" (Helenek, p. 3, ¶0026, emphasis added). Helenek does not teach or suggest that each of the iron carbohydrate complexes recited in ¶0021 are suitable for use in that invention by way of having an iron release rate greater than IDI—rather, only that those complexes having a release rate greater than IDI read on the dosage recitation in ¶0051 of Helenek. Helenek provides iron release rates for only iron gluconate (Ferrlecit), iron sucrose (Venofer), and iron dextran (Dexferrum and INFeD) (see Helenek, FIG. 1, Table 2).

As described above, the teachings of Helenek apply only to those iron carbohydrate complexes having an iron release rate greater than IDI (see Declaration, ¶5). As shown in the accompanying Declaration, VIT-45, an iron carboxymaltose complex, has an iron release rate less than IDI. These iron carbohydrate complexes are thus not implicated by the teachings of Helenek (see Declaration, ¶7).

Second, the Office selectively represents the disclosure of Helenek with respect to optimized dosage of iron carbohydrate complexes having an iron release rate greater than IDI. The pertinent passage of Helenek is as follows (emphasis added):

> An appropriate dosage level will generally be about 10 mg to 1000 mg of elemental iron per dose, which can be administered in single **or multiple doses**, particularly at least 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, 1000.0, and 2000.0 milligrams of elemental iron, and furthermore **up to the maximal tolerated dose (MTD) per administration**. Preferably, the dosage level will be about 0.1 to about 1000 mg per dose; most preferably about 100 mg to about 500 mg per dose.

As noted above, these teachings apply only to those iron carbohydrate complexes having an iron release rate greater than IDI.

Furthermore, the above passage recites that the 10 to 1000 mg of elemental iron can be administered in multiple doses with each administration not exceeding the maximal tolerated dose (MTD). The only example of a single 1000 mg dose in Helenek is for iron sucrose (see e.g., Helenek, p. 5, ¶0052; p. 7, ¶0095), which is an iron carbohydrate not recited in claim 1.

And, as evidenced by the Office's species election requirement, a teaching of dosage for iron sucrose does not necessarily apply to other patentably distinct species of the genus of iron carbohydrate complexes.

Thus, the Office has failed to establish that Helenek teaches elevated levels of iron in a single dose for iron carbohydrate complexes recited in claim 1.

Insufficient Reason to Modify References to Reach Claims

In a determination of obviousness, the proper question is whether one of ordinary skill in the art would have seen an obvious benefit to upgrading conventional methods of treating iron deficiency with an iron carbohydrate complex so as to reach the requirements of claim 1 (*see KSR Int'l Co.*, at 6). The mere fact that references can be combined or modified does not render the resultant combination obvious unless there is some reason that suggests the desirability of the combination. MPEP §2143.01(III).

As shown above, Lawrence is a generic reference directed to treatment of iron deficiency anemia with a ferric oxyhydroxide-dextran composition. Helenek is directed to a subset of iron carbohydrate complexes having an iron release rate greater than iron dextran (IDI). Disclosure of Helenek regarding dosage is consistent with multiple sessions of single lower dosage to achieve a targeted elevated dose. To the extent that Helenek discloses single unit elevated dosage, such disclosure is limited to iron sucrose.

As shown by the species restriction requirement, each of the various claimed species of iron carbohydrate complexes are patentably distinct from one another. A *prima facie* obviousness showing requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art, or motivate one skilled in the art to select the claimed species from the disclosed prior art genus. MPEP § 2144.08(II)(4). The Office has failed to show why one of ordinary skill would select the claimed compounds.

Furthermore, there is insufficient reason shown to modify any complex disclosed by Helenek so as to reach the species of iron carboxymaltose presently under examination. The Office incorrectly (and without required support, see infra Unsupported Assertions) asserts that:

> One of ordinary skill would be motivated to combine iron polymaltose taught by Helenek et al. made by the process taught by Landry et al. [sic] in order to give the iron carboxymaltose complex because Landry et al. [sic] teaches the terminal carboxyl group as gluconate has superior chelation properties. Action, p. 7, ln. 2-5.

Again, it is noted that Applicants presume the Office intended to recite "Lawrence", rather than "Landry" in the above passage.

Lawrence recites at col. 5, ln. 47-60:

> We believe that the reaction of the iron dextran complex with an oxidized dextran under alkaline conditions converts the terminal unit of oxidized dextran from δ-Gluconolactone to sodium gluconate. The resulting solution contains dextran that is both bound and unbound to the iron complex where the molecular weight distributions of the bound and unbound

> dextrans are in equilibrium. Without wishing to be bound by any particular mechanism of action, we believe that the oxidized dextran at this stage of processing of iron dextran compositions minimizes or substantially eliminates aggregate complexes in which two iron cores might be bound to the same dextran molecule. Moreover, oxidized dextran has a terminal carboxyl group and has superior chelating abilities.

As evidenced by the Declaration (of Lawrence, an inventor of the presently claimed subject matter as well as an inventor listed on the Lawrence prior art reference) filed herewith, Lawrence (the cited prior art reference) describes a 1:1 reaction of iron dextran with oxidized dextran to form a stable, soluble colloid that more readily ionizes at neutral pH (see Declaration, ¶10). Such reaction, if applied to iron polymaltose (i.e., reaction of iron polymaltose with oxidized polymaltose) would not form an iron carboxymaltose as that complex is described in the present '986 application (see Declaration, ¶10). Furthermore, the "superior chelation properties" cited by the Examiner pertain only to making the iron colloid water soluble so as to provide for formation of the iron colloid during the method of manufacture (see Declaration, ¶10). There is no reason or desirability shown for alteration of the solubility properties of iron polymaltose and such alteration would not lead to formation of an iron carboxymaltose, even if the reaction described in Lawrence could be extended to iron polymaltose.

Further evidence that one of skill in the art would not have seen a benefit to modifying an iron polymaltose so as to reach an iron carboxymaltose is the Office acknowledgement that such species of iron carbohydrate complexes are patentably distinct. For any species restriction to be proper, the species must be patentably distinct. MPEP §806.04; 37 CFR 1.146. Because an iron polymaltose and an iron carboxymaltose are patentably distinct, it would not be obvious to modify one to reach the other.

Thus, the Examiner has failed to show the desirability of modifying any compound disclosed by Helenek to reach the species of iron carboxymaltose presently being examined and, furthermore, has failed to show any means by which to achieve such modification even if desirable.

Teaching Away

Various references teach away from relatively high dose administration of iron carbohydrate complexes. A prior art disclosure teaches away where it criticizes, discredits, or otherwise discourages the solution claimed (*see* MPEP §2141.02(VI)).

Macdougall (1999) discloses that "[t]he only i.v. iron preparation that can be given as a single dose of 500 to 1000 mg is iron dextran" (see Macdougall, p. 64, col. 2). Similarly, Geisser at al. 1992 Arnzneimittelforschung 42, 1439-1452 (cited in the Application at ¶0007) discloses that doses of iron carbohydrate complexes higher than 200 mg of iron are generally unsuitable and that the conventional therapy prescribes repeated applications of lower doses over several days.

Auerbach (2008 Kidney International 73, 528-530), in a retrospective summary of intravenous iron therapy, discloses the conventional understanding that doses of ferric gluconate larger than about 300 mg elemental iron are associated with high incidence of vasoactive and are "proscribed" (see Auerbach, p. 73, col. 3; citing Chandler et al. 2001 Am J Kidney Dis 38, 988-991). Such disclosure demonstrates that around 2001 and continuing through at least 2008, elevated dosages of ferric gluconate gluconate were strongly discouraged for intravenous administration. Similarly, Macdougall 1999 Kidney International 55(69), 61-66, disclose that iron sodium gluconate is useful for only low-dose administration "because its toxicity limits the dose to a maximum single administration of 62.5 to 125 mg" (see Macdougall, p. 64, col. 1). Landry et al. 2005 Am J Nephrology 25, 400-410, at 408, reports the maximum total dose of a carboxylated reduced polysaccharide iron oxide complex (i.e., ferumoxytol) to be up to 420 mg per injection (see Application, ¶0078).

Thus is demonstrated teaching away in several references from administration of an iron carbohydrate complex (other than iron dextran) in a single dosage unit of at least about 0.6 grams of elemental iron, as recited in claim 1.

No Equivalency

The Office asserts it is *prima facie* obvious to substitute one equivalent component known for the same purpose for another known for the same purpose. Yet this assertion is at odds with the Office's acknowledgement that various species of the genus of iron carbohydrate complexes for use in methods according to claim 1 are patentably distinct and nonobvious over one another (see supra, Species Restriction Establishes Nonobviousness of Iron Carboxymaltose Complex). Furthermore, as reflected in Zager 2006 Clin J Am Soc Nephrol 1, S24-S31, differential degrees of iron toxicity exist for iron carbohydrate complexes depending on the nature of the CHO carrier (see Zager, p. S26, col. 2) and various iron carbohydrate complexes differentially exert acute toxicity and a proinflammatory effect (see Zager, p. S29, col. 1).

Given that the species of iron carbohydrate complexes are patentably distinct, *prima facie* obviousness requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art, or motivate one skilled in the art to select the claimed species from the disclosed prior art genus. MPEP § 2144.08(II)(4).

Unsupported Assertions

Without providing any analysis or supporting citation, the Office asserts that:

> One of ordinary skill would be motivated to combine iron polymaltose taught by Helenek et al. made by the process taught by Landry et al. [sic] in order to give the iron carboxymaltose complex because Landry et al. [sic] teaches the terminal carboxyl group as gluconate has superior chelation properties. Action, p. 7, ln. 2-5.

Assertions of technical facts in the areas of specific knowledge of the prior art must *always* be supported by citation to some reference work recognized as standard in the pertinent art. MPEP § 2144.03(A). Official notice unsupported by documentary evidence should only be taken in an Action where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known. MPEP § 2144.03(A).

Applicants request the Office to substantiate or withdraw the unsupported assertion.

As evidenced by the Declaration filed herewith, Applicants respectfully assert that the Office cannot substantiate the above assertion because it is incorrect. Recitation of pertinent passages of Lawrence are recited above. Lawrence describes a 1:1 reaction of iron dextran with oxidized dextran to form a stable, soluble colloid that more readily ionizes at neutral pH. Such reaction, if applied to iron polymaltose (i.e., reaction of iron polymaltose with oxidized polymaltose) would not form an iron carboxymaltose as that complex is described in the present '986 application.

Dose Criticality

The Office asserts that the instantly claimed concentrations do not support patentability unless there is evidence indicating such concentration is critical (citing MPEP §2144.05(II)(A)).

It is first noted that the claims recite an amount of elemental iron per single unit dose, which is not a "concentration" per se.

The present Application discloses that while iron dextran compositions can be given at high dose, the immune response and risk of anaphylaxis limits its use. The present Application, citing Geisser at al. 1992 Arnzneimittelforschung 42, 1439-1452 at ¶0007, also discloses that doses of iron carbohydrate complexes higher than 200 mg of iron are generally unsuitable and that conventional therapy prescribes repeated applications of lower doses of iron carbohydrate complexes over several days. To achieve iron repletion under current therapy models, a total dose of 1 g of elemental iron typically requires 5 to 10 sessions over an extended period of time, incurring significant expense for supplies, nursing time, and patient inconvenience (see Application, ¶0007).

The present Application provides a method of treating iron associated diseases, disorders, or conditions with iron carbohydrate complexes that can be administered parenterally at relatively high single unit dosages, thereby providing a safe and efficient

means for delivery of a total dose of iron in fewer sessions over the course of therapeutic treatment (see ¶0008).

Thus, it is demonstrated that the claimed levels of elemental iron administered in a single unit dose are critical in the context of MPEP §2144.05(II)(A)) and thereby provide support for patentability.

For at least the above reasons, claims 1-5, 10-30, 33-43, 45-49, and 56-60 are nonobvious over Lawrence et al. in view of Helenek.

CONCLUSION

Applicants respectfully request withdrawal of the rejections and believe that the claims as presented represent allowable subject matter. If the Examiner desires, Applicants welcome a telephone interview to expedite prosecution. Applicants believe there are no fees due at this time. The Commissioner is hereby authorized to deduct any deficiency or credit any overpayment with respect to this response to Deposit Account No. 19-3140.

Respectfully submitted,

By: /G. Harley Blosser/ (Reg. 33,650)
G. Harley Blosser
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. Box 061080
Wacker Drive Station, Sears Tower
Chicago, IL 60606-1080
Telephone: 314/259-5806
Fax: 312/876-7934

ATTORNEYS FOR APPLICANT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **11/620,986**	Examiner: **LAU, Jonathan S**
Applicant: **HELENEK, Mary Jane**	Group Art Unit: **1623**
Filed: **January 1, 2007**	Confirmation No.: **1325**
Title: **30015730-0043**	Customer No.: **26263**
Docket No.: **Methods and Compositions for Administration of Iron**	

FILED ELECTRONICALLY VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, Richard P. Lawrence, declare and state as follows:

1. I am Director of Research and Development for Luitpold Pharmaceuticals, Inc.

2. I have a B.S. Degree/Fairleigh Dickinson University, with a focus in Chemistry.

I am a named inventor in the following US patents:

7,169,359 Bioequivalence test for iron-containing formulations

6,911,342 Bioequivalence test for iron-containing formulations

5,624,668 Iron Dextran Formulations

I have authored the peer-reviewed manuscript:

Lawrence, "Development and Comparison of Iron Dextran Products," *PDA Journal of Pharmaceutical Science &*

Technology, Vol. 52, No. 5, September-October 1998, pp. 190-197.

The following provides a brief overview of my experience:

Training:

BS: Chemistry/Mathematics, Fairleigh Dickinson University, Madison, New Jersey, June 1979

Positions:

Luitpold Pharmaceuticals, Inc. (Shirley, New York)

04/03 – Present	Director, Research & Development
09/02 – 04/03	Director, Quality Assurance
05/02 – 09/02	Director, Quality Control
03/83 – 05/02	Manager, Product Development

Gibco Invenex (Milburn, New Jersey)

10/79 – 03/83	Research Chemist

3. I am a named inventor of the subject matter claimed in present U.S. Patent Application 11/620,986 (the "'986 application"), entitled "Methods and Compositions for Administration of Iron", filed on January 1, 2007.

4. We measured the iron release rate of an iron carboxymaltose complex, polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-O-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate ("VIT-45") according to the methods of Van Wyck et al. 2004 Nephrol Dial Transplant 19, 561-565. Sample size for each measurement was 3. Polled serum volume was 1.5 ml. Results are presented in the Table A below.

TABLE A: Iron Release Rates for VIT-45 and Dexferrum

Iron Carbohydrate Complex	Concentration of Iron Agent Added (µg/dl)	Mean Iron Release Rate (µg/dl)	Std. Dev. Iron Release Rate (µg/dl)
VIT-45	6875	72	33.7
VIT-45	3438	69	23.1
Dexferrum	6875	64	4.7
Dexferrum	3438	73	7.2

5. I have reviewed Helenek et al., US 2004/0180849, issued as US 6,960,571 ("Helenek"). Iron carbohydrate complexes for use in the methods of Helenek are required to have an iron release rate greater than IDI, as quantified by an iron release rate of at least 115 µg/dl at a concentration of at least 2000 µg/dl (see Helenek, ¶0026). The disclosure of ¶0051 related to dosage pertains to iron carbohydrate complexes of the Helenek invention, *i.e.*, an iron carbohydrate complex having an iron release rate greater than IDI, as quantified by an iron release rate of at least 115 µg/dl at a concentration of at least 2000 µg/dl.

6. The iron release rates for Dexferrum presented in Helenek (see Helenek , Table 2) are consistent with the iron release rates for Dexferrum in Table A above. Thus, the reported iron release rate for VIT-45, an iron carboxymaltose complex, are lower than the "at least 115 µg/dl at a concentration of at least 2000 µg/dl" threshold for iron carbohydrate complexes of Helenek (see Helenek, ¶0026). In other words, VIT-45 does not have an iron release rate of "greater than IDI" as that term is defined in Helenek.

7. Because VIT-45, an iron carboxymaltose complex, has an iron release rate "less than IDI", as that term is defined in Helenek, disclosure of dosage in Helenek does not directly apply to VIT-45.

8. I am a named inventor on U.S. Patent No. 5,624,668 ("Lawrence"), entitled "Iron Dextran Formulations", issued on April 29, 1997. Lawrence recites at col. 5, ln. 47-60:

> We believe that the reaction of the iron dextran complex with an oxidized dextran under alkaline conditions converts the terminal unit of oxidized dextran from δ-Gluconolactone to sodium gluconate. The resulting solution contains dextran that is both bound and unbound to the iron complex where the molecular weight distributions of the bound and unbound dextrans are in equilibrium. Without wishing to be bound by any particular mechanism of action, we believe that the oxidized dextran at this stage of processing of iron dextran compositions minimizes or substantially eliminates aggregate complexes in which two iron cores might be bound to the same dextran molecule. Moreover, oxidized dextran has a terminal carboxyl group and has superior chelating abilities.

9. The Examiner incorrectly asserts that "One of ordinary skill would be motivated to combine iron polymaltose taught by Helenek et al. made by the process taught by [Lawrence] et al. in order to give the iron carboxymaltose complex because [Lawrence] et al. [sic] teaches the terminal carboxyl group as gluconate has superior chelation properties." Action, p. 7, ln. 2-5.

10. Lawrence describes a 1:1 reaction of iron dextran with oxidized dextran to form a stable, soluble colloid that more readily ionizes at neutral pH. Such reaction, if applied to iron polymaltose (i.e., reaction of iron polymaltose with oxidized polymaltose) would not form an iron carboxymaltose as that complex is described in the present '986 application. Furthermore, the "superior chelation properties" cited by the Examiner pertain only to making the iron colloid water soluble so as to provide for formation of the iron colloid during the method of manufacture. There is no reason or desirability shown for alteration of the solubility properties of iron polymaltose and such alteration would

not lead to formation of an iron carboxymaltose, even if the reaction described in Lawrence could be extended to iron polymaltose. Thus, the Examiner has failed to show the desirability of modifying an iron polymaltose to reach an iron carboxymaltose and, furthermore, has failed to show any means by which to achieve such modification even if desirable.

11. I hereby declare that the statements made of my own knowledge are true and that all statements made on information made on belief are believed to be true. I acknowledge that willful false statements and alike are punishable by fine or imprisonment or both (18 U.S.C. § 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Date: August 18, 2009

Richard P. Lawrence

Electronic Acknowledgement Receipt	
EFS ID:	5954455
Application Number:	11620986
International Application Number:	
Confirmation Number:	1325
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	George H. Blosser/Dennis Harney
Filer Authorized By:	George H. Blosser
Attorney Docket Number:	30015730-0043
Receipt Date:	26-AUG-2009
Filing Date:	08-JAN-2007
Time Stamp:	11:58:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	ROA_30015730_0043_Aug26_2009.pdf	134482 a16fb5c87bdf06a283f62fce030d0c568147f853	no	21
Warnings:					
Information:					

2	Rule 130, 131 or 132 Affidavits	Declaration_Lawrence_30015730_0043_Aug_2009.pdf	1294469 6cd8b14ad2601f11e4c0feca7a6873cc12e3d459	no	5
Warnings:					
Information:					
			Total Files Size (in bytes):	1428951	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/620,986	Filing Date 01/08/2007	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	08/26/2009	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 58	Minus	** 60	= 0	X $26 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $110 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ROCHELLE C. GETER/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043	1325

26263 7590 05/29/2009
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
05/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/620,986	HELENEK ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *6-9,31,32,44 and 50-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10-30,33-43,45-49 and 56-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 January 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 pgs / 24 Jan 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a domestic application, filed 08 Jan 2007; and claims benefit of provisional application 60/757,119, filed 06 Jan 2006.

Claims 1-60 are pending in the current application. Claims 6-9, 31, 32, 44 and 50-55, drawn to non-elected species, are withdrawn. Claims 1-5, 10-30, 33-43, 45-49 and 56-60 are examined on the merits herein.

Election of Species

Applicant's election of **first** species of iron deficiency anemia associated with chronic blood loss, **second** species of iron carboxymaltose complex and **third** species of intravenous infusion in the reply filed on 03 Mar 2009 is acknowledged.

Claims 6-9, 31, 32, 44 and 50-55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election of species was made in the reply filed on 03 Mar 2009.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 10-24, 33-43, 45-49 and 56-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "an iron carbohydrate complex … wherein the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component and substantially no cross reactivity with anti-dextran antibodies." Claims 2-5, 10-24, 33-43, 45-49 and 56-57 depend from claim 1 and incorporate all limitations therein, and do not particularly point out structural requirements of the carbohydrate component. The cited phrase renders the claim indefinite because the claimed functions of "substantially non-immunogenic" and "substantially no cross reactivity with anti-dextran antibodies" do not particularly point out any structural information of the carbohydrate component or the iron carbohydrate complex. Therefore one of ordinary skill in the art would not be readily apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 10-30, 33-43, 45-49 and 56-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawrence et al. (US Patent 5,624,668, issued 29 Apr 1997, cited in PTO-892) and in view of Helenek et al. (US Patent Application Publication 2004/0180849, published 16 Sep 2004, cited in PTO-892, issued as US Patent 6,960,571, provided by Applicant in IDS mailed 24 Jan 2008).

Lawrence et al. teaches ferric oxyhydroxide-dextran compositions for treating iron deficiency anemia (abstract). Lawrence et al. teaches a method of treating pathological or dialysis-associated, or chronic, blood loss by intravenous iron treatment (column 10, lines 60-65). Lawrence et al. teaches the iron core with a diameter between 3 nm and an outer diameter of 13 nm in a ferric-dextran complex (column 1, lines 48-54). Lawrence et al. teaches the iron core size of about 3.5 to 5.5 nanometers and an iron particle size in the range of 25 to 45 nm (column 3, lines 61-67). Lawrence et al. teaches sorbitol can also be added as a stabilizing agent (column 6, lines 38-40). Lawrence et al. teaches it is known in the art to administer the iron in a solution adjusted to have physiological tonicity and a pH between 5.2 and 6.5 (column 1, lines 40-45). Lawrence et al. teaches the use of iron dextran compositions having a molecular weight about 150,000 to 350,000 daltons (column 3, lines 55-60). Lawrence et al. teaches the

optimization of the ratio the amount of iron to the amount of carbohydrate from about 1:2 to 1:5 is known (column 5, lines 25-30). Lawrence et al. teaches the method of making the dextran complex results in formation of a terminal carboxyl group as gluconate having superior chelation properties (column 5, lines 45-60). Lawrence et al. teaches a method comprises administration by intravenous infusion (column 11, lines 55-65). Lawrence et al. teaches an embodiment of the method wherein the iron is administered at weekly intervals in which no adverse reaction is observed (column 12, lines 40-50).

Landry et al. does not specifically teach the method comprising administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron, wherein the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component and substantially no cross reactivity with anti-dextran antibodies (instant claim 1). Landry et al. does not specifically teach the single unit dosage of instant claim 10-16. Landry et al. does not specifically teach the time in which the single dosage is administered (instant claims 18-20). Landry et al. does not specifically teach a blood half-life of between about 10 hours to about 20 hours (instant claim 22). Landry et al. does not specifically teach the method wherein the iron carbohydrate complex contains about 24% to about 32% elemental iron; contains about 25% to about 50% carbohydrate (instant claim 23). Landry et al. does not specifically teach the iron carbohydrate complex is an iron carboxymaltose complex, iron mannitol complex, iron polyisomaltose complex, iron polymaltose complex, iron gluconate complex, iron sorbitol complex, or an iron

hydrogenated dextran complex (instant claim 25). Landry et al. does not specifically teach the iron carbohydrate complex is an iron carboxymaltose complex (instant claims 26-30 and 58-60). Landry et al. does not specifically teach the iron carbohydrate complex particle mean size of instant claims 40-43. Landry et al. does not specifically teach the concentration of the carbohydrate complex (instant claims 47-49).

Helenek et al. teaches intravenous administration of iron carbohydrate complexes for anemia of a chronic disease is known in the prior art (page 2, paragraphs 10 and 11). Helenek et al. teaches examples of the iron carbohydrate complexes include iron polymaltose (page 3, paragraph 21). Helenek et al. teaches it is known in the art to optimize the amount of elemental iron per dose up to 2.0 g/dose (page 5, paragraph 51) and to optimize different dosing schedules and concentrations (page 5, paragraphs 52-53) by routine experimentation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Landry et al. in view of Helenek et al. Both Landry et al. in view of Helenek et al. are drawn to pharmaceutical formulations of iron carbohydrate complexes for intravenous infusion. Both Landry et al. in view of Helenek et al. teach the formulation is useful for treatment of anemia of a chronic disease. It is *prima facie* obvious to substitute one equivalent component known for the same purpose for another known for the same purpose. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious, see MPEP 2144.06 II. Regarding the carboxymaltose, the process of making the iron carbohydrate complex taught by Landry et al. necessarily results in

formation of a terminal carboxyl group as gluconate having superior chelation properties. One of ordinary skill in the art would be motivated to combine iron polymaltose taught by Helenek et al. made by the process taught by Landry et al. in order to give the iron carboxymaltose complex because Landry et al. teaches the terminal carboxyl group as gluconate has superior chelation properties. Regarding the instantly claimed concentrations recited above, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical, see MPEP 2144.05 II.A. Both Landry et al. and Helenek et al. teach optimization of the cited ranges and particle sizes results from routine experimentation that is well within the level of ordinary skill in the art.

Claims 28 and 59 recite a method of using a product-by-process. It is apparent from what is disclosed that the product-by-process used as claimed is substantially identical as the product taught by iron polymaltose taught by Helenek et al. made by the process taught by Landry et al. in order to give the iron carboxymaltose complex. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer

was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623

Notice of References Cited	Application/Control No. 11/620,986	Applicant(s)/Patent Under Reexamination HELENEK ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,624,668	04-1997	Lawrence et al.	424/78.17
*	B	US-2004/0180849	09-2004	Helenek et al.	514/053
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

SEARCHED			
Class	**Subclass**	**Date**	**Examiner**

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
EAST - see attached notes	5/22/2009	JSL
Google Scholar - see attached notes	5/22/2009	JSL
EAST - inventor name search (Mary Helenek; Marc Tokars; Richard Lawrence)	5/22/2009	JSL

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/17/2008	02/12/2009	05/22/2009						
	1	÷	÷	✓						
	2	÷	÷	✓						
	3	÷	÷	✓						
	4	÷	÷	✓						
	5	÷	÷	✓						
	6	÷	÷	N						
	7	÷	÷	N						
	8	÷	÷	N						
	9	÷	÷	N						
	10	÷	÷	✓						
	11	÷	÷	✓						
	12	÷	÷	✓						
	13	÷	÷	✓						
	14	÷	÷	✓						
	15	÷	÷	✓						
	16	÷	÷	✓						
	17	÷	÷	✓						
	18	÷	÷	✓						
	19	÷	÷	✓						
	20	÷	÷	✓						
	21	÷	÷	✓						
	22	÷	÷	✓						
	23	÷	÷	✓						
	24	÷	÷	✓						
	25	÷	÷	✓						
	26	÷	÷	✓						
	27	÷	÷	✓						
	28	÷	÷	✓						
	29	÷	÷	✓						
	30	÷	÷	✓						
	31	÷	÷	N						
	32	÷	÷	N						
	33	÷	÷	✓						
	34	÷	÷	✓						
	35	÷	÷	✓						
	36	÷	÷	✓						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/17/2008	02/12/2009	05/22/2009						
	37	÷	÷	✓						
	38	÷	÷	✓						
	39	÷	÷	✓						
	40	÷	÷	✓						
	41	÷	÷	✓						
	42	÷	÷	✓						
	43	÷	÷	✓						
	44	÷	÷	N						
	45	÷	÷	✓						
	46	÷	÷	✓						
	47	÷	÷	✓						
	48	÷	÷	✓						
	49	÷	÷	✓						
	50	÷	÷	N						
	51	÷	÷	N						
	52	÷	÷	N						
	53	÷	÷	N						
	54	÷	÷	N						
	55	÷	÷	N						
	56	÷	÷	✓						
	57	÷	÷	✓						
	58	÷	÷	✓						
	59	÷	÷	✓						
	60	÷	÷	✓						

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 1325

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/620,986	01/08/2007	514	1623	30015730-0043

APPLICANTS

Mary Jane Helenek, Brookville, NY;
Marc L. Tokars, Douglassville, PA;
Richard P. Lawrence, Calverton, NY;

**** CONTINUING DATA **************************

This appln claims benefit of 60/757,119 01/06/2006

**** FOREIGN APPLICATIONS **************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **

01/23/2007

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /JONATHAN S LAU/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NY	2	60	2

ADDRESS

SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606-1080
UNITED STATES

TITLE

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

FILING FEE RECEIVED		
1490	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	1	iron and (anemia or anaemia) and carboxymaltose	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 14:14
S2	2	iron and carboxymaltose	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:05
S3	5	vit-45	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:18
S4	18339	(iron or ferric or ferrous) and glucon$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:25
S5	2913	(iron or ferric or ferrous) near9 glucon$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:26
S6	2444	S5 and @ad<="20060106"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:26
S7	427	S6 and anemia	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:26
S8	451	S6 and (anemia or anaemia)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:26
S9	305	S8 and (bolus or infusion)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:27
S10	42	S9 and (iron or ferric or ferrous).ti,ab,clm.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:27
S11	3	S10 and (polygl?con$4 or (poly near3 gl?con$4))	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:28
S12	1	"6,693,211".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:29
S13	615	(polygl?con$4 or (poly near3 gl?con$4))	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:41
S14	99	S13 and glucon$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:41

S15	3611	oxidized starch	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:52
S16	1178	(iron or ferric or ferrous) and (oxidized near3 starch)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:53
S17	984	S16 and @ad<="20060106"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:53
S18	3	S17 and (anemia or anaemia)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:53
S19	4627	oxidized near3 (starch or dextrin or maltose or (malt sugar) or maltotriose)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:55
S20	1328	S19 and (iron or ferric or ferrous)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:55
S21	1104	S20 and @ad<="20060106"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:55
S22	4	S21 and (anemia or anaemia)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:55
S23	9	((MARY) near2 (HELENEK)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:57
S24	4	((MARC) near2 (TOKARS)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:57
S25	386	((RICHARD) near2 (LAWRENCE)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:58
S26	388	S23 or S24 or S25	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:58
S27	37	S26 and (iron or ferric or ferrous)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:58
S28	8	S27 and anemia	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 15:59
S29	1	glucosyl gluconate	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 16:18
S30	0	polyglucosyl gluconate	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 16:22

S31	1	poly-glucosyl gluconate	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 16:23
S32	1	"4985553".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 16:25
S33	1	glucosyl near3 gluconate	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 16:28
S34	1	"20040180849".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/02 16:39
S35	3131	iron near9 (carbohydrate or sugar or sucrose or dextrin or starch or mal$4tose or saccharide)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/05 14:04
S36	2203	S35 and @ad<="20060106"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/05 14:04
S37	244	S36 and (anemia or anaemia)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/05 14:04
S38	125	S37 and iron near9 complex	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/05 14:04
S39	84	S38 and (parenteral or intravenous or inject$5)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/02/05 14:05
S40	3214	iron near9 (carbohydrate or sugar or sucrose or dextrin or starch or mal$4tose or saccharide)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 08:46
S41	2216	S40 and @ad<="20060106"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 08:46
S42	247	S41 and (anemia or anaemia)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 08:46
S43	126	S42 and iron near9 complex	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 08:46
S44	84	S43 and (parenteral or intravenous or inject$5)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 08:46
S45	67	S44 and (carboxymaltose or mannitol or poly$3maltose or $5gluconate or sorbitol)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 08:46

S46	24	S45 and (iron near9 size)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 08:47
S47	27	S45 and ((iron near9 size) or nanoparticle or (core near9 size))	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 08:48
S48	9	((MARY) near2 (HELENEK)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 09:25
S49	5	((MARC) near2 (TOKARS)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 09:25
S50	389	((RICHARD) near2 (LAWRENCE)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 09:25
S51	391	S48 or S49 or S50	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 09:25
S52	37	S51 and (iron or ferric or ferrous)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 09:25
S53	9	S52 and (iron near9 (carbohydrate or sugar or sucrose or dextrin or starch or mal$4tose or saccharide or carboxymaltose))	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 09:25
S54	3	Ferumoxytol	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 09:34
S55	1	"6,599,498".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 09:35
S56	1	"5624668".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 11:32
S57	1	S56 and chronic and blood and loss and anemia	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 11:35
S58	0	"6599498".pn. and ($maltose or carboxy-maltose)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 15:02
S59	0	"6599498".pn. and ($malt$5 or carboxy-maltose)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 15:03
S60	4	iron and (carboxymaltose or carboxy-maltose or vit-45 or Ferumoxytol)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/05/22 15:04

5/22/2009 4:43:51 PM

C:\ Documents and Settings\ jlau1\ My Documents\ EAST\ Workspaces\ 11620986 - iron complex.wsp

PTO/SB/08A (01-08)
Approved for use through 01/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | | of | |

Complete if Known	
Application Number	11/620,986
Filing Date	January 8, 2007
First Named Inventor	HELENEK, Mary
Art Unit	1623
Examiner Name	TBA
Attorney Docket Number	30015730-0043

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/J.L./		US- 6,960,571	09-16-2004	Helenek et al.	
/J.L./		US- 6,599,498	07-29-2003	Groman et al.	
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/Jonathan Lau/	Date Considered	05/22/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08B (01-08)
Approved for use through 01/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/620,986
Filing Date	January 8, 2007
First Named Inventor	HELENEK, Mary
Art Unit	1623
Examiner Name	TBA
Attorney Docket Number	30015730-0043

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.L./	3	BAILIE GR, et al., Hypersensitivity reactions and deaths associated with intravenous iron preparations, Nephrol. Dial. Transplant, 2005, pp. 1443-9, vol. 20(7)	
	4	BESHARA S, et al., Pharmacokinetics and red cell utilization of 52Fe/59Fe-labelled iron polymaltose in anaemic patients using positron emission tomography, Br. J. Haematol., 2003, pp. 853-9, vol. 120(5)	
	5	FISHBANE S, Safety in iron management, Am. J. Kidney Dis., 2003, pp. 19-26, vol. 41(5 Suppl)	
	6	GEISSER P, et al., Structure/histotoxicity relationship of parenteral iron preparations, Arzneimittelforschung, 1992, pp. 1439-52, vol. 42(12)	
	7	KUDASHEVA DS, et al., Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanoparticles in parenteral formulations, J. Inorg. Biochem., 2004, pp. 1757-69, vol. 98(11)	
	8	LANDRY R, et al., Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients, Am. J. Nephrol., 2005, pp. 400-10, vol. 25(4)	
	9	NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000, Am. J. Kidney Dis., 2001, pp. S182-238, vol. 37(1 Suppl 1)	
	10	SPINOWITZ BS, et al., The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients, Kidney Int., 2005, pp. 1801-7, vol. 68(4)	
	11	VAN WYCK DB, et al., Making sense: a scientific approach to intravenous iron therapy, J. Am. Soc. Nephrol., 2004, pp. S91-2, vol. 15 Suppl 2	
/J.L./	12	VAN WYCK DB, Labile iron: manifestations and clinical implications, J. Am. Soc. Nephrol., 2004, pp. S107-11, vol. 15 Suppl 2	

Examiner Signature	/Jonathan Lau/	Date Considered	05/22/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Google Scholar BETA

Web Images Video News Maps more »

iron carboxymaltose OR carboxy-maltose OR 1900 - 2005 Search

Advanced Scholar Search
Scholar Preferences
Scholar Help

Scholar All articles - Recent articles Results 1 - 10 of about 35 for iron carboxymaltose OR carboxy-maltose OR vit-45 OR Ferumoxytol. (0.03 seconds)

Did you mean: iron carboxymaltose OR *carboxymaltose* OR vit-45 OR Ferumoxytol

... uptake of ferumoxtran-10 and **ferumoxytol**, ultrasmall superparamagnetic **iron** oxide contrast agents ...
AD Yancy, AR Olzinski, TC Hu, SC Lenhard, K ... - Journal of magnetic resonance imaging: JMRI, 2005 - ncbi.nlm.nih.gov
Differential uptake of ferumoxtran-10 and **ferumoxytol**, ultrasmall superparamagnetic
iron oxide contrast agents in rabbit: critical determinants of ...
Cited by 35 - Related articles - Web Search

... in humans using **ferumoxytol**, a novel ultrasmall superparamagnetic **iron** oxide (USPIO)-based blood ...
W Li, S Tutton, AT Vu, L Pierchala, BSY Li, JM ... - Journal of Magnetic Resonance Imaging, 2005 - interscience.wiley.com
... MR, Zhang HL, Chabra SG, Jacobs P, Wang Y. A pilot investigation of new
superparamagnetic **iron** oxide (**ferumoxytol**) as a contrast agent for cardiovascular ...
Cited by 35 - Related articles - Web Search - All 2 versions

Pharmacokinetic study of **ferumoxytol**: a new **iron** replacement therapy in normal subjects and ...
R Landry, PM Jacobs, R Davis, M Shenouda, WK ... - Am J Nephrol, 2005 - content.karger.com
... In this study, we demonstrated that the new intravenous **iron** drug **ferumoxytol** can
safely be administered at rates as high as 1,800 mg of **iron**/min. ...
Cited by 8 - Related articles - Web Search - BL Direct - All 5 versions

The safety and efficacy of **ferumoxytol** therapy in anemic chronic kidney disease patients
BS Spinowitz, MH Schwenk, PM Jacobs, WK Bolton, MR ... - Kidney international, 2005 - nature.com
... These increases demonstrate that the **iron** contained in **ferumoxytol** is bioavailable,
and is used to promote increased hemoglobin synthesis and reticulocytosis. ...
Cited by 16 - Related articles - Web Search - BL Direct - All 5 versions

Imaging, Distribution, and Toxicity of Superparamagnetic **Iron** Oxide Magnetic Resonance Nanoparticles ...
LL Muldoon, M Sandor, KEBA Pinkston, EAMD Neuwelt - Neurosurgery, 2005 - neurosurgery-online.com
... D, whole rat brain coronal sections stained for hematoxylin and eosin, myelin, and
DAB-enhanced **iron**, 92 days after **ferumoxytol** 25 μg inoculation. ...
Cited by 36 - Related articles - Web Search - All 3 versions

A pilot investigation of new superparamagnetic **iron** oxide (**ferumoxytol**) as a contrast agent for ...
MR Prince, HL Zhang, SG Chabra, P Jacobs, Y Wang - Journal of X-Ray Science and Technology, 2003 - IOS Press
... 231 IOS Press A pilot investigation of new superparamagnetic **iron** oxide
(**ferumoxytol**) as a contrast agent for cardiovascular MRI **...**
Cited by 5 - Related articles - Web Search

[CITATION] ... and safety study of **ferumoxytol**: a new blood pool and macrophage specific superparamagnetic **iron** ...
PM Jacobs, M Shenouda - Radiological Society of North America Scientific Assembly ..., 2003
Cited by 4 - Related articles - Web Search

[CITATION] A phase I pharmacokinetics and safety study of **ferumoxytol**, a new intravenous **iron** therapy (abstr)
P Jacobs, M Shenouda - J Am Soc Nephrol, 2003
Cited by 3 - Related articles - Web Search

Ultrasmall Superparamagnetic **Iron**-Oxide–enhanced MR Imaging of Normal Bone Marrow in Rodents: ...
GH Simon, HJ Raatschen, MF Wendland, J von ... - Academic radiology, 2005 - Elsevier
... AT Vu et al., First-pass contrast-enhanced magnetic resonance angiography in humans
using **ferumoxytol**, a novel ultrasmall superparamagnetic **iron** oxide (USPIO **...**
Cited by 10 - Related articles - Web Search - All 9 versions

[CITATION] ... transferrin saturation in the serum of patients receiving either **ferumoxytol**, **iron** gluconate or **iron** ...
P Jacobs, JM Lewis, TB Frigio - J Am Soc Nephrol, 2004
Cited by 2 - Related articles - Web Search

Key authors: **P Jacobs** - **A Yancy** - **W Li** - **R Edelman** - **L Muldoon**

Did you mean to search for: iron carboxymaltose OR ***carboxymaltose*** OR vit-45 OR Ferumoxytol

Goooogle ▶
Result Page: 1 2 3 4 **Next**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **11/620,986**	Examiner: **LAU, Jonathan S**
Applicant: **HELENEK, MARY JANE**	Group Art Unit: **1623**
Filed: **January 1, 2007**	Confirmation No.: **1325**
Docket No.: **30015730-0043**	Customer No.: **26263**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	

March 3, 2009

FILED ELECTRONICALLY FILED VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION AND ELECTION REQUIREMENTS

Sir:

In response to the Restriction and Election Requirments of February 23, 2009, Applicants request the Office consider the following remarks.

REMARKS

Applicants acknowledge withdrawal of the Action of October 23, 2008 and the entry of the present Action, which the Office provides to clarify the Election of Species requirement as requested by Applicant in the prior Response.

Election of Species

In the Action of February 23, 2009, the Office required under 35 U.S.C. 121 an election of a first species of disease, disorder, or condition; a second species of iron carbohydrate complex; and a third species of route of administration. The Office acknowledges that at all claims are generic to the first specie of disease, disorder, or condition; claims 1-25 and 35-57 are generic to the second specie of iron carbohydrate complex; and claims 1-43 and 57-60 are generic to the third specie of route of administration.

Election of Species

For the first species, Applicants elect iron deficiency anemia associated with chronic blood loss. Claims readable on the elected species of iron deficiency anemia include claims 1-4 and 10-60.

For the second species, Applicants elect iron carboxymaltose complex. Claims readable on the elected species of iron carboxymaltose complex include claims 1-30 and 33-60.

For the third species, Applicants elect intravenous infusion. Claims readable on the elected species of intravenous infusion include claims 1-49 and 54-60.

Rejoinder

In electing the above species, Applicants reserve the right to request REJOINDER, under MPEP § 821.04, and examination of the non-elected species upon allowance of any claims generic to the non-elected species.

Conclusion

Applicants believe that the claims as presented represent allowable subject matter. If the Examiner desires, Applicants welcome a telephone interview to expedite prosecution. As always, the Examiner is free to call the undersigned at the number below. Applicants believe there are no additional fees due at this time. However, the Commissioner is hereby authorized to charge any applicable fees to Deposit Account No. 19-3140.

Respectfully submitted,

SONNENSCHEIN NATH & ROSENTHAL LLP

By: /G. Harley Blosser/ (Reg. 33,650)
G. Harley Blosser
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. Box 061080
Wacker Drive Station, Sears Tower
Chicago, IL 60606-1080
Telephone: 314.259.5806
Fax: 312.876.7934

Electronic Acknowledgement Receipt	
EFS ID:	4897545
Application Number:	11620986
International Application Number:	
Confirmation Number:	1325
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	George H. Blosser/Dennis Harney
Filer Authorized By:	George H. Blosser
Attorney Docket Number:	30015730-0043
Receipt Date:	03-MAR-2009
Filing Date:	08-JAN-2007
Time Stamp:	18:38:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Election / Restriction Filed	RRR_30015730_0043_March3_2009.pdf	58940 4f8d708b5db175765cfac1af103848ef68000cc1	no	3
Warnings:					
Information:					

Total Files Size (in bytes):	58940

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043	1325

26263 7590 02/23/2009
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
02/23/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/620,986	HELENEK ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-60* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is Responsive to Applicant's Amendment and Remarks, mailed 21 Nov 2008.

Response to Amendment

The reply filed on 21 Nov 2008 is not fully responsive to the prior Office Action because of the following omission(s) or matter(s): Applicant's election of First species of "iron deficiency anemia" is deemed to be the non-responsive election of a subgenus encompassing multiple species. See 37 CFR 1.111. For example, the First species of iron deficiency anemia associated with chronic blood loss, iron deficiency anemia associated with parasitic infections and anemia of the chronic disease inflammatory bowel disease each possess a distinct etiology, associated symptoms and patient population, and are not obvious variants of each other based on the current record. However, in view of the election of a subgenus deemed non-responsive and confusion regarding the Third species of route of administration, the previous Office Action, mailed 23 Oct 2008, is withdrawn and a new Election of Species Requirement is detailed below.

Withdrawal of Previous Office Action

Responsive to Applicant's Remarks, filed 21 Nov 2008, the previous Office Action, mailed 23 Oct 2008, is withdrawn in order to clarify the Election of Species

requirement and more clearly indicate and explain what constitutes a non-responsive election of a subgenus.

Election of Species Requirement

This application contains claims directed to the following patentably distinct **First** species of disease, disorder or condition; **Second** species of iron carbohydrate complex and **Third** species of route of administration. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Examples of a **First** specie of disease, disorder or condition are:

1a) iron deficiency anemia associated with chronic blood loss, disclosed in claim 4,

1b) iron deficiency anemia associated with surgery or acute trauma, disclosed in claim 4,

1c) iron deficiency anemia associated with parasitic infections, disclosed in claim 4,

1d) anemia of the chronic disease inflammatory bowel disease, disclosed in claim 6,

1e) anemia of the chronic disease rheumatoid arthritis, disclosed in claim 6, and

1e) restless leg syndrome, disclosed in claim 9.

Examples of a **Second** specie of iron carbohydrate complex are:

2a) iron mannitol complex, disclosed in claim 25,

2b) iron polymaltose complex, disclosed in claim 25,

2c) iron carboxymaltose complex, disclosed in claims 25 and 26, and

2d) iron polyglucose sorbitol carboxymethyl ether complex, disclosed in claim 31.

Examples of a **Third** specie of route of administration are:

3a) intravenously infused, disclosed in claim 46,

3b) intravenously injected as a bolus, disclosed in claim 50, and

3c) intramuscularly, disclosed in claim 54.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Applicant is cautioned that election of a subgenus, such as iron deficiency anemia or anemia of a chronic disease, will be considered non-responsive. Currently, all claims are generic to the First specie of disease, disorder or condition, claims 1-25 and 33-57 are generic to the Second specie of iron carbohydrate complex and claims 1-43 and 57-60 are generic to the Third specie of route of administration.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. For example, iron deficiency anemia associated with chronic blood loss, iron deficiency anemia associated with parasitic

infections and anemia of the chronic disease inflammatory bowel disease each possess a distinct etiology, associated symptoms and patient population, and are not obvious variants of each other based on the current record. The species require a different field of search (e.g., employing different search queries for methods of treating different patient populations); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/17/2008	02/12/2009							
	1	÷	÷							
	2	÷	÷							
	3	÷	÷							
	4	÷	÷							
	5	÷	÷							
	6	÷	÷							
	7	÷	÷							
	8	÷	÷							
	9	÷	÷							
	10	÷	÷							
	11	÷	÷							
	12	÷	÷							
	13	÷	÷							
	14	÷	÷							
	15	÷	÷							
	16	÷	÷							
	17	÷	÷							
	18	÷	÷							
	19	÷	÷							
	20	÷	÷							
	21	÷	÷							
	22	÷	÷							
	23	÷	÷							
	24	÷	÷							
	25	÷	÷							
	26	÷	÷							
	27	÷	÷							
	28	÷	÷							
	29	÷	÷							
	30	÷	÷							
	31	÷	÷							
	32	÷	÷							
	33	÷	÷							
	34	÷	÷							
	35	÷	÷							
	36	÷	÷							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/17/2008	02/12/2009							
	37	÷	÷							
	38	÷	÷							
	39	÷	÷							
	40	÷	÷							
	41	÷	÷							
	42	÷	÷							
	43	÷	÷							
	44	÷	÷							
	45	÷	÷							
	46	÷	÷							
	47	÷	÷							
	48	÷	÷							
	49	÷	÷							
	50	÷	÷							
	51	÷	÷							
	52	÷	÷							
	53	÷	÷							
	54	÷	÷							
	55	÷	÷							
	56	÷	÷							
	57	÷	÷							
	58	÷	÷							
	59	÷	÷							
	60	÷	÷							

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **11/620,986**	Examiner: **LAU, Jonathan S**
Applicant: **HELENEK, MARY JANE**	Group Art Unit: **1623**
Filed: **January 1, 2007**	Confirmation No.: **1325**
Docket No.: **30015730-0043**	Customer No.: **26263**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	

November 21, 2008

FILED ELECTRONICALLY FILED VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION AND ELECTION REQUIREMENTS

Sir:

In response to the Restriction and Election Requirments of October 23, 2008, Applicants request the Office consider the following remarks.

Election of Invention

Species Restriction

In the Action of October 23, 2008, the Office required under 35 U.S.C. 121 an election of a first species of disease, disorder, or condition; a second species of iron carbohydrate complex; and a third species of route of adminstration. The Office acknowledges that at all claims are generic to the first specie of disease, disorder, or condition; claims 1-25 and 35-57 are generic to the second specie of iron carbohydrate complex; and claims 1-43 and 57-60 are generic to the third specie of route of administration.

Election of Species

For the first species, Applicants elect iron deficiency anemia. Claims readable on the elected species of iron deficiency anemia include claims 1-4 and 10-60.

For the second species, Applicants elect iron carboxymaltose complex. Claims readable on the elected species of iron carboxymaltose complex include claims 1-30 and 33-60.

The Office requires election of a third species from: parenteral, intravenosuly infused, and intravenously injected. For the third species, Applicants elect parenteral administration. Claims readable on the elected species of parenteral administration include claims 1-60. Applicants note that parenteral administration is defined by the Specification to include both intravenous and intramuscular injection (*see* ¶0036). Intravenous injection is defined to include both bolus and infusion (*see* ¶0036). As such, the Office appears to have misunderstood the genus/species organization. If so required, Applicants would elect intravenous injection as a sub-species (readable on claims 1-60), and intravenous infusion as a sub-sub-species (readable on claims 1-49 anf 54-60). Applicants request clarification from the Office regarding the third species election requirement of record.

Rejoinder

In electing the above species, Applicants reserve the right to request REJOINDER, under MPEP § 821.04, and examination of the non-elected species upon allowance of any claims generic to the non-elected species.

Conclusion

Applicants believe that the claims as presented represent allowable subject matter. If the Examiner desires, Applicants welcome a telephone interview to expedite prosecution. As always, the Examiner is free to call the undersigned at the number below. Applicants believe there are no additional fees due at this time. However, the Commissioner is hereby authorized to charge any applicable fees to Deposit Account No. 19-3140.

Respectfully submitted,

SONNENSCHEIN NATH & ROSENTHAL LLP

By: /G. Harley Blosser/ (Reg. 33,650)
G. Harley Blosser
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. Box 061080
Wacker Drive Station, Sears Tower
Chicago, IL 60606-1080
Telephone: 314.259.5806
Fax: 312.876.7934

Electronic Acknowledgement Receipt	
EFS ID:	4337017
Application Number:	11620986
International Application Number:	
Confirmation Number:	1325
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	George H. Blosser/Dennis Harney
Filer Authorized By:	George H. Blosser
Attorney Docket Number:	30015730-0043
Receipt Date:	21-NOV-2008
Filing Date:	08-JAN-2007
Time Stamp:	18:03:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Election / Restriction Filed	RRR_30015730_0043_Nov21_2008.pdf	66485 b926daca662fd49c4b3450495f78b9d827bf a58c	no	3
Warnings:					
Information:					

Total Files Size (in bytes):	66485

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043	1325

26263 7590 10/23/2008

SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
10/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No.	Applicant(s)	
	11/620,986	HELENEK ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-60* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election of Species Requirement

This application contains claims directed to the following patentably distinct **First** species of disease, disorder or condition; **Second** species of iron carbohydrate complex and **Third** species of route of administration. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Examples of a **First** specie of disease, disorder or condition are:

1a) chronic blood loss, disclosed in claim 4,

1b) surgery or acute trauma, disclosed in claim 4,

1c) inflammatory bowel disease, disclosed in claim 6, and

1d) restless leg syndrome, disclosed in claim 9.

Examples of a **Second** specie of iron carbohydrate complex are:

2a) iron mannitol complex, disclosed in claim 25,

2b) iron polymaltose complex, disclosed in claim 25,

2c) iron carboxymaltose complex, disclosed in claims 25 and 26, and

2d) iron polyglucose sorbitol carboxymethyl ether complex, disclosed in claim 31.

Examples of a **Third** specie of route of administration are:

3a) parenterally, disclosed in claim 44,

3b) intravenously infused, disclosed in claim 46, and

3c) intravenously injected as a bolus, disclosed in claim 50.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, all claims are generic to the First specie of disease, disorder or condition, claims 1-25 and 33-57 are generic to the Second specie of iron carbohydrate complex and claims 1-43 and 57-60 are generic to the Third specie of route of administration.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner
Art Unit 1623

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/17/2008								
	1	÷								
	2	÷								
	3	÷								
	4	÷								
	5	÷								
	6	÷								
	7	÷								
	8	÷								
	9	÷								
	10	÷								
	11	÷								
	12	÷								
	13	÷								
	14	÷								
	15	÷								
	16	÷								
	17	÷								
	18	÷								
	19	÷								
	20	÷								
	21	÷								
	22	÷								
	23	÷								
	24	÷								
	25	÷								
	26	÷								
	27	÷								
	28	÷								
	29	÷								
	30	÷								
	31	÷								
	32	÷								
	33	÷								
	34	÷								
	35	÷								
	36	÷								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11620986	HELENEK ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/17/2008								
	37	÷								
	38	÷								
	39	÷								
	40	÷								
	41	÷								
	42	÷								
	43	÷								
	44	÷								
	45	÷								
	46	÷								
	47	÷								
	48	÷								
	49	÷								
	50	÷								
	51	÷								
	52	÷								
	53	÷								
	54	÷								
	55	÷								
	56	÷								
	57	÷								
	58	÷								
	59	÷								
	60	÷								

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **11/620,986**	Examiner: **TBA**
Applicant: **HELENEK, Mary**	Group Art Unit: **1623**
Filed: **January 8, 2007**	Confirmation No.: **1325**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	Customer No.: **26263**
Docket No.: **30015730-0043**	

January 18, 2008

FILED ELECTRONICALLY VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT

UNDER 37 C.F.R. §1.97(b)

Sir:

In accordance with the provisions of 37 C.F.R. § 1.56, Applicants request citation and examination of the references identified on the attached PTO-SB08A and PTO-SB08B forms, in accordance with 37 C.F.R. §1.98, be made during the course of examination of the above-referenced application for United States Letters Patent.

Under 37 C.F.R. § 1.97(b), the information disclosure statement submitted herewith is being filed ***before*** the mailing of a first Office action on the merits.

Items cited in a PCT International Search Report in a counterpart PCT application (PCT International No. PCT/US2007/000176 filed January 8, 2007) are included. Copies of the above-identified references are being submitted herewith.

The filing of this information disclosure statement shall not be construed as a representation that a search has been made, an admission that the information cited is, or is considered to be, material to patentability, or that no other material information exists (*see* 37 C.F.R. § 1.97(g)). The filing of this information disclosure statement shall not be construed as

an admission against interest in any manner. Notice of January 9, 1992, 1135 O.G. 13-25, at 25.

Applicants believe no fee is due at this time. But the Commissioner is hereby authorized to charge any required fees to Deposit Account No. 19-3140.

Respectfully submitted,

SONNENSCHEIN NATH & ROSENTHAL LLP

/G. Harley Blosser/
By: _____
G. Harley Blosser
Reg. No. 33,650
Telephone No. 314.259.5806

ATTORNEYS FOR APPLICANT

23184342\V-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **11/620,986**	Examiner: **TBA**
Applicant: **HELENEK, Mary**	Group Art Unit: **1623**
Filed: **January 8, 2007**	Confirmation No.: **1325**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	Customer No.: **26263**
Docket No.: **30015730-0043**	

January 18, 2008

FILED ELECTRONICALLY VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT

UNDER 37 C.F.R. §1.97(b)

Sir:

In accordance with the provisions of 37 C.F.R. § 1.56, Applicants request citation and examination of the references identified on the attached PTO-SB08A and PTO-SB08B forms, in accordance with 37 C.F.R. §1.98, be made during the course of examination of the above-referenced application for United States Letters Patent.

Under 37 C.F.R. § 1.97(b), the information disclosure statement submitted herewith is being filed ***before*** the mailing of a first Office action on the merits.

Items cited in a PCT International Search Report in a counterpart PCT application (PCT International No. PCT/US2007/000176 filed January 8, 2007) are included. Copies of the above-identified references are being submitted herewith.

The filing of this information disclosure statement shall not be construed as a representation that a search has been made, an admission that the information cited is, or is considered to be, material to patentability, or that no other material information exists (*see* 37 C.F.R. § 1.97(g)). The filing of this information disclosure statement shall not be construed as

an admission against interest in any manner. Notice of January 9, 1992, 1135 O.G. 13-25, at 25.

Applicants believe no fee is due at this time. But the Commissioner is hereby authorized to charge any required fees to Deposit Account No. 19-3140.

Respectfully submitted,

SONNENSCHEIN NATH & ROSENTHAL LLP

/G. Harley Blosser/
By: _____
G. Harley Blosser
Reg. No. 33,650
Telephone No. 314.259.5806

ATTORNEYS FOR APPLICANT

23184342\V-2

PTO/SB/08A (01-08)
Approved for use through 01/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | | of | |

Complete if Known	
Application Number	11/620,986
Filing Date	January 8, 2007
First Named Inventor	HELENEK, Mary
Art Unit	1623
Examiner Name	TBA
Attorney Docket Number	30015730-0043

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US- 6,960,571	09-16-2004	Helenek et al.	
		US- 6,599,498	07-29-2003	Groman et al.	
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08B (01-08)
Approved for use through 01/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/620,986
Filing Date	January 8, 2007
First Named Inventor	HELENEK, Mary
Art Unit	1623
Examiner Name	TBA
Attorney Docket Number	30015730-0043

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	3	BAILIE GR, et al., Hypersensitivity reactions and deaths associated with intravenous iron preparations, Nephrol. Dial. Transplant, 2005, pp. 1443-9, vol. 20(7)	
	4	BESHARA S, et al., Pharmacokinetics and red cell utilization of 52Fe/59Fe-labelled iron polymaltose in anaemic patients using positron emission tomography, Br. J. Haematol., 2003, pp. 853-9, vol. 120(5)	
	5	FISHBANE S, Safety in iron management, Am. J. Kidney Dis., 2003, pp. 19-26, vol. 41(5 Suppl)	
	6	GEISSER P, et al., Structure/histotoxicity relationship of parenteral iron preparations, Arzneimittelforschung, 1992, pp. 1439-52, vol. 42(12)	
	7	KUDASHEVA DS, et al., Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanoparticles in parenteral formulations, J. Inorg. Biochem., 2004, pp. 1757-69, vol. 98(11)	
	8	LANDRY R, et al., Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients, Am. J. Nephrol., 2005, pp. 400-10, vol. 25(4)	
	9	NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000, Am. J. Kidney Dis., 2001, pp. S182-238, vol. 37(1 Suppl 1)	
	10	SPINOWITZ BS, et al., The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients, Kidney Int., 2005, pp. 1801-7, vol. 68(4)	
	11	VAN WYCK DB, et al., Making sense: a scientific approach to intravenous iron therapy, J. Am. Soc. Nephrol., 2004, pp. S91-2, vol. 15 Suppl 2	
	12	VAN WYCK DB, Labile iron: manifestations and clinical implications, J. Am. Soc. Nephrol., 2004, pp. S107-11, vol. 15 Suppl 2	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

Electronic Acknowledgement Receipt	
EFS ID:	2760094
Application Number:	11620986
International Application Number:	
Confirmation Number:	1325
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	George H. Blosser/Chris Marion
Filer Authorized By:	George H. Blosser
Attorney Docket Number:	30015730-0043
Receipt Date:	24-JAN-2008
Filing Date:	08-JAN-2007
Time Stamp:	13:04:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement Letter	SNR30015730-0043_IDS_Transmittal.pdf	476242 a77e77db15dd96f2fdf277f30d59c33298bee6f9	no	2
Warnings:					
Information:					

2	Information Disclosure Statement (IDS) Filed	SNR30015730-0043_IDS_sb08.pdf	240407 b7e26595a12a9a16de7f95e98efd75d1ed857ae7	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	NPL Documents	Bailie_2000.pdf	106998 43f02524d64b4dfcf1ad52a17f33648306753cb3	no	7
Warnings:					
Information:					
4	NPL Documents	Beshara_2003.pdf	1008919 4d415c7f84bb93d3577f9578ba0daedf54d6e84f	no	7
Warnings:					
Information:					
5	NPL Documents	Fishbane_2003.pdf	2058134 576263a476d78d2f089b14831349afda041ba4d1	no	9
Warnings:					
Information:					
6	NPL Documents	Geisser_1992.pdf	2219478 f51c4513badd700680b0f82668f8239fa70ed0ed	no	16
Warnings:					
Information:					
7	NPL Documents	Kudasheva_2004.pdf	1044435 a9be8089fe176aeb127549da1b081ad4702defd1	no	14
Warnings:					
Information:					
8	NPL Documents	Landry_2005.pdf	2658699 d6d65b5e6f7c3e77f089296cd36c89ba2fedda73	no	12
Warnings:					
Information:					
9	NPL Documents	NKF-K_2001.pdf	3066658 255b23843ca4bce198c3d49b98b0f7fc7ba8dd9d	no	53
Warnings:					
Information:					
10	NPL Documents	Spinowitz_2005.pdf	1149035 4ec822bb03b57959940fb864bd542f096d98337d	no	7

Warnings:					
Information:					
11	NPL Documents	VanWyck_2004a.pdf	43726 e3bb85dae9448117d2e4b2ef77a95a00303e44a3	no	2
Warnings:					
Information:					
12	NPL Documents	VanWyck_2004b.pdf	86937 6a4e7b37b4caf75a595668c4897adbf716017339	no	5
Warnings:					
Information:					
			Total Files Size (in bytes):	14159668	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043

CONFIRMATION NO. 1325

26263
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL60606-1080

Title: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

Publication No. US-2007-0161600-A1
Publication Date: 07/12/2007

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Pre-Grant Publication Division, 703-605-4283

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043

CONFIRMATION NO. 1325

26263
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL60606-1080

Title: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

Publication No. US-2007-0161600-A1
Publication Date: 07/12/2007

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Pre-Grant Publication Division, 703-605-4283

Effective October 1, 2003

11620986

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	minus 20=	*
INDEPENDENT CLAIMS	minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐ OR OTHER THAN SMALL ENTITY

RATE	FEE	OR	RATE	FEE
BASIC FEE	385.00	OR	BASIC FEE	770.00
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY OR OTHER THAN SMALL ENTITY

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

1/8/07

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 20	Minus	** 20	=
Independent	* 2	Minus	*** 2	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/620,986	01/08/2007	1623	1490	30015730-0043	60	2

CONFIRMATION NO. 1325

UPDATED FILING RECEIPT

26263
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL60606-1080

Date Mailed: 03/30/2007

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Mary Jane Helenek, Brookville, NY;
Marc L. Tokars, Douglassville, PA;
Richard P. Lawrence, Calverton, NY;

Assignment For Published Patent Application

Luitpold Pharmaceuticals, Inc., Shirley, NY

Power of Attorney: The patent practitioners associated with Customer Number 26263

Domestic Priority data as claimed by applicant

This appln claims benefit of 60/757,119 01/06/2006

Foreign Applications

If Required, Foreign Filing License Granted: 01/23/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US11/620,986**

Projected Publication Date: 07/12/2007

Non-Publication Request: No

Early Publication Request: No

** SMALL ENTITY **

Title

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under

37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043

CONFIRMATION NO. 1325

FORMALITIES LETTER

26263
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606-1080

Date Mailed: 01/25/2007

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

• To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$65** for a small entity

- **$65** Surcharge.

RECEIVED
JAN 30 2007
4:48 P.M.

Replies should be mailed to: Mail Stop Missing Parts

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199, or 1-800-972-6382
PART 1 - ATTORNEY/APPLICANT COPY

APPLICATION DATA SHEET

Application Information

Application Type::	Non-Provisional
Subject Matter::	Utility
Title::	Methods and Compositions for Administration of Iron
Attorney Docket Number::	30015730-0043
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	2
Small Entity?::	Yes
Petition Included?::	No
Secrecy Order in Parent?::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Mary
Middle Name::	Jane
Family Name::	Helenek
City of Residence::	Brookville
State or Province of Residence::	New York
Country of Residence::	US
Street of Mailing Address::	13 Evans Drive
City of Mailing Address::	Brookville
State or Province of Mailing Address::	New York
Postal Code of Mailing Address::	11545

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Marc
Middle Name::	L.
Family Name::	Tokars
City of Residence::	Douglassville
State or Province of Residence::	Pennsylvania
Country of Residence::	US
Street of Mailing Address::	202 Farmingdale Drive
City of Mailing Address::	Douglassville
State or Province of Mailing Address::	Pennsylvania
Postal Code of Mailing Address::	19618

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Richard
Middle Name::	P.
Family Name::	Lawrence
City of Residence::	Calverton
State or Province of Residence::	New York
Country of Residence::	US
Street of Mailing Address::	94 Young Avenue
City of Mailing Address::	Calverton
State or Province of Mailing Address::	New York
Postal Code of Mailing Address::	11933

Correspondence Information

Correspondence Customer Number:: 26263

Representative Information

Representative Customer Number:: 26263

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This application is a	Non-Provisional of;	60/757,119	January 1, 2006

Assignee Information

Luitpold Pharmaceuticals, Inc.

One Luitpold Drive

Shirley, New York 11967

23214905\V-1

Docket No. 30015730-0043

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am an original and first inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

the specification filed on January 8, 2007, and assigned Application Serial No. 11/620,986.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

POWER OF ATTORNEY

I hereby appoint the attorney(s) and agent(s) of Sonnenschein Nath & Rosenthal associated with Customer Number 26263, with full power of revocation and substitution, to prosecute this application and to transact all business with the United States Patent and Trademark Office in connection therewith.

SEND CORRESPONDENCE AND DIRECT TELEPHONE CALLS TO:

G. Harley Blosser
SONNENSCHEIN NATH & ROSENTHAL
314.259.5806
Customer Number 26263

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the

like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Inventor:	Mary Jane Helenek
Inventor's Signature:	Mary Jane Helenek
Date:	Mar 12 2007
Country of Citizenship:	USA
Residence and Post Office Address:	13 Evans Drive Brookville, NY 11545

Inventor:	Marc L. Tokars
Inventor's Signature:	
Date:	3-1-2007
Country of Citizenship:	USA
Residence and Post Office Address:	202 Farmingdale Drive Douglassville, PA 19618

Inventor:	Richard P. Lawrence
Inventor's Signature:	
Date:	3/2/07
Country of Citizenship:	USA
Residence and Post Office Address:	94 Youngs Avenue Calverton, NY 11933

Electronic Patent Application Fee Transmittal

Application Number:	11620986
Filing Date:	08-Jan-2007
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Filer:	George H. Blosser/Drenda Nemeth
Attorney Docket Number:	30015730-0043
Filed as Small Entity	

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	2051	1	65	65
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**65**

Electronic Acknowledgement Receipt	
EFS ID:	1620545
Application Number:	11620986
International Application Number:	
Confirmation Number:	1325
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	George H. Blosser/Drenda Nemeth
Filer Authorized By:	George H. Blosser
Attorney Docket Number:	30015730-0043
Receipt Date:	23-MAR-2007
Filing Date:	08-JAN-2007
Time Stamp:	17:31:05
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$65
RAM confirmation Number	827
Deposit Account	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)

1	Miscellaneous Incoming Letter	Notice_To_File_Missing_Parts_30015730_0043.pdf	129139	no	2
Warnings:					
Information:					
2	Application Data Sheet	Application_Data_Sheet_30015730_0043.pdf	102519	no	3
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Oath or Declaration filed	Declaration_Power_of_Attorney_30015730_0043.pdf	150643	no	2
Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	8176	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	390477		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
11/620,986	01/08/2007	1614	1425	30015730-0043	2	60	2

CONFIRMATION NO. 1325

FILING RECEIPT

26263
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL60606-1080

Date Mailed: 01/25/2007

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Mary Jane Helenek, Brookville, NY;
Marc L. Tokars, Douglassville, PA;
Richard P. Lawrence, Calverton, NY;

Assignment For Published Patent Application

Luitpold Pharmaceuticals, Inc., Shirley, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 60/757,119 01/06/2006

Foreign Applications

If Required, Foreign Filing License Granted: 01/23/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US11/620,986**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

** SMALL ENTITY **

Title

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/620,986	01/08/2007	Mary Jane Helenek	30015730-0043

CONFIRMATION NO. 1325

FORMALITIES LETTER

26263
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606-1080

Date Mailed: 01/25/2007

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$65** for a small entity

- **$65** Surcharge.

Replies should be mailed to: Mail Stop Missing Parts

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199, or 1-800-972-6382
PART 3 - OFFICE COPY

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.:	30015730-0043
First Named Inventor:	HELENEK, Mary Jane, et al.
Title:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
Filed Electronically via:	EFS Web
Date of Deposit:	January 8, 2007

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1. ☒ This Form includes the Fee Transmittal (See Box 19) *(Submit an original and a duplicate for fee processing)*
2. ☒ Applicant claims small entity status. (See 37 CFR 1.27)
3. ☒ Specification [*Total Pages* 50]
4. ☒ Drawing(s) (35 USC 113) [*Total Sheets* 2]
5. ☐ Declaration and Power of Attorney [*Total Pages* _____]
   a. ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 18 completed)*
      i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☒ Application Data Sheet. See 37 CFR 1.76
7. ☐ CD-ROM or CD-R in duplicate, large table or Computer Program (Appendix)
   ☐ Landscape Table on CD
8. ☐ Nucleotide and/or Amino Acid Sequence Submission
   a. ☐ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R in duplicate; or
      ii. ☐ paper
   c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ Assignment Papers *(cover sheet & document(s))* Name of Assignee _____
10. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney
11. ☐ English Translation Document (*if applicable*)
12. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
13. ☐ Preliminary Amendment
14. ☐ Return Receipt Postcard (MPEP 503)
15. ☐ Certified copy of _____ Priority Document: Document No. _____, filed on _____.
16. ☐ Nonpublication Request under 35 U.S.C. 122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or its equivalent.
17. ☐ Other: _____

18. If a **CONTINUING APPLICATION**, check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:
☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) *of prior application no.:* _____/_____
Prior application information: Examiner Name: _____ Group Art Unit: _____

19. **FEE CALCULATIONS:**

(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) SUBTOTAL
TOTAL CLAIMS	60 - 20 =	40	x $25.00	$1,000.00
INDEPENDENT CLAIMS	2 - 3 =	0	x $100.00	$0.00
MULTIPLE DEPENDENT CLAIMS				$0.00
APPLICATION SIZE FEE (37 CFR 1.16(s)) If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41 (a)(1)(G) and 37 CFR 1.16(s).				$0.00
BASIC FEE				$75.00
SEARCH FEE				$250.00
EXAMINATION FEE				$100.00
			TOTAL:	$1,425.00

a. ☒ *In connection with this application*, the Director is hereby authorized to credit overpayments or to charge any additional fee required to Deposit Account No. 19-3140. ***A duplicate copy of this sheet is enclosed.***
b. ☒ Credit card payment in the amount of $ 1,425.00 is submitted herewith via EFS-Web.

20. ☒ **CUSTOMER NO. 26263**

Dated: January 8, 2007

SIGNATURE: D. Harley Blosser
G. Harley Blosser, (Reg. No. 33,650)

APPLICATION DATA SHEET

Application Information

Application Type::	Non-Provisional
Subject Matter::	Utility
Title::	Methods and Compositions for Administration of Iron
Attorney Docket Number::	30015730-0043
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	2
Small Entity?::	Yes
Petition Included?::	No
Secrecy Order in Parent?::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Mary
Middle Name::	Jane
Family Name::	Helenek
City of Residence::	Brookville
State or Province of Residence::	New York
Country of Residence::	US
Street of Mailing Address::	13 Evans Drive
City of Mailing Address::	Brookville
State or Province of Mailing Address::	New York
Postal Code of Mailing Address::	11545

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Marc
Middle Name::	L.
Family Name::	Tokars
City of Residence::	Douglassville
State or Province of Residence::	Pennsylvania
Country of Residence::	US
Street of Mailing Address::	202 Farmingdale Drive
City of Mailing Address::	Douglassville
State or Province of Mailing Address::	Pennsylvania
Postal Code of Mailing Address::	19618

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Richard
Middle Name::	P.
Family Name::	Lawrence
City of Residence::	Calverton
State or Province of Residence::	New York
Country of Residence::	US
Street of Mailing Address::	94 Young Avenue
City of Mailing Address::	Calverton
State or Province of Mailing Address::	New York
Postal Code of Mailing Address::	11933

Correspondence Information

Correspondence Customer Number:: 26263

Representative Information

Representative Customer Number:: 26263

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This application is a	Non-Provisional of;	60/757,119	January 1, 2006

Assignee Information

Luitpold Pharmaceuticals, Inc.

One Luitpold Drive

Shirley, New York 11967

23214905\V-1

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Application Serial No. 60/757,119 filed on January 1, 2006, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention generally relates to treatment of iron-related conditions with iron carbohydrate complexes.

BACKGROUND

[0003] Parenteral iron therapy is known to be effective in a variety of diseases and conditions including, but not limited to, severe iron deficiency, iron deficiency anemia, problems of intestinal iron absorption, intestinal iron intolerance, cases where regular intake of an oral iron preparation is not guaranteed, iron deficiency where there is no response to oral therapy (*e.g.*, dialysis patients), and situations where iron stores are scarcely or not at all formed but would be important for further therapy (*e.g.*, in combination with erythropoietin). Geisser et al., Arzneimittelforschung (1992) 42(12), 1439-1452. There exist various commercially available parenteral iron formulations. But many currently available parenteral iron drugs, while purportedly effective at repleting iron stores, have health risks and dosage limitations associated with their use.

[0004] Currently available parenteral iron formulations approved for use in the U.S. include iron dextran (*e.g.*, InFed, Dexferrum), sodium ferric gluconate complex in sucrose (Ferrlecit), and iron sucrose (Venofer). Although serious and life-threatening reactions occur most frequently with iron dextran, they are also known to occur with other parenteral iron products. In addition, non-life threatening reactions such as arthralgia, back pain, hypotension, fever, myalgia, pruritus, vertigo, and vomiting also occur. These reactions, while not life-threatening, often preclude further dosing and therefore iron repletion.

[0005] Iron dextran, the first parenteral iron product available in the United States (US), has been associated with an incidence of anaphylactoid-type reactions (*i.e.*, dyspnea, wheezing, chest pain, hypotension, urticaria, angioedema). *See generally* Fishbane, Am J Kidney Dis (2003) 41(5Suppl), 18-26; Landry et al. (2005) Am J Nephrol 25, 400-410, 407. This high incidence of anaphylactoid reactions is believed to be caused by the formation of antibodies to the dextran moiety. Other parenteral iron products (*e.g.*, iron sucrose and iron gluconate) do not contain the dextran moiety, and the incidence of anaphylaxis with these products is markedly lower. Fishbane, Am J Kidney Dis (2003) 41(5Suppl), 18-26; Geisser et al., Arzneimittelforschung (1992) 42(12), 1439-52. However, the physical characteristics of, for example, iron gluconate and iron sucrose lead to dosage and administration rate limitations. Negative characteristics include high pH, high osmolarity, low dosage limits (*e.g.*, maximum 500 mg iron once per week, not exceeding 7 mg iron/kg body weight), and the long duration of administration (*e.g.*, 100 mg iron over at least 5 minutes as an injection; 500 mg iron over at least 3.5 hours as a drip infusion). Furthermore, injectable high molecular mass substances produce more allergic reactions than the corresponding low molecular mass substances. Geisser et al. (1992) *Arzneimittelforschung* 42: 1439-1452.

[0006] Ferumoxytol is a newer parenteral iron formulation but limited information is available as to its efficacy and administration. *See e.g.*, Landry et al. (2005) Am J Nephrol 25, 400-410, 408; and Spinowitz et al. (2005) Kidney Intl 68, 1801-1807; U.S. Patent No. 6,599,498.

[0007] Various pharmacokinetic studies suggest that doses of iron complexes higher than 200 mg of iron are generally unsuitable and that the conventional therapy model prescribes repeated applications of lower doses over several days. *See* Geisser et al., (1992) *Arzneimittelforschung* 42: 1439-1452. For example, to achieve iron repletion under current therapy models, a total dose of 1 g typically requires 5 to 10 sessions over an extended period of time. These delivery modes incur significant expense for supplies such as tubing and infusate, costly nursing time, multiple administrations, and patient inconvenience.

SUMMARY OF THE INVENTION

[0008] Among the various aspects of the present invention is the provision of a method of treatment of iron-associated diseases, disorders, or conditions with iron formulations. Briefly, therefore, the present invention is directed to use of iron carbohydrate complexes that can be administered parenterally at relatively high single unit dosages, thereby providing a safe and efficient means for delivery of a total dose of iron in fewer sessions over the course of therapeutic treatment.

[0009] The present teachings include methods of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism through the administration of at least 0.6 grams of elemental iron via a single unit dosage of an iron carbohydrate complex to a subject that is in need of such therapy.

[0010] In various embodiments, the method treats anemia. In some embodiments, the anemia is an iron deficiency anemia, such as that associated with chronic blood loss; acute blood loss; pregnancy; childbirth; childhood development; psychomotor and cognitive development in children; breath holding spells; heavy uterine bleeding; menstruation; chronic recurrent hemoptysis; idiopathic pulmonary siderosis; chronic internal bleeding; gastrointestinal bleeding; parasitic infections; chronic kidney disease; dialysis; surgery or acute trauma; and chronic ingestion of alcohol, chronic ingestion of salicylates, chronic ingestion of steroids; chronic ingestion of non-steroidial anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents. In some aspects, the anemia is anemia of chronic disease, such as rheumatoid arthritis; cancer; Hodgkins leukemia; non-Hodgkins leukemia; cancer chemotherapy; inflammatory bowel disease; ulcerative colitis thyroiditis; hepatitis; systemic lupus erythematosus; polymyalgia rheumatica; scleroderma; mixed connective tissue disease; Sojgren's syndrome; congestive heart failure / cardiomyopathy; or idiopathic geriatric anemia. In some embodiments, the anemia is due to impaired iron absorption or poor nutrition, such as anemia associated with Crohn's Disease; gastric surgery; ingestion of drug products that

inhibit iron absorption; and chronic use of calcium. In various embodiments, the method treats restless leg syndrome; blood donation; Parkinson's disease; hair loss; or attention deficit disorder.

[0011] In various embodiments, the single dosage unit of elemental iron is between at least about 0.6 grams and 2.5 grams. In some embodiments, the single dosage unit of elemental iron is at least about 0.7 grams; at least about 0.8 grams; at least about 0.9 grams; at least about 1.0 grams; at least about 1.1 grams; at least about 1.2 grams; at least about 1.3 grams; at least about 1.4 grams; at least about 1.5 grams; at least about 1.6 grams; at least about 1.7 grams; at least about 1.8 grams; at least about 1.9 grams; at least about 2.0 grams; at least about 2.1 grams; at least about 2.2 grams; at least about 2.3 grams; at least about 2.4 grams; or at least about 2.5 grams.

[0012] In various embodiments, the single dosage unit of elemental iron is administered in about 15 minutes or less. In some embodiments, the single dosage unit of elemental iron is administered in about 10 minutes or less, about 5 minutes or less, or about 2 minutes or less.

[0013] In various embodiments, the subject does not experience a significant adverse reaction to the single dosage unit administration.

[0014] In various embodiments, the iron carbohydrate complex has a pH between about 5.0 to about 7.0; physiological osmolarity; an iron core size no greater than about 9 nm; a mean diameter particle size no greater than about 35 nm; a blood half-life of between about 10 hours to about 20 hours; a substantially non-immunogenic carbohydrate component; and substantially no cross reactivity with anti-dextran antibodies.

[0015] In various embodiments, the iron carbohydrate complex contains about 24% to about 32% elemental iron; contains about 25% to about 50% carbohydrate; has a molecular weight of about 90,000 daltons to about 800,000 daltons, or some combination thereof.

In various embodiments, the iron carbohydrate complex is an iron monosaccharide complex, an iron disaccharide complex, or an iron polysaccharide complex. In some embodiments, the iron carbohydrate complex

is iron carboxymaltose complex, iron mannitol complex, iron polyisomaltose complex, iron polymaltose complex, iron gluconate complex, iron sorbitol complex, or an iron hydrogenated dextran complex. In some embodiments, the iron carbohydrate complex is an iron polyglucose sorbitol carboxymethyl ether complex. In some preferred embodiments, the iron carboxymaltose complex contains about 24% to about 32% elemental iron, about 25% to about 50% carbohydrate, and is about 100,000 daltons to about 350,000 daltons. In some preferred embodiments, the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between 5 and 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between 5 and 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between 2 and 20. In some preferred embodiments, the iron carboxymaltose complex has a chemical formula of $[FeO_x(OH)_y(H_2O)_z]_n[\{(C_6H_{10}O_5)_m(C_6H_{12}O_7)\}_l]_k$, where n is about 103, m is about 8, l is about 11, and k is about 4; contains about 28% elemental iron; and has a molecular weight of about 150,000 Da. In some preferred embodiments, the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

[0016] In various embodiments, the iron carbohydrate complex comprises an iron core with a mean iron core size of no greater than about 9 nm. In some embodiments, the mean iron core size is at least about 1 nm but no greater than about 9 nm; at least about 3 nm but no greater than about 7 nm; or at least about 4 nm but not greater than about 5 nm.

[0017] In various embodiments, the mean size of a particle of the iron carbohydrate complex is no greater than about 35 nm. In some embodiments, the particle mean size is no greater than about 30 nm. In some embodiments, the particle mean size is no greater than about 25 nm. In some embodiments, the particle mean size is no greater than about 20 nm; no greater than about 15

nm; no greater than about 10 nm; or at least about 6 nm but no greater than about 7 nm.

[0018] In various embodiments, the iron carbohydrate complex is administered parenterally, for example intravenously or intramuscularly. In some embodiments, the iron carbohydrate complex is intravenously infused. In certain embodiments, the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, for example, about 250 ml of diluent or about 215 ml of diluent. In some embodiments, the iron carbohydrate complex is intravenously injected as a bolus. In certain embodiments, the iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, for example, about 250 ml of diluent or about 215 ml of diluent. In some embodiments, the iron carbohydrate complex is intramuscularly infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, for example, about 250 ml of diluent or about 215 ml of diluent. In some embodiments, the iron carbohydrate complex is intramuscularly infused at a concentration of about 500 mg elemental iron in less than about 10 ml diluent.

[0019] In various embodiments, the method also includes a second administration of the iron carbohydrate complex upon recurrence of at least one symptom of the treated disease, disorder, or condition.

[0020] In various embodiments, the method also includes a second administration of the iron carbohydrate complex after 1 day to 12 months after the first administration.

[0021] In a preferred embodiment, the method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism comprises intravenously administering to a subject in need thereof an iron carboxymaltose complex in a single dosage unit of at least about 1000 mg of elemental iron in about 200 ml to about 300 ml of diluent in about 5 minutes or less; wherein the iron carboxymaltose complex comprises an iron core with a mean iron core size of at least about 1 nm but no greater than about

9 nm; mean size of a particle of the iron carboxymaltose complex is no greater than about 35 nm; and the iron carboxymaltose complex is administered intravenously infused or intravenously injected at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent. In some these embodiments, the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. In some these embodiments, the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between about 5 and about 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between about 5 and about 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between about 2 and about 20.

[0022] Other objects and features will be in part apparent and in part pointed out hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Those of skill in the art will understand that the drawings, described below, are for illustrative purposes only. The drawings are not intended to limit the scope of the present teachings in any way.

[0024] FIG 1 is a series of electron micrographs that depict the particle size of three iron carbohydrate complexes. FIG 1A is an electron micrograph depicting the particle size of Dexferrum (an iron dextran). FIG 1B is an electron micrograph depicting the particle size of Venofer (an iron sucrose). FIG 1C is an electron micrograph depicting the particle size of polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate (“VIT-45”, an iron carboxymaltose complex).

[0025] FIG 2 is a schematic representation of an exemplary iron carboxymaltose complex.

DETAILED DESCRIPTION OF THE INVENTION

[0026] The present invention makes use of iron carbohydrate complexes that can be administered parenterally at relatively high single unit dosages for the therapeutic treatment of a variety of iron-associated diseases, disorders, or conditions. Generally, states indicative of a need for therapy with high single unit dosages of iron carbohydrate complexes include, but are not limited to iron deficiency anemia, anemia of chronic disease, and states characterized by dysfunctional iron metabolism. Efficacious treatment of these, and other, diseases and conditions with parenteral iron formulations (supplied at lower single unit dosages than those described herein) is generally known in the art. *See e.g.*, Van Wyck et al. (2004) J Am Soc Nephrol 15, S91-S92. The present invention is directed to use of iron carbohydrate complexes that can be administered parenterally at relatively high single unit dosages, thereby providing a safe and efficient means for delivery of a total dose of iron in fewer sessions over the course of therapeutic treatment.

[0027] Iron deficiency anemia is associated with, for example, chronic blood loss; acute blood loss; pregnancy; childbirth; childhood development; psychomotor and cognitive development in children; breath holding spells; heavy uterine bleeding; menstruation; chronic recurrent hemoptysis; idiopathic pulmonary siderosis; chronic internal bleeding; gastrointestinal bleeding; parasitic infections; chronic kidney disease; dialysis; surgery or acute trauma; and chronic ingestion of alcohol, chronic ingestion of salicylates, chronic ingestion of steroids; chronic ingestion of non-steroidial anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents.

[0028] Anemia of chronic disease is associated with, for example, rheumatoid arthritis; cancer; Hodgkins leukemia; non-Hodgkins leukemia; cancer chemotherapy; inflammatory bowel disease; ulcerative colitis thyroiditis; hepatitis; systemic lupus erythematosus; polymyalgia rheumatica; scleroderma; mixed connective tissue disease; Sojgren's syndrome; congestive heart failure / cardiomyopathy; and idiopathic geriatric anemia.

[0029] Anemia is also associated with, for example, Crohn's Disease; gastric surgery; ingestion of drug products that inhibit iron absorption; and chronic use of calcium.

[0030] States characterized by dysfunctional iron metabolism and treatable with the single unit dosages of iron carbohydrate complexes described herein include, but are not limited to, restless leg syndrome; blood donation; Parkinson's disease; hair loss; and attention deficit disorder.

[0031] Again, each of the above listed states, diseases, disorders, and conditions, as well as others, can benefit from the treatment methodologies described herein. Generally, treating a state, disease, disorder, or condition includes preventing or delaying the appearance of clinical symptoms in a mammal that may be afflicted with or predisposed to the state, disease, disorder, or condition but does not yet experience or display clinical or subclinical symptoms thereof. Treating can also include inhibiting the state, disease, disorder, or condition, *e.g.*, arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof. Furthermore, treating can include relieving the disease, *e.g.*, causing regression of the state, disease, disorder, or condition or at least one of its clinical or subclinical symptoms.

[0032] The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician. Measures of efficacy of iron replacement therapy are generally based on measurement of iron-related parameters in blood. The aim of treatment is usually to return both Hb and iron stores to normal levels. Thus, efficacy of iron replacement therapy can be interpreted in terms of the ability to normalise Hb levels and iron stores. The effectiveness of treatment with one or more single unit doses of iron carbohydrate complex, as described herein, can be demonstrated, for example, by improvements in ferritin and transferrin saturation, and in raising hemoglobin levels in anemic patients. Iron stores can be assessed by interpreting serum ferritin levels. TfS is frequently used, in addition, to diagnose absolute or functional iron deficiencies. In patients with iron deficiency, serum transferrin is elevated and will decrease following successful iron treatment.

[0033] Administration

[0034] Methods of treatment of various diseases, disorders, or conditions with iron complex compositions comprise the administration of the complex in single unit dosages of at least 0.6 grams of elemental iron to about at least 2.5 grams of elemental iron. Administration of single unit dosages can be, for example, over pre-determined time intervals or in response to the appearance and/or reappearance of symptoms. For example, the iron carbohydrate complex can be re-administered upon recurrence of at least one symptom of the disease or disorder. As another example, the iron carbohydrate complex can be re-administered at some time period after the initial administration (*e.g.*, after 4 days to 12 months).

[0035] Any route of delivery of the single unit dose of iron carbohydrate complex is acceptable so long as iron from the iron complex is released such that symptoms are treated. The single unit dose of iron carbohydrate complex can be administered parenterally, for example intravenously or intramuscularly. Intravenous administration can be delivered as a bolus or preferably as an infusion. For example, the single unit dose of iron carbohydrate complex can be intravenously infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, preferably about 215 ml of diluent or about 250 ml of diluent. The iron carbohydrate complex can be intravenously injected as a bolus. For example, the iron carbohydrate complex can be intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, preferably about 215 ml of diluent or about 250 ml of diluent. The iron carbohydrate complex can be intramuscularly infused at a concentration of, for example, about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, preferably, about 250 ml of diluent or about 215 ml of diluent. If applied as an infusion, the iron carbohydrate complex can be diluted with sterile saline (*e.g.*, polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate ("VIT-45") 0.9% m/V NaCl or 500 mg iron in up to 250 mL NaCl). The iron carbohydrate complex can be intravenously injected as a bolus without dilution. As an example, the iron carbohydrate complex can be

intramuscularly injected at a concentration of about 500 mg elemental iron in less than about 10 ml diluent, preferably about 5 ml.

[0036] Generally, total iron dosage will depend on the iron deficit of the patient. One skilled in the art can tailor the total iron dose required for a subject while avoiding iron overload, as overdosing with respect to the total required amount of iron has to be avoided, as is the case for all iron preparations.

[0037] The total iron dosage can be delivered as a single unit dosage or a series of single unit dosages. An appropriate single unit dosage level will generally be at least 0.6 grams of elemental iron, particularly at least 0.7 grams; at least 0.8 grams; at least 0.9 grams; at least 1.0 grams; at least 1.1 grams; at least 1.2 grams; at least 1.3 grams; at least 1.4 grams; at least 1.5 grams; at least 1.6 grams; at least 1.7 grams; at least 1.8 grams; at least 1.9 grams; at least 2.0 grams; at least 2.1 grams; at least 2.2 grams; at least 2.3 grams; at least 2.4 grams; or at least 2.5 grams. For example, a single unit dosage is at least 1.0 grams of elemental iron. As another example, a single unit dosage is at least 1.5 grams of elemental iron. As a further example, a single unit dosage is at least 2.0 grams of elemental iron. In yet another example, a single unit dosage is at least 2.5 grams of elemental iron.

[0038] An appropriate single unit dosage level can also be determined on the basis of patient weight. For example, an appropriate single unit dosage level will generally be at least 9 mg of elemental iron per kg body weight, particularly at least 10.5 mg/kg, at least 12 mg/kg, at least 13.5 mg/kg, at least 15 mg/kg, at least 16.5 mg/kg, at least 18 mg/kg, at least 19.5 mg/kg, at least 21 mg/kg, at least 22.5 mg/kg, at least 24 mg/kg, at least 25.5 mg/kg, at least 27 mg/kg, at least 28.5 mg/kg, at least 30 mg/kg, at least 31.5 mg/kg, at least 33 mg/kg, at least 34.5 mg/kg, at least 36 mg/kg, or at least 37.5 mg/kg.

[0039] Preferably, a single unit dosage can be administered in 15 minutes or less. For example, the single unit dosage can be administered in 14 minutes or less, 13 minutes or less, 12 minutes or less, 11 minutes or less, 10 minutes or less, 9 minutes or less, 8 minutes or less, 7 minutes or less, 6

minutes or less, 5 minutes or less, 4 minutes or less, 3 minutes or less, or 2 minutes or less.

[0040] Administration of iron can occur as a one-time delivery of a single unit dose or over a course of treatment involving delivery of multiple single unit doses. Multiple single unit doses can be administered, for example, over pre-determined time intervals or in response to the appearance and reappearance of symptoms. The frequency of dosing depends on the disease or disorder being treated, the response of each individual patient, and the administered amount of elemental iron. An appropriate regime of dosing adequate to allow the body to absorb the iron from the bloodstream can be, for example, a course of therapy once every day to once every eighteen months.

[0041] Such consecutive single unit dosing can be designed to deliver a relatively high total dosage of iron over a relatively low period of time. For example, a single unit dose (*e.g.*, 1000 mg) can be administered every 24 hours. As illustration, a total dose of 2000, 2500, 3000, 3500, 4000, 4500, or 5000 mg of elemental iron can be delivered via consecutive daily single unit doses of about 600 mg to about 1000 mg of elemental iron. Given that a single unit dose of 1000 mg can be intravenously introduced into a patient in a concentrated form over, for example, two minutes, such administrative protocol provides a practitioner and patient with an effective, efficient, and safe means to deliver elemental iron.

[0042] As another example, a single unit dose can be administered every 3-4 days. As a further example, a single unit dose can be administered once per week. Alternatively, the single unit doses of iron complex may be administered *ad hoc*, that is, as symptoms reappear, as long as safety precautions are regarded as practiced by medical professionals.

[0043] It will be understood, however, that the specific dose and frequency of administration for any particular patient may be varied and depends upon a variety of factors, including the activity of the employed iron complex, the metabolic stability and length of action of that complex, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug

combination, the severity and nature of the particular condition, and the host undergoing therapy.

[0044] The following provides but a few examples of treatment protocols for various diseases or disorders.

[0045] Iron carbohydrate complex can be given as a single unit dose for the treatment of Restless Leg Syndrome. For example, 1000 mg of elemental iron from an iron carboxymaltose (*e.g.*, polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate) can be intravenously injected as a single dose (*e.g.*, 1.5-5 mg iron/ml in normal saline) to a subject suffering from Restless Leg Syndrome. A single intravenous treatment can provide relief of symptoms for an extended period of time, approximately two to twelve months, although relief may be granted for shorter or longer periods. *See* U.S. Patent Pub. No. 2004/0180849, incorporated herein by reference. If desired, post-infusion changes in central nervous system iron status can be monitored using measurements of cerebral spinal fluid (CSF) ferritin (and other iron-related proteins) and of brain iron stores using MRI. Post-infusion changes in Restless Leg Syndrome are assessed using standard subjective (*e.g.*, patient diary, rating scale) and objective (*e.g.*, P50, SIT, Leg Activity Meters) measures of clinical status. If desired, to better evaluate RLS symptom amelioration, CSF and serum iron values, MRI measures of brain iron and full clinical evaluations with sleep and immobilization tests are obtained prior to treatment, approximately two weeks after treatment, and again twelve months later or when symptoms return. Clinical ratings, Leg Activity Meter recordings and serum ferritin are obtained monthly after treatment. CSF ferritin changes can also be used to assess symptom dissipation.

[0046] Iron carbohydrate complex can be given as a single unit dose for the treatment of iron deficiency anemia secondary to heavy uterine bleeding. For example, a single unit dose of 1,000 mg of elemental iron from an iron carboxymaltose in about 250 cc normal saline can be intravenously injected into a subject suffering from iron deficiency anemia secondary to heavy uterine

bleeding over 15 minutes every week until a calculated iron deficit dose has been administered. The iron deficit dose can be calculated as follows:

> If baseline TSAT < 20% or Baseline Ferritin < 50 ng/ml: Dose = Baseline weight (kg) x (15-Baseline Hgb [g/dL]) x 2.4 + 500 mg
>
> OR
>
> If baseline TSAT >20% and Baseline Ferritin > 50 ng/mL: Dose = Baseline weight (kg) x (15-Baseline Hgb [g/dL]) x 2.4
>
> (NOTE: Baseline Hgb equals the average of the last two central lab Hgb's)

[0047] Iron carbohydrate complex can be given as a single unit dose for the treatment of iron deficiency anemia. A subject diagnosed as suffering from iron deficiency anemia can be, for example, intravenously injected with a dose of 1,000 mg of iron as VIT- 45 (or 15 mg/kg for weight < 66 kg) in 250 cc of normal saline over 15 minutes. Subjects with iron deficiency anemia secondary to dialysis or non-dialysis dependent-Chronic Kidney Disease (CKD) as per K/DOQI guidelines will generally have Hgb < 12 g/dL; TSAT < 25%; and Ferritin < 300 ng/mL. Subjects with iron deficiency anemia secondary to Inflammatory Bowel Disease will generally have Hgb < 12 g/dL; TSAT < 25%; and Ferritin < 300 ng/mL. Subjects with iron deficiency anemia secondary to other conditions will generally have Hgb < 12 g/dL; TSAT < 25%; and Ferritin < 100 ng/mL.

[0048] Subject in need thereof

[0049] Single unit dosages of intravenous iron described herein can be administered to a subject where there is a clinical need to deliver iron rapidly or in higher doses and/or in subjects with functional iron deficiency such as those on erythropoietin therapy. A determination of the need for treatment with parenteral iron is within the abilities of one skilled in the art. For example, need can be assessed by monitoring a patient's iron status. The diagnosis of iron deficiency can be based on appropriate laboratory tests, for example, haemoglobin (Hb), serum ferritin, serum iron, transferrin saturation (TfS), and hypochromic red cells.

[0050] A determination of the need for treatment with high dosages of parenteral iron can be also be determined through diagnosis of a patient as suffering from a disease, disorder, or condition that is associated with iron deficiency or dysfunctional iron metabolism. For example, many chronic renal failure patients receiving erythropoietin will require intravenous iron to maintain target iron levels. As another example, most hemodialysis patients will require repeated intravenous iron administration, due to dialysis-associated blood loss and resulting negative iron balance.

[0051] Monitoring frequency can depend upon the disease, disorder, or condition the patient is afflicted with or at risk for. For example, in a patient initiating erythropoietin therapy, iron indices are monitored monthly. As another example, in patients who have achieved target range Hb or are receiving intravenous iron therapy, TSAT and ferritin levels can be monitored every 3 months.

[0052] A patient's iron status can be indicative of an absolute or a functional iron deficiency, both of which can be treated with the compositions and methods described herein. An absolute iron deficiency occurs when an insufficient amount of iron is available to meet the body's requirements. The insufficiency may be due to inadequate iron intake, reduced bioavailability of dietary iron, increased utilization of iron, or chronic blood loss. Prolonged iron deficiency can lead to iron deficiency anemia—a microcytic, hypochromic anemia in which there are inadequate iron stores. Absolute iron deficiency is generally indicated where TSAT <20% and Ferritin <100 ng/mL.

[0053] Functional iron deficiency can occur where there is a failure to release iron rapidly enough to keep pace with the demands of the bone marrow for erythropoiesis, despite adequate total body iron stores. In these cases, ferritin levels may be normal or high, but the supply of iron to the erythron is limited, as shown by a low transferrin saturation and an increased number of microcytic, hypochromic erythrocytes. Functional iron deficiency can be characterized by the following characteristics: Inadequate hemoglobin response to erythropoietin; Serum ferritin may be normal or high; Transferrin saturation

(TSAT) usually <20%; and/or reduced mean corpuscular volume (MCV) or mean corpuscular hemoglobin concentration (MCHC) in severe cases. Functional iron deficiency (*i.e.*, iron stores are thought to be adequate but unavailable for iron delivery) is generally indicated where TSAT <20% and Ferritin >100 ng/mL.

[0054] Assessing the need for intravenous iron therapy as described herein can be according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative. *See* NKF-K/DOQI, Clinical Practice Guidelines for Anemia of Chronic Kidney Disease (2000); Am J Kidney Dis (2001) 37(supp 1), S182-S238. The DOQI provides optimal clinical practices for the treatment of anemia in chronic renal failure. The DOQI guidelines specify intravenous iron treatment of kidney disease based on hemoglobin, transferrin saturation (TSAT), and ferritin levels.

[0055] Assessment of need for intravenous iron therapy can also be according to a patient's target iron level. For example, the target hemoglobin level of a patient can be selected as 11.0 g/dL to 12.0 g/dL (hematocrit approximately 33% to 36%). To achieve target hemoglobin with optimum erythropoietin doses, sufficient iron, supplied via an iron carbohydrate complex, is provided to maintain TSAT ≥20% and ferritin ≥100 ng/mL. In erythropoietin-treated patients, if TSAT levels are below 20%, the likelihood that hemoglobin will rise or erythropoietin doses fall after iron administration is high. Achievement of target hemoglobin levels with optimum erythropoietin doses is associated with providing sufficient iron to maintain TSAT above 20%.

[0056] Iron therapy can be given to maintain target hemoglobin while preventing iron deficiency and also preventing iron overload. Adjusting dosage of iron to maintain target levels of hemoglobin, hematocrit, and laboratory parameters of iron storage is within the normal skill in the art. For example, where a patient is anemic or iron deficient, intravenous iron can be administered when a patient has a ferritin <800, a TSAT<50, and/or a Hemoglobin <12. Iron overload can be avoided by withholding iron for TSAT >50% and/or ferritin >800 ng/mL.

[0057] Where a patient is not anemic or iron deficient but is in need of iron administration, for example a patient suffering from Restless Leg Syndrome, hemoglobin and TSAT levels are not necessarily relevant, while ferritin >800 can still provides a general cut off point for administration.

[0058] Iron Carbohydrate Complex

[0059] Iron carbohydrate complexes are commercially available, or have well known syntheses. Examples of iron carbohydrate complexes include iron monosaccharide complexes, iron disaccharide complexes, iron oligosaccharide complexes, and iron polysaccharide complexes, such as: iron carboxymaltose, iron sucrose, iron polyisomaltose (iron dextran), iron polymaltose (iron dextrin), iron gluconate, iron sorbitol, iron hydrogenated dextran, which may be further complexed with other compounds, such as sorbitol, citric acid and gluconic acid (for example iron dextrin-sorbitol-citric acid complex and iron sucrose-gluconic acid complex), and mixtures thereof.

[0060] Applicants have discovered that certain characteristics of iron carbohydrate complexes make them amenable to administration at dosages far higher than contemplated by current administration protocols. Preferably, iron carbohydrate complexes for use in the methods described herein are those which have one or more of the following characteristics: a nearly neutral pH (*e.g.*, about 5 to about 7); physiological osmolarity; stable carbohydrate component; an iron core size no greater than about 9 nm; mean diameter particle size no greater than about 35 nm, preferably about 25 nm to about 30 nm; slow and competitive delivery of the complexed iron to endogenous iron binding sites; serum half-life of over about 7 hours; low toxicity; non-immunogenic carbohydrate component; no cross reactivity with anti-dextran antibodies; and/or low risk of anaphylactoid / hypersensitivity reactions.

[0061] It is within the skill of the art to test various characteristics of iron carbohydrate complexes as so determine amenability to use in the methods described herein. For example, pH and osmolarity are straightforward determinations performed on a sample formulation. Likewise, techniques such as electron micrograph imaging, transmission electron microscopy, and atomic

force microscopy provide direct methods to analyze both iron core and particle size. *See e.g.*, Figure 1; Table 1. The stability of the carbohydrate complex can be assessed through physicochemical properties such as kinetic characteristics, thermodynamic characteristics, and degradation kinetics. *See* Geisser et al., Arzneimittelforschung (1992) 42(12), 1439-1452. Useful techniques to assess physical and electronic properties include absorption spectroscopy, X-ray diffraction analysis, transmission electron microscopy, atomic force microscopy, and elemental analysis. *See* Kudasheva et al. (2004) J Inorg Biochem 98, 1757-1769. Pharmacokinetics can be assessed, for example, by iron tracer experiments. Hypersensitivity reactions can be monitored and assessed as described in, for example, Bailie et al. (2005) Nephrol Dial Transplant, 20(7), 1443-1449. Safety, efficacy, and toxicity in human subjects can be assessed, for example, as described in Spinowitz et al. (2005) Kidney Intl 68, 1801-1807.

[0062] A particularly preferred iron carbohydrate complex will have a pH between 5.0-7.0; physiological osmolarity; an iron core size no greater than 9 nm; mean diameter particle size no greater than 30 nm; serum half-life of over 10 hours; a non-immunogenic carbohydrate component; and no cross reactivity with anti-dextran antibodies. One example of a preferred iron carbohydrate complex for use in the methods described herein is an iron carboxy-maltose complex (*e.g.*, polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate, "VIT-45"). Another example of a preferred iron carbohydrate complex for use in the methods described herein is a carboxyalkylated reduced polysaccharide iron oxide complex (*e.g.*, ferumoxytol, described in U.S. Patent No. 6,599,498).

[0063] Preferably, an iron carbohydrate complex, for use in methods disclosed herein, contains about 24% to about 32% elemental iron, more preferably about 28% elemental iron. Preferably, an iron carbohydrate complex, for use in methods disclosed herein, contains about 25% to about 50% carbohydrate (*e.g.*, total glucose). Preferably, an iron carbohydrate complex, for use in methods disclosed herein, is about 90,000 daltons to about 800,000 daltons, more preferably 100,000 daltons to about 350,000 daltons.

[0064] Iron carboxymaltose complex

[0065] One preferred iron carbohydrate complex for use in the methods described herein is an iron carboxymaltose complex. An example of an iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate ("VIT-45"). VIT-45 is a Type I polynuclear iron (III) hydroxide carbohydrate complex that can be administered as parenteral iron replacement therapy for the treatment of various anemia-related conditions as well as other iron-metabolism related conditions. VIT-45 can be represented by the chemical formula: [FeOx(OH)y(H2O)z]n [{(C6H10O5)m (C6H12O7)}l]k, where n is about 103, m is about 8, l is about 11, and k is about 4). The molecular weight of VIT-45 is about 150,000 Da. An exemplary depiction of VIT-45 is provided in Figure 2.

[0066] The degradation rate and physicochemical characteristics of the iron carbohydrate complex (*e.g.*, VIT-45) make it an efficient means of parenteral iron delivery to the body stores. It is more efficient and less toxic than the lower molecular weight complexes such as iron sorbitol/citrate complex, and does not have the same limitations of high pH and osmolarity that leads to dosage and administration rate limitations in the case of, for example, iron sucrose and iron gluconate.

[0067] The iron carboxymaltose complex (*e.g.*, VIT-45) generally does not contain dextran and does not react with dextran antibodies; therefore, the risk of anaphylactoid /hypersensitivity reactions is very low compared to iron dextran. The iron carboxymaltose complex (*e.g.*, VIT-45) has a nearly neutral pH (5.0 to 7.0) and physiological osmolarity, which makes it possible to administer higher single unit doses over shorter time periods than other iron-carbohydrate complexes. The iron carboxymaltose complex (*e.g.*, VIT-45) can mimic physiologically occurring ferritin. The carbohydrate moiety of iron carboxymaltose complex (*e.g.*, VIT-45) is metabolized by the glycolytic pathway. Like iron dextran, the iron carboxymaltose complex (*e.g.*, VIT-45) is more stable than iron gluconate and sucrose. The iron carboxymaltose complex (*e.g.*, VIT-45) produces a slow and competitive delivery of the complexed iron to

endogenous iron binding sites resulting in an acute toxicity one-fifth that of iron sucrose. These characteristics of the iron carboxymaltose complex (*e.g.*, VIT-45) allow administration of higher single unit doses over shorter periods of time than, for example, iron gluconate or iron sucrose. Higher single unit doses can result in the need for fewer injections to replete iron stores, and consequently is often better suited for outpatient use.

[0068] After intravenous administration, the iron carboxymaltose complex (*e.g.*, VIT-45) is mainly found in the liver, spleen, and bone marrow. Pharmacokinetic studies using positron emission tomography have demonstrated a fast initial elimination of radioactively labeled iron (Fe) $^{52}Fe/^{59}Fe$ VIT-45 from the blood, with rapid transfer to the bone marrow and rapid deposition in the liver and spleen. *See e.g.*, Beshara et al. (2003) Br J Haematol 2003; 120(5): 853-859. Eight hours after administration, 5 to 20% of the injected amount was observed to be still in the blood, compared with 2 to 13% for iron sucrose. The projected calculated terminal half-life ($t_{½}$) was approximately 16 hours, compared to 3 to 4 days for iron dextran and 6 hours for iron sucrose.

[0069] The iron in the iron carboxymaltose complex (*e.g.*, VIT-45) slowly dissociates from the complex and can be efficiently used in the bone marrow for Hgb synthesis. Under VIT-45 administration, red cell utilization, followed for 4 weeks, ranged from 61% to 99%. Despite the relatively higher uptake by the bone marrow, there was no saturation of marrow transport systems. Thus, high red cell utilization of iron carboxymaltose complex occurs in anemic patients. In addition, the reticuloendothelial uptake of this complex reflects the safety of polysaccharide complexes. Non-saturation of transport systems to the bone marrow indicated the presence of a large interstitial transport pool (*e.g.*, transferrin).

[0070] Other studies in patients with iron deficiency anemia revealed increases in exposure roughly proportional with VIT-45 dose (maximal total serum iron concentration was approximately 150 µg/mL and 320 µg/mL following 500 mg and 1000 mg doses, respectively). In these studies, VIT-45

demonstrated a monoexponential elimination pattern with a $t_{1/2}$ in the range 7 to 18 hours, with negligible renal elimination.

[0071] Single-dose toxicity studies have demonstrated safety and tolerance in rodents and dogs of intravenous doses of an iron carboxymaltose complex (VIT-45) up to 60 times more than the equivalent of an intravenous infusion of 1,000 mg iron once weekly in humans. Pre-clinical studies in dogs and rats administered VIT-45 in cumulative doses up to 117 mg iron/kg body weight over 13 weeks showed no observed adverse effect level in dose-related clinical signs of iron accumulation in the liver, spleen, and kidneys. No treatment-related local tissue irritation was observed in intra-arterial, perivenous, or intravenous tolerance studies in the rabbit. In vitro and in vivo mutagenicity tests provided no evidence that VIT-45 is clastogenic, mutagenic, or causes chromosomal damage or bone marrow cell toxicity. There were no specific responses to VIT-45 in a dextran antigenicity test.

[0072] Approximately 1700 subjects have been treated with an iron carboxymaltose complex (VIT-45) in open label clinical trials (*see e.g.*, Example 5). Many of these subjects have received at least one dose of 15mg/kg (up to a maximum dose of 1,000 mg) of VIT-45 over 15 minutes intravenously. Few adverse events and no serious adverse events or withdrawals due to adverse events related to VIT-45 administration have been reported. No clinically relevant adverse changes in safety laboratories have been seen.

[0073] The physicochemical characteristics of the iron carboxymaltose complex (*e.g.*, VIT-45), the pattern of iron deposition, and the results of the above described studies demonstrate that iron carboxymaltose complex can be safely administered at high single unit therapeutic doses as described herein.

[0074] Polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite

[0075] Another preferred iron carbohydrate complex for use in the methods described herein is a polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite (*e.g.*, “ferumoxytol”). Ferumoxytol is known in the art to be effective for treating anemia (at single unit doses lower than described

herein). *See e.g.*, Spinowitz et al. (2005) Kidney Intl 68, 1801-1807. Ferumoxytol is a superparamagnetic iron oxide that is coated with a low molecular weight semi-synthetic carbohydrate, polyglucose sorbitol carboxymethyl ether. Ferumoxytol and its synthesis are described in U.S. Patent No. 6,599,498, incorporated herein by reference. Safety, efficacy, and pharmacokinetics of ferumoxytol are as described, for example, in Landry et al. (2005) Am J Nephrol 25, 400-410, 408; and Spinowitz et al. (2005) Kidney Intl 68, 1801-1807.

[0076] The iron oxide of ferumoxytol is a superparamagnetic form of non-stoichiometric magnetite with a crystal size of 6.2 to 7.3 nm. Average colloidal particle size can be about 30 nm, as determined by light scattering. Molecular weight is approximately 750 kD. The osmolarity of ferumoxytol is isotonic at 297 mOsm/kg and the pH is neutral. The blood half-life of ferumoxytol is approximately 10-14 hours. It has been previously reported that ferumoxytol can be given by direct intravenous push over 1-5 minutes in doses up to 1,800 mg elemental iron per minute, with maximal total dose up to 420 mg per injection. Landry et al. (2005) Am J Nephrol 25, 400-410, 408.

[0077] Core and Particle Size

[0078] Intravenous iron agents are generally spheroidal iron-carbohydrate nanoparticles. At the core of each particle is an iron-oxyhydroxide gel. The core is surrounded by a shell of carbohydrate that stabilizes the iron-oxyhydroxide, slows the release of bioactive iron, and maintains the resulting particles in colloidal suspension. Iron agents generally share the same core chemistry but differ from each other by the size of the core and the identity and the density of the surrounding carbohydrate. *See* Table 1; Figure 1.

Table 1: Core and Particle Size of Iron Carbohydrate Complexes

Iron (III) Control Release Test	Size of the Particle (nm) +/- SEM

	T_{75} (min)	Iron core	Total Particle
Dexferrum (an iron dextran)	122.5	11.8 ± 4	27 ± 6
VIT -45 (an iron carboxymaltose)	117.8	4.4 ±1.4	6.7 ± 2.5
Venofer (an iron sucrose)	10.2	2.8 ± 1	6.5 ± 4

[0079] Differences in core size and carbohydrate chemistry can determine pharmacological and biological differences, including clearance rate after injection, iron release rate in vitro, early evidence of iron bioactivity in vivo, and maximum tolerated dose and rate of infusion.

[0080] One of the primary determinants of iron bioactivity is the size of the core and the surface area to volume ratio. Generally, the rate of labile iron release in each agent is inversely related to the size of its iron core. Van Wyck (2004) J. Am. Soc. Nephrology 15, S107-S111, S109. Furthermore, in vitro iron donation to transferrin is inversely related to core size. Core size can depend upon the number of iron atoms contained within. For example, the number of iron atoms contained within a 1 nm core is calculated to be 13, while a 10 nm core is calculated to contain 12770 iron atoms. Where agents share the same core chemistry, the rate of iron release per unit surface area is likely similar, differing perhaps by the strength of the carbohydrate ligand-core iron bound. But for the same total amount of core iron, surface area available for iron release increases dramatically as core radius decreases. That is to say, for equal amounts of iron, the smaller the core, the greater the surface area available for iron release. Of course, the explanation for this non-linear trend is the fact that volume is radius cubed. In short, a collection of many small spheres exposes a greater total surface area than does a collection of an equal mass of fewer, larger spheres.

[0081] A smaller iron core size of an iron complex administered for the treatment of various diseases, disorders, or conditions allows wider distribution through tissues, a greater rate of labile iron release, and increased in vitro iron

donation to transferrin. Furthermore, the iron complex is more evenly distributed and metabolizes faster due to the smaller core size. But if the core size is too small, the iron complex can move into cells unable to metabolize iron. In one embodiment, an iron complex with a mean iron core size of no greater than about 9 nm is administered. In various embodiments, mean iron core size is less than about 9 nm but greater than about 1 nm, about 2 nm, about 3 nm, about 4 nm, about 5 nm, about 6 nm, about 7 nm, or about 8 nm. Mean iron core size can be, for example, between about 1 nm and about 9 nm; between about 3 nm and about 7 nm; or between about 4 nm and about 5 nm.

[0082] The molecular weight (*i.e.*, the whole molecular weight of the agent) is considered a primary determinant in the pharmacokinetics, or in other words, how quickly it is cleared from the blood stream. The amount of labile (*i.e.*, biologicaly available) iron is inversely correlated with the molecular weight of the iron-carbohydrate complex. Van Wyck (2004) J. Am. Soc. Nephrology 15, S107-S111, S109. That is to say, the magnitude of labile iron effect is greatest in iron-carbohydrate compounds of lowest molecular weight and least in those of the highest molecular weight. Generally, there is a direct relationship between the molecular weight of the agent and the mean diameter of the entire particle (*i.e.*, the iron core along with the carbohydrate shell). In various embodiments, the mean diameter size of a particle of the iron carbohydrate complex is no greater than about 35 nm. For example, the particle mean size can be no greater than about 30 nm. As another example, the particle mean size can be no greater than about 25 nm. As another example, the particle mean size can be no greater than about 20 nm. As another example, the particle mean size can be no greater than about 15 nm. As a further example, the particle mean size can be no greater than about 10 nm. As another example, the particle mean size can be no greater than about 7 nm.

[0083] Absence of Significant Adverse Reaction to the Single Dosage Unit Administration

[0084] Generally, a safe and effective amount of an iron carbohydrate complex is, for example, that amount that would cause the desired therapeutic

effect in a patient while minimizing undesired side effects. The dosage regimen will be determined by skilled clinicians, based on factors such as the exact nature of the condition being treated, the severity of the condition, the age and general physical condition of the patient, and so on. Generally, treatment-emergent adverse events will occur in less than about 5% of treated patients. For example, treatment-emergent adverse events will occur in less than 4% or 3% of treated patients. Preferably, treatment-emergent adverse events will occur in less than about 2% of treated patients.

[0085] For example, minimized undesirable side effects can include those related to hypersensitivity reactions, sometimes classified as sudden onset closely related to the time of dosing, including hypotension, bronchospasm, laryngospasm, angioedema or uticaria or several of these together. Hypersensitivity reactions are reported with all current intravenous iron products independent of dose. *See generally* Bailie et al. (2005) Nephrol Dial Transplant, 20(7), 1443-1449. As another example, minimized undesirable side effects can include those related to labile iron reactions, sometimes classified as nausea, vomiting, cramps, back pain, chest pain, and/or hypotension. Labile iron reactions are more common with iron sucrose, iron gluconate, and iron dextran when doses are large and given fast.

[0086] Pharmaceutical Formulations

[0087] In many cases, a single unit dose of iron carbohydrate complex may be delivered as a simple composition comprising the iron complex and the buffer in which it is dissolved. However, other products may be added, if desired, for example, to maximize iron delivery, preservation, or to optimize a particular method of delivery.

[0088] A “pharmaceutically acceptable carrier” includes any and all solvents, dispersion media, coatings, antibacterial and anti-fungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration (*see e.g.*, Banker, Modern Pharmaceutics, Drugs and the Pharmaceutical Sciences, 4th ed. (2002) ISBN 0824706749; Remington The Science and Practice of Pharmacy, 21st ed. (2005) ISBN 0781746736).

Preferred examples of such carriers or diluents include, but are not limited to, water, saline, Finger's solutions and dextrose solution. Supplementary active compounds can also be incorporated into the compositions. For intravenous administration, the iron carbohydrate complex is preferably diluted in normal saline to approximately 2-5 mg/ml. The volume of the pharmaceutical solution is based on the safe volume for the individual patient, as determined by a medical professional.

[0089] An iron complex composition of the invention for administration is formulated to be compatible with the intended route of administration, such as intravenous injection. Solutions and suspensions used for parenteral, intradermal or subcutaneous application can include a sterile diluent, such as water for injection, saline solution, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. Preparations can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

[0090] Pharmaceutical compositions suitable for injection include sterile aqueous solutions or dispersions for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF; Parsippany, N.J.) or phosphate buffered saline (PBS). The composition must be sterile and should be fluid so as to be administered using a syringe. Such compositions should be stable during manufacture and storage and must be preserved against contamination from microorganisms, such as bacteria and fungi. The carrier can be a dispersion medium containing, for example, water, polyol (such as glycerol, propylene glycol, and liquid polyethylene glycol), and other compatible, suitable mixtures. Various antibacterial and anti-fungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, and thimerosal, can contain microorganism contamination. Isotonic agents such as sugars,

polyalcohols, such as manitol, sorbitol, and sodium chloride can be included in the composition. Compositions that can delay absorption include agents such as aluminum monostearate and gelatin.

[0091] Sterile injectable solutions can be prepared by incorporating an iron complex in the required amount in an appropriate solvent with a single or combination of ingredients as required, followed by sterilization. Methods of preparation of sterile solids for the preparation of sterile injectable solutions include vacuum drying and freeze-drying to yield a solid containing the iron complex and any other desired ingredient.

[0092] Active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable or biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Such materials can be obtained commercially from ALZA Corporation (Mountain View, CA) and NOVA Pharmaceuticals, Inc. (Lake Elsinore, CA), or prepared by one of skill in the art.

[0093] A single unit dose of iron carbohydrate complex may be intravenously administered in a volume of pharmaceutically acceptable carrier of, for example, about 1000 mg of elemental iron in about 200 ml to about 300 ml of diluent. For example, a single unit dose of iron carbohydrate complex may be intravenously administered in a volume of pharmaceutically acceptable carrier of about 1000 mg of elemental iron in about 250 ml of diluent. As another example, a single unit dose of iron carbohydrate complex may be intravenously administered in a volume of pharmaceutically acceptable carrier of about 1000 mg of elemental iron in about 215 ml of diluent.

[0094] A preferred pharmaceutical composition for use in the methods described herein contains VIT-45 as the active pharmaceutical ingredient (API) with about 28% weight to weight (m/m) of iron, equivalent to about 53% m/m iron (III)-hydroxide, about 37% m/m of ligand, ≤6% m/m of NaCl, and ≤10% m/m of water.

[0095] Kits for pharmaceutical compositions

[0096] Iron complex compositions can be included in a kit, container, pack or dispenser, together with instructions for administration according to the methods described herein. When the invention is supplied as a kit, the different components of the composition may be packaged in separate containers, such as ampules or vials, and admixed immediately before use. Such packaging of the components separately may permit long-term storage without losing the activity of the components. Kits may also include reagents in separate containers that facilitate the execution of a specific test, such as diagnostic tests.

[0097] The reagents included in kits can be supplied in containers of any sort such that the life of the different components are preserved and are not adsorbed or altered by the materials of the container. For example, sealed glass ampules or vials may contain lyophilized iron complex or buffer that have been packaged under a neutral non-reacting gas, such as nitrogen. Ampules may consist of any suitable material, such as glass, organic polymers, such as polycarbonate, polystyrene, *etc*., ceramic, metal or any other material typically employed to hold reagents. Other examples of suitable containers include bottles that are fabricated from similar substances as ampules, and envelopes that consist of foil-lined interiors, such as aluminum or an alloy. Other containers include test tubes, vials, flasks, bottles, syringes, *etc*.. Containers may have a sterile access port, such as a bottle having a stopper that can be pierced by a hypodermic injection needle. Other containers may have two compartments that are separated by a readily removable membrane that, upon removal, permits the components to mix. Removable membranes may be glass, plastic, rubber, *etc*.

[0098] Kits may also be supplied with instructional materials. Instructions may be printed on paper or other substrate, and/or may be supplied on an electronic-readable medium, such as a floppy disc, CD-ROM, DVD-ROM, mini-disc, SACD, Zip disc, videotape, audio tape, *etc*. Detailed instructions may not be physically associated with the kit; instead, a user may be directed to an internet web site specified by the manufacturer or distributor of the kit, or supplied as electronic mail.

[0099] Having described the invention in detail, it will be apparent that modifications, variations, and equivalent embodiments are possible without departing the scope of the invention defined in the appended claims. It should be understood that all references cited are incorporated herein by reference. Furthermore, it should be appreciated that all examples in the present disclosure are provided as non-limiting examples.

EXAMPLES

[0100] The following non-limiting examples are provided to further illustrate the present invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent approaches the inventors have found function well in the practice of the invention, and thus can be considered to constitute examples of modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1: NON-TOXICITY STUDIES

[0101] Nonclinical toxicity of VIT-45 is very low, as is normal for Type I polynuclear iron (III)-hydroxide carbohydrate complexes. The single dose toxicity is so low that the LD_{50} could not be estimated and is higher than 2000 mg iron/kg b.w. Mice tested with a single dose of 250 mg iron/kg b.w., injected within 2 seconds, showed no signs of illness. The highest non-lethal dose level of 1000 mg iron/kg b.w. in mice and rats is also very high in comparison to a single unit dose of, for example, 15 mg iron/kg b.w. once per week in humans. These results provide factors of about 70-fold a human dose, demonstrating a large safety margin for acute toxicity of the product.

EXAMPLE 2: PHARMOKINETIC STUDIES

[0102] Pharmacokinetic and red blood cell measurements of $^{52}Fe/^{59}Fe$ labelled VIT-45 following i.v. administration using PET in 6 patients showed a red

blood cell utilization from 61 to 99%. The 3 patients with iron deficiency anemia showed a utilization of radiolabelled iron of 91 to 99% after 24 days, compared to 61 to 84% for 3 patients with renal anaemia. The terminal $t_{1/2}$ for VIT-45 was calculated to be approximately 16 hours, compared to about 6 hours for iron sucrose. In two further studies in patients with iron deficiency anemia, pharmacokinetic analyses revealed increases in exposure roughly proportional with VIT-45 dose (Cmax approximately 150 µg/mL and 320 µg/mL following 500 mg and 1000 mg doses, respectively). VIT-45 demonstrated a monoexponential elimination pattern with a $t_{1/2}$ in the range 7 to 18 hours. There was negligible renal elimination.

EXAMPLE 3: EFFICACY STUDIES

[0103] The main pharmacodynamic effects of VIT-45 were transient elevations of serum iron levels, TfS and serum ferritin. These effects were seen in all studies (where measured), following both single doses and repeated doses. The increase in serum ferritin levels illustrated the replenishment of the depleted iron stores, which is a well-identified and desired effect of iron therapy. In addition, transiently elevated TfS indicated that iron binding capacity was almost fully utilized following VIT-45 infusion.

[0104] Efficacy of iron replacement therapy is interpreted mainly in terms of the ability to normalise Hb levels and iron stores. In the multiple dose studies, patients demonstrated a slowly-developing, sustained increase in Hb levels during study participation. In one study, 37% and 48% of patients in Cohorts 1 and 2, respectively, had achieved normal Hb levels at the 4-week follow-up visit, and 75% and 73%, respectively, had achieved a ≥20 g/L increase in Hb on at least 1 occasion.

[0105] In another study (patients receiving regular haemodialysis), the majority of patients (61.7%) achieved an increase of Hb of ≥10 g/L at any point during the study. Serum ferritin and TfS levels showed a more prolonged elevation following repeated VIT-45 infusions, indicating a sustained replenishment of iron stores. However, elevated levels of ferritin and TfS

indicating iron overload were avoided. In both of these studies, there was a gradual decrease in transferrin over time, also indicating successful iron replacement.

EXAMPLE 4: SAFETY ASSESSMENTS

[0106] Safety assessments were made in 73 patients with iron deficiency anemia (27 single-dose, 46 repeated-dose), and 166 patients with renal anaemia (3 single-dose, 163 repeated-dose) who received VIT-45 at individual iron doses of 100 mg up to 1000 mg (cumulative doses of 100 to 2200 mg). These studies showed a safety profile equal to, or exceeding, currently available parenteral iron formulations.

[0107] In the single-dose studies, there were few adverse events and no serious adverse events or withdrawals due to adverse events. There were also no related clinically relevant adverse changes in vital signs, 12-lead ECGs or laboratory safety tests.

[0108] In the repeated-dose studies, there were no deaths attributed to VIT-45, while 10 patients experienced serious adverse events. All of these cases occurred in patients with renal anaemia receiving haemodialysis and were considered not related to the VIT-45 treatment. Very few patients were withdrawn from the studies due to treatment-emergent adverse events, and only 2 withdrawals (due to allergic skin reactions) were considered possibly related to treatment. In each of the repeated-dose studies, no patients experienced clinically significant changes in 12-lead ECGs that were related to treatment. There were no consistent changes in laboratory safety parameters, although there was a low incidence (total 6 patients) of laboratory values reported as treatment-related treatment-emergent adverse events (elevated CRP, AST, ALT and GGT, abnormal liver function tests and elevated WBC).

[0109] Although many patients in these 2 studies had serum ferritin above 500 µg/L on at least 1 occasion during the study, very few patients also had TfS values >50%. Generally, the elevations of ferritin and TfS were of short

duration. Iron overload was avoided using the dosing schedules defined in the studies.

EXAMPLE 5: INTEGRATED SAFETY STUDIES

[0110] The following example demonstrates the safety and effectiveness of parenteral VIT-45 in the treatment of anemia in a variety of patient populations, as determined from several integrated safety studies.

[0111] A total of 2429 subjects were treated with VIT-45 or control agents over 10 studies that provide safety data for VIT-45. Of these, 1709 subjects received VIT-45 (1095 in completed multicenter studies, 584 in placebo-controlled, single-dose, crossover studies and 30 in pharmacokinetic studies). The mean total dose of VIT-45 administered among the 1095 subjects in the completed multicenter studies was approximately 1300 mg; however, some subjects received VIT-45 doses as high as 3400 mg. The majority of the subjects treated were able to receive their calculated iron requirement in only 1 or 2 doses.

[0112] Table 2 provides a summary of VIT-45 studies described in this example.

[0113] Study A was a single-center, single-dose escalation, randomized, double-blind, placebo-controlled pharmacokinetic study. Subjects were male and female, between 18 and 45 years of age, inclusive, with mild iron-deficiency anemia. Treatment was a single IV bolus injection of VIT-45 at 100 mg, 500 mg, 800 mg, or 1000 mg. Examined pharmacokinetic parameters included total serum iron and pharmacodynamic (serum ferritin and transferrin, iron binding capacity, %TSATpost, hemoglobin, reticulocyte, and serum transferrin receptor concentrations) endpoints. Examined safety parameters included adverse events, clinical laboratory evaluations, vital signs, ECG, and physical examinations.

[0114] Study B was a single-center, single-dose, open label, uncontrolled pharmacokinetic study. Subjects were between 18 and 75 years of age with iron-deficiency or renal anemia with no other cause of anaemia.

Inclusion criteria included hemoglobin concentration between 9 and 13 g/dL, no blood transfusions in the previous 3 months, and no history of treatment with intravenous iron in the last 2 weeks. Treatment was a single IV bolus injection of VIT-45 at 100 mg labelled with ^{52}Fe and ^{59}Fe. Examined primary pharmacokinetic parameters included the distribution of ^{52}Fe and incorporation of ^{59}Fe into red blood cells. Examined safety parameters included adverse events, clinical laboratory evaluations, vital signs, and physical examinations.

[0115] Study C was an open-label, multicenter, randomized, multiple-dose, active-controlled postpartum anemia study. Subjects were female, postpartum within 10 days after delivery, with hemoglobin ≤10 g/dL at Baseline based on the average of 2 hemoglobin values drawn ≥18 hours postpartum. Treatment was once weekly doses of VIT-45 for six weeks. VIT-45 dosage was based on the calculated iron deficit (≤2500 mg total). Where screening serum transferrin saturation (TSAT) was ≤20% or screening ferritin was ≤50 ng/mL, dosage = pre-pregnancy weight (kg) x (15-baseline hemoglobin [g/dL]) x 2.4 + 500 mg. Where screening TSAT was >20% and screening ferritin was >50 ng/mL, dosage = pre-pregnancy weight (kg) x (15-baseline hemoglobin [g/dL]) x 2.4. Infusion of VIT-45 was as follows: ≤200 mg, administered as an undiluted intravenous push (IVP) over 1-2 minutes; 300-400 mg, administered in 100 cc normal saline solution (NSS) over 6 minutes; 500-1,000 mg administered in 250 cc NSS over 15 minutes. For primary efficacy, “success” was defined as an increase in hemoglobin of ≥2 g/dL anytime between baseline and end of study or time of intervention, while “failure” was defined as <2 g/dL increase in hemoglobin at all times between baseline and end of study or time of intervention. Examined safety parameters included adverse events, clinical laboratory evaluations, vital signs, and physical examinations.

[0116] Study D was a multicenter, open-label, randomized, active-controlled, multiple-dose postpartum anemia study. Subjects were adult women ≥18 years old with postpartum anaemia within 6 days after delivery. Treatment was administered once-weekly for a maximum of 3 infusions. Patients received IV infusions of 16.7 mL/min to deliver a maximum dose of 1000 mg iron per

infusion. Patients received VIT-45 infusions once weekly for up to 3 occasions until the calculated cumulative dose was reached. Patients ≤66 kg received a minimum dose of 200 mg and a maximum dose of 15 mg iron/kg during each infusion. Patients >66 kg received a dose of 1000 mg on the first dosing occasion, and a minimum dose of 200 mg and a maximum dose of 1000 mg at each subsequent dosing. Doses of 200-400 mg were diluted in 100 cc NSS and 500-1000 mg were diluted in 250 cc NSS. Primary efficacy was examined as change from baseline levels of hemoglobin to Week 12. Examined safety parameters included adverse events in the mother and breast-fed infant, adverse events leading to discontinuation of treatment, vital signs, 12-lead electrocardiogram (ECG), physical examinations, and clinical laboratory panels.

[0117] Study E was a multicenter, open-label, randomized, active-controlled, multiple-dose hemodialysis-associated anemia study. Subjects were adult male or female subjects between the ages of 18 and 80 years (inclusive) requiring haemodialysis with iron deficiency secondary to chronic renal failure. Dosing started on Day 1, Week 0 for both treatment arms and continued 2 or 3 times weekly until the individual calculated cumulative dose was reached. Patients received 200 mg VIT-45 during their scheduled haemodialysis sessions (2-3 sessions/week) until the calculated cumulative dose was reached. Cumulative total iron requirement was calculated for each patient using the Ganzoni formula. Primary Efficacy was examined as the percentage of patients reaching an increase in hemoglobin ≥10 g/L at 4 weeks after baseline. Examined safety parameters included adverse events, vital signs, 12-lead ECG, physical examinations, and clinical laboratory evaluations.

[0118] Study F was a multicenter, open-label, multiple dose, uncontrolled hemodialysis-associated anemia study. Subjects were male and female patients 18-65 years of age, inclusive, with haemodialysis-associated anaemia undergoing maintenance haemodialysis. Treatment duration was a maximum of six weeks. Patients received 200 mg VIT-45 during their scheduled haemodialysis sessions (2-3 sessions/week) until the calculated cumulative dose was reached. Cumulative total iron requirement was calculated for each patient using the Ganzoni formula. Efficicacy was examined as correction of iron

deficiency and hemoglobin concentration of the patient. Examined safety parameters included adverse events, vital signs, 12-lead ECG, physical examinations, haematology and blood chemistry profiles, and urea reduction ratio.

[0119] Study G was a multicenter, multiple-dose open-label, uncontrolled gastrointestinal disorder-associated anemia study. Subjects were males and females between 18 and 60 years of age, inclusive, with moderate stable iron-deficiency anemia secondary to a gastrointestinal disorder and a calculated total iron requirement ≥1000 mg; ≥50% of patients in each cohort were to require ≥1500 mg total iron. Duration of treatment was single doses at weekly intervals for up to 4 weeks (Cohort 1) or 2 weeks (Cohort 2). Administration of VIT-45 was by IV bolus injection of 500 mg (Cohort 1) or 1000 mg (Cohort 2), where total iron requirement for each patient, which determined how many weekly infusions were received, was calculated using the formula of Ganzoni. Examined pharmacokinetic parameters included total serum iron and pharmacodynamic (hemoglobin, ferritin, TSAT) endpoints. Examined safety parameters included adverse events, clinical laboratory evaluations, vital signs, ECG, physical examinations, and elevated serum ferritin (>500 μg/L) AND elevated TSAT (>45%).

[0120] Study H was a multicenter, multiple-dose randomized, open-label, active-controlled gastrointestinal disorder-associated anemia study. Subjects were males and females aged 18 to 80 years, inclusive, with iron-deficiency anaemia secondary to chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease) and a calculated total iron requirement of at least 1000 mg total iron. Treatment was weekly VIT-45 infusions, with a maximum of 3 infusions permitted in a single treatment cycle. Administration consisted of an infusion on Day 1, with subsequent infusions at weekly intervals up to a maximum of 1000 mg iron per dose. The doses were continued until the patient received the cumulative dose based on their individual requirement for iron. Primary efficacy was examined as change from baseline to Week 12 in hemoglobin. Examined safety parameters included adverse events, vital signs, 12-lead ECG, physical examinations, and clinical laboratory evaluations.

[0121] Study I was an open label, multiple-dose, multicenter, randomized, active-control anemia due to heavy uterine bleeding study. Subjects were females at least 18 years of age with iron-deficiency anemia secondary to heavy uterine bleeding. Duration of treatment was six weeks. VIT-45 dosage was based on the calculated iron deficit as follows: where baseline TSAT ≤20% or baseline ferritin ≤50 ng/mL, VIT-45 total dose in mg = baseline weight (kg) x (15-baseline hemoglobin [g/dL]) x 2.4 + 500; where baseline TSAT >20% and baseline ferritin >50 ng/mL, VIT-45 total dose in mg = baseline weight (kg) x (15-baseline hemoglobin [g/dL]) x 2.4. For administration, ≤200 mg was administered as an undiluted IVP over 1-2 minutes; 300-400 mg was administered in 100 cc NSS over 6 minutes; and 500-1,000 mg was administered in 250 cc NSS over 15 minutes. Primary efficacy was examined as the proportion of subjects achieving success, defined as an increase in hemoglobin of ≥2.0 g/dL anytime between baseline and end of study or time of intervention. Examined safety parameters included adverse events, clinical laboratory evaluations, vital signs, and physical examinations.

[0122] Study J was a multicenter, single-dose blinded, randomized, placebo-controlled crossover iron deficiency anemia study. Subjects were male or female, at least 18 years of age, with a hemoglobin ≤12 g/dL, TSAT ≤25%, and ferritin <300 ng/mL (iron-deficiency anemia due to dialysis or non-dialysis dependent chronic kidney disease or inflammatory bowel disease), or ferritin ≤100 ng/mL (iron-deficiency anemia due to other conditions). Treatment was two single doses seven days apart. Administration of VIT-45 occurred over 15 minutes and was ≤1000 mg (15 mg/kg for weight ≤66 kg). For pharmacokinetic variables, total serum iron was assessed using Atomic Absorption methodology. Examined safety parameters included adverse events, clinical laboratory evaluations, vital signs, and physical examinations.

TABLE 2: Summary of Safety Studies of VIT-45

Study Number	Subjects	Intravenous Dose(s) of VIT-45	Comparator
Pharmacokinetic Studies			
A	Total: 32 VIT-45: 24	Single doses of: 100 mg via bolus injection 500 mg, 800 mg, 1000 mg diluted in 250 mL of NSS administered by IV infusion over 15 minutes	Placebo
B	Total: 6 VIT-45: 6	Single dose of 100 mg labelled with ^{52}Fe and ^{59}Fe administered as an IV injection over 10 minutes	None
Studies in Subjects with Postpartum Anemia			
C	Total: 352 VIT-45: 174	Cumulative total iron requirement was calculated for each patient. Patients received IV infusions to deliver a maximum dose of 1000 mg iron per infusion. Patients received VIT-45 infusions once weekly until the calculated cumulative dose was reached or a maximum of 2500 mg had been administered. Doses ≤200 mg were administered IV push over 1-2 minutes; doses of 300-400 mg were diluted in 100 cc NSS and administered over 6 minutes; doses of 500-1000 mg were diluted in 250 cc NSS and administered over 15 minutes.	Oral iron (ferrous sulfate) 325 mg TID for 6 weeks
D	Total: 344 VIT-45: 227	Cumulative total iron requirement was calculated for each patient using the Ganzoni formula.	Oral iron (ferrous sulfate) 100 mg BID for 12 weeks
Studies in Subjects Undergoing Hemodialysis			
E	Total: 237 VIT-45: 119	Patients received 200 mg IV bolus injection of study drug during their scheduled hemodialysis sessions (2-3 sessions/week) until the calculated cumulative dose was reached. Cumulative total iron requirement was calculated for each patient using the Ganzoni formula.	Venofer®; patients received 200 mg IV injection over 10 minutes of study drug during their scheduled hemodialysis sessions (2-3 sessions/week) until the calculated cumulative dose was reached. Cumulative total iron requirement was calculated for each patient using the Ganzoni formula.[a]
F	Total: 163 VIT-45: 162	Patients received 200 mg IV push of study drug during their scheduled hemodialysis sessions (2-3 sessions/week) until the calculated cumulative dose was reached. Cumulative total iron requirement was calculated for each patient using the Ganzoni formula.	None
Studies in Subjects with Gastrointestinal Disorders			
G	Total: 46 VIT-45: 46	500 mg or 1000 mg iron by IV infusion at weekly intervals for up to 4 weeks (500 mg) or 2 weeks (1000 mg); maximum total dose of 2000 mg. The last dose could have been less, depending on the calculated total iron requirement. Doses were diluted in 250 cc NSS and administered by IV infusion over 15 minutes.	None
H	Total: 200 VIT-45: 137	Cumulative total iron requirement was calculated for each patient using the Ganzoni formula.	Oral iron (ferrous sulfate) 100 mg BID for 12 weeks

Study in Subjects with Heavy Uterine Bleeding			
I	Total: 456 VIT-45: 230	≤1000 mg/week (15 mg/kg for weight ≤66 kg); patients received VIT-45 infusions once weekly until the calculated cumulative dose was reached or a maximum of 2500 mg had been administered. Doses ≤200 mg were administered IV push over 1-2 minutes; doses of 300-400 mg were diluted in 100 cc NSS and administered over 6 minutes; doses of 500-1000 mg were diluted in 250 cc NSS and administered over 15 minutes.	Oral iron (ferrous sulfate) 325 mg TID for 6 weeks
Study in Subjects with Iron Deficiency Anemia			
J	Total: 594 VIT-45: 584	Single dose of ≤1000 mg by IV infusion over 15 minutes (15 mg/kg for weight ≤66 kg). Doses ≤500 mg were diluted in 100 cc NSS and doses of >500-1000 mg were diluted in 250 cc NSS. Pharmacokinetic subjects: single 1,000 mg dose by IV infusion	Placebo

[0123] The majority of the subjects who received VIT-45 completed the study. The incidence of premature discontinuations in the completed multicenter studies was 10% in the VIT-45 group which is comparable to that observed in the oral iron (9.6%) and Venofer (13.6%) groups. Reasons for premature discontinuation were generally comparable among the treatment groups, except that the incidence of adverse events leading to discontinuation were higher in the Venofer group (5.9%) compared to the VIT-45 (1.8%) and oral iron (2.1%) groups, demonstrating the overall tolerability of VIT-45.

[0124] The overall incidences of treatment-emergent adverse events were comparable between the VIT-45 (49.5%) and oral iron (51.2%) groups in the completed multicenter studies; the incidence in the Venofer group was lower (39.0%); however, the number of subjects in the VIT-45 group is almost 10-fold that of the Venofer group. Treatment-emergent adverse events experienced by ≥2% of the 1095 VIT-45 subjects included headache (8.6%), abdominal pain (2.5%), nausea (2.4%), blood phosphate decreased (2.4%), hypertension (2.2%), nasopharyngitis (2.0%), and hypotension (2.0%). As expected, the most notable difference between subjects treated with VIT-45 and those treated with oral iron was for the incidence of gastrointestinal events (31.0% vs. 12.8%), specifically the incidences of constipation, diarrhea, nausea, and vomiting, which were more than double that observed in the VIT-45 group.

[0125] In the calculated dose/first-dose 1,000 mg studies, no statistically significant difference was observed between the VIT-45 (49.5%) and oral iron (51.2%) groups for the overall incidence of treatment-emergent adverse events. The incidence of gastrointestinal disorders was statistically significantly ($p<0.0001$) higher in the oral iron group (31.0%) compared to the VIT-45 group (15.2%), while the incidences of adverse events associated with investigations and skin and subcutaneous tissue disorders were statistically significantly higher in the VIT-45 group (9.1% and 7.3%, respectively) compared to the oral iron group (3.9% and 2.4%, respectively). Among the gastrointestinal disorders, greater proportions of subjects in the oral iron group than the VIT-45 group experienced constipation, nausea, diarrhoea, and vomiting, while a greater proportion of VIT-45 subjects experienced abdominal pain than oral iron subjects. Among the adverse events associated with investigations, greater proportions of VIT-45 subjects experienced blood phosphate decreased and GGT increased than oral iron subjects. Among the adverse events associated with skin and subcutaneous tissue disorders, greater proportions of VIT-45 subjects experienced rash and pruritus than oral iron subjects.

[0126] The only drug-related treatment-emergent adverse events reported by at least 2% of VIT-45 subjects in the calculated dose/first-dose 1,000 mg studies were headache (3.9%) and blood phosphate decreased (3.3%). The incidence of treatment-emergent adverse events reported on the first day of dosing in the calculated dose/first-dose 1,000 mg studies was statistically significant higher in the VIT-45 group compared to the oral iron group (6.8% vs. 2.7%). On the first day of dosing, the VIT-45 group had statistically significantly greater proportions of subjects who experienced general disorders and administration site conditions, primarily events associated with the site of study drug infusion, and skin and subcutaneous tissue disorders, primarily rash and urticaria, compared to the oral iron group.

[0127] The overall incidence of treatment-emergent adverse events was similar among VIT-45 subjects treated with either the 200 mg or 1000 mg doses. The only notable difference was for the higher incidence of headache in the 1000-mg group, which was almost double that observed for the 200-mg

group. No meaningful trends were apparent with respect to the incidence of treatment-emergent adverse events when analyzed by gender, age, race, weight, or etiology of anemia.

[0128] There were no deaths in the study attributed to VIT-45. The incidence of other serious adverse events among VIT-45 subjects was low (3% in all completed multicenter studies and 0.3% in the placebo-controlled, single-dose crossover study) and none were considered related to study drug. The incidence of premature discontinuation due to adverse events was comparable between the VIT-45 group (2.1%) and the other active treatment groups (3.1% oral iron and 2.5% Venofer). The incidence of drug-related treatment-emergent adverse events of hypersensitivity was 0.2%, the same as that observed with oral iron (0.2%). Drug-related mild or moderate hypotension was observed in 4 (0.2%) VIT-45 subjects, none of which were considered serious, led to premature discontinuation, or were symptomatic. Treatment-emergent adverse events indicative of potential allergic reactions including rash, pruritus, and urticaria were reported by <2% of subjects who were treated with VIT-45; none of these events was considered serious and few led to premature discontinuation.

[0129] Laboratory evaluations of mean changes from baseline and potentially clinically significant values demonstrated no clinically meaningful changes for the majority of the parameters evaluated. However, during the conduct of the latter portion of the clinical program, transient, asymptomatic decreases in blood phosphate levels were observed among subjects treated with VIT-45. The decreases were apparent approximately 7 days after the initial dose of VIT-45 and the median time to recovery was approximately 2 weeks. No subjects reported an adverse event that was related to serum phosphate and no subject discontinued from the study due to decreased serum phosphate. The only predictor of change in serum phosphate was that subjects with higher baseline serum phosphate values had larger decreases in serum phosphate. The fact that the majority of oral iron-treated subjects also had a post-baseline decrease in phosphate and the negative correlation of baseline serum phosphate with changes in serum phosphate for both the VIT-45 and oral iron

treatment groups suggest that the mechanism is intrinsic to iron therapy in this severely anemic population.

[0130] Overall, no clinically meaningful changes in vitals signs evaluations were associated with VIT-45 administration.

[0131] Safety data from more than 1700 subjects demonstrate the safety and tolerability of VIT-45.

CLAIMS

What is claimed is:

1. A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism, comprising administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron, wherein the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component and substantially no cross reactivity with anti-dextran antibodies.

2. The method of claim 1 wherein the disease, disorder, or condition is anemia.

3. The method of claim 2 wherein the anemia is iron deficiency anemia.

4. The method of claim 3 wherein the iron deficiency anemia is associated with chronic blood loss; acute blood loss; pregnancy; childbirth; childhood development; psychomotor and cognitive development in children; breath holding spells; heavy uterine bleeding; menstruation; chronic recurrent hemoptysis; idiopathic pulmonary siderosis; chronic internal bleeding; gastrointestinal bleeding; parasitic infections; chronic kidney disease; dialysis; surgery or acute trauma; and chronic ingestion of alcohol, chronic ingestion of salicylates, chronic ingestion of steroids; chronic ingestion of non-steroidial anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents.

5. The method of claim 2 wherein the anemia is anemia of chronic disease.

6. The method of claim 5 wherein the chronic disease is selected from the group consisting of rheumatoid arthritis; cancer; Hodgkins leukemia; non-Hodgkins leukemia; cancer chemotherapy; inflammatory bowel disease; ulcerative colitis thyroiditis; hepatitis; systemic lupus erythematosus; polymyalgia

rheumatica; scleroderma; mixed connective tissue disease; Sojgren's syndrome; congestive heart failure / cardiomyopathy; and idiopathic geriatric anemia.

7. The method of claim 2 wherein the anemia is due to impaired iron absorption or poor nutrition.

8. The method of claim 7, wherein the anemia is associated with Crohn's Disease; gastric surgery; ingestion of drug products that inhibit iron absorption; or chronic use of calcium.

9. The method of claim 1 wherein the disease, disorder, or condition is selected from the group consisting of restless leg syndrome; blood donation; Parkinson's disease; hair loss; and attention deficit disorder.

10. The method of claim 1 wherein the single dosage unit of elemental iron is at least about 0.7 grams.

11. The method of claim 10 wherein the single dosage unit of elemental iron is at least about 0.8 grams.

12. The method of claim 11 wherein the single dosage unit of elemental iron is at least about 0.9 grams.

13. The method of claim 12 wherein the single dosage unit of elemental iron is at least about 1.0 grams.

14. The method of claim 13 wherein the single dosage unit of elemental iron is at least about 1.5 grams.

15. The method of claim 14 wherein the single dosage unit is at least about 2.0 grams.

16. The method of claim 15 wherein the single dosage unit of elemental iron is at least about 2.5 grams.

17. The method of claim 1 wherein the single dosage unit of elemental iron is administered in about 15 minutes or less.

18. The method of claim 17 wherein the single dosage unit of elemental iron is administered in about 10 minutes or less.

19. The method of claim 18, wherein the single dosage unit of elemental iron is administered in about 5 minutes or less.

20. The method of claim 19, wherein the single dosage unit of elemental iron is administered in about 2 minutes or less.

21. The method of claim 1 wherein the subject does not experience a significant adverse reaction to the single dosage unit administration.

22. The method of claim 1 wherein the iron carbohydrate complex has a pH between about 5.0 to about 7.0; physiological osmolarity; an iron core size no greater than about 9 nm; a mean diameter particle size no greater than about 35 nm; and a blood half-life of between about 10 hours to about 20 hours.

23. The method of claim 1 wherein the iron carbohydrate complex contains about 24% to about 32% elemental iron; contains about 25% to about 50% carbohydrate; and has a molecular weight of about 90,000 daltons to about 800,000 daltons.

24. The method of claim 1 wherein the iron carbohydrate complex is an iron monosaccharide complex, an iron disaccharide complex, or an iron polysaccharide complex.

25. The method of claim 1 wherein the iron carbohydrate complex is an iron carboxymaltose complex, iron mannitol complex, iron polyisomaltose complex, iron polymaltose complex, iron gluconate complex, iron sorbitol complex, or an iron hydrogenated dextran complex.

26. The method of claim 25 wherein the iron carbohydrate complex is an iron carboxymaltose complex.

27. The method of claim 26 wherein the iron carboxymaltose complex contains about 24% to about 32% elemental iron, about 25% to about 50% carbohydrate, and is about 100,000 daltons to about 350,000 daltons.

28. The method of claim 26 wherein the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between about 5 and about 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between about 5 and about 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between about 2 and about 20.

29. The method of claim 26 wherein:

the iron carboxymaltose complex has a chemical formula of $[FeO_x(OH)_y(H_2O)_z]_n[\{(C_6H_{10}O_5)_m(C_6H_{12}O_7)\}_l]_k$, where n is about 103, m is about 8, l is about 11, and k is about 4;

contains about 28% elemental iron; and

has a molecular weight of about 150,000 Da.

30. The method of claim 26 wherein the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

31. The method of claim 25 wherein the iron carbohydrate complex is an iron polyglucose sorbitol carboxymethyl ether complex.

32. The method of claim 31 wherein the iron polyglucose sorbitol carboxymethyl ether complex is a polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite complex.

33. The method of any one of claims 1 wherein the iron carbohydrate complex comprises an iron core with a mean iron core size of no greater than about 9 nm.

34. The method of claim 33 wherein the mean iron core size is at least about 1 nm but no greater than about 9 nm.

35. The method of claim 34 wherein the mean iron core size is at least about 3 nm but no greater than about 7 nm.

36. The method of claim 35 wherein the mean iron core size is at least about 4 nm but not greater than about 5 nm.

37. The method of claim 1 wherein mean size of a particle of the iron carbohydrate complex is no greater than about 35 nm.

38. The method of claim 37 wherein the particle mean size is no greater than about 30 nm.

39. The method of claim 38 wherein the particle mean size is no greater than about 25 nm.

40. The method of claim 39 wherein the particle mean size is no greater than about 20 nm.

41. The method of claim 40 wherein the particle mean size is no greater than about 15 nm.

42. The method of claim 41 wherein the particle mean size is no greater than about 10 nm.

43. The method of claim 42 wherein the particle mean size is at least 6 nm but no greater than about 7 nm.

44. The method of claim 1 wherein the iron carbohydrate complex is administered parenterally.

45. The method of claim 44 wherein the iron carbohydrate complex is administered intravenously.

46. The method of claim 45 wherein the iron carbohydrate complex is intravenously infused.

47. The method of claim 46 wherein the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent.

48. The method of claim 47 wherein the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 250 ml of diluent.

49. The method of claim 47 wherein the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 215 ml of diluent.

50. The method of claim 45 wherein the iron carbohydrate complex is intravenously injected as a bolus.

51. The method of claim 50 wherein the single unit dose of iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent.

52. The method of claim 51 wherein the single unit dose of iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 250 ml of diluent.

53. The method of claim 51 wherein the single unit dose of iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 215 ml of diluent.

54. The method of claim 44 wherein the iron carbohydrate complex is administered intramuscularly.

55. The method of claim 54 wherein the iron carbohydrate complex is intramuscularly injected at a concentration of about 500 mg elemental iron in less than about 10 ml diluent.

56. The method of claim 1 further comprising a second administration of said iron carbohydrate complex upon recurrence of at least one symptom of the disease, disorder, or condition.

57. The method of claim 1 further comprising a second administration of said iron carbohydrate complex after 1 day to 12 months after the first administration.

58. A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism, comprising:

intravenously administering to a subject in need thereof an iron carboxymaltose complex in a single dosage unit of at least about 1000 mg of elemental iron in about 200 ml to about 300 ml of diluent in about 5 minutes or less;

wherein the iron carboxymaltose complex comprises an iron core with a mean iron core size of at least about 1 nm but no greater than about 9 nm;

wherein mean size of a particle of the iron carboxymaltose complex is no greater than about 35 nm;

wherein the iron carboxymaltose complex is administered intravenously infused or intravenously injected at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent

59. The method of claim 58 wherein the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between about 5 and about 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between about 5 and about 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between about 2 and about 20.

60. The method of claim 58 wherein the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

ABSTRACT

The present invention generally relates to treatment of iron-related conditions with iron carbohydrate complexes. One aspect of the invention is a method of treatment of iron-related conditions with a single unit dosage of at least about 0.6 grams of elemental iron via an iron carbohydrate complex. The method generally employs iron carbohydrate complexes with nearly neutral pH, physiological osmolarity, and stable and non-immunogenic carbohydrate components so as to rapidly administer high single unit doses of iron intravenously to patients in need thereof.

FIGURE 1

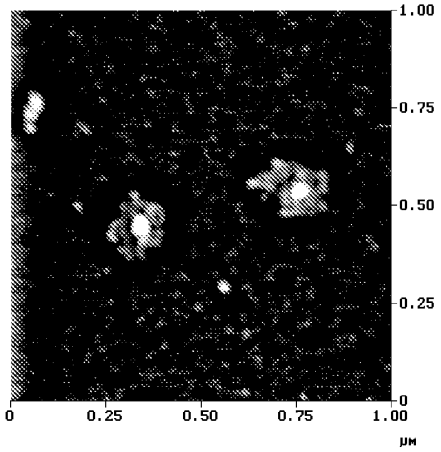


FIG. 1A

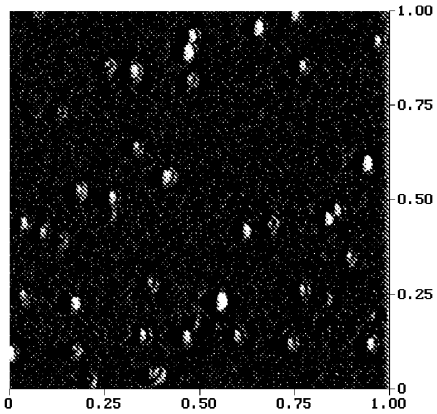


FIG. 1B

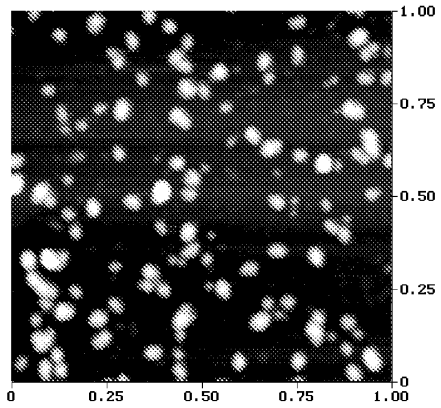
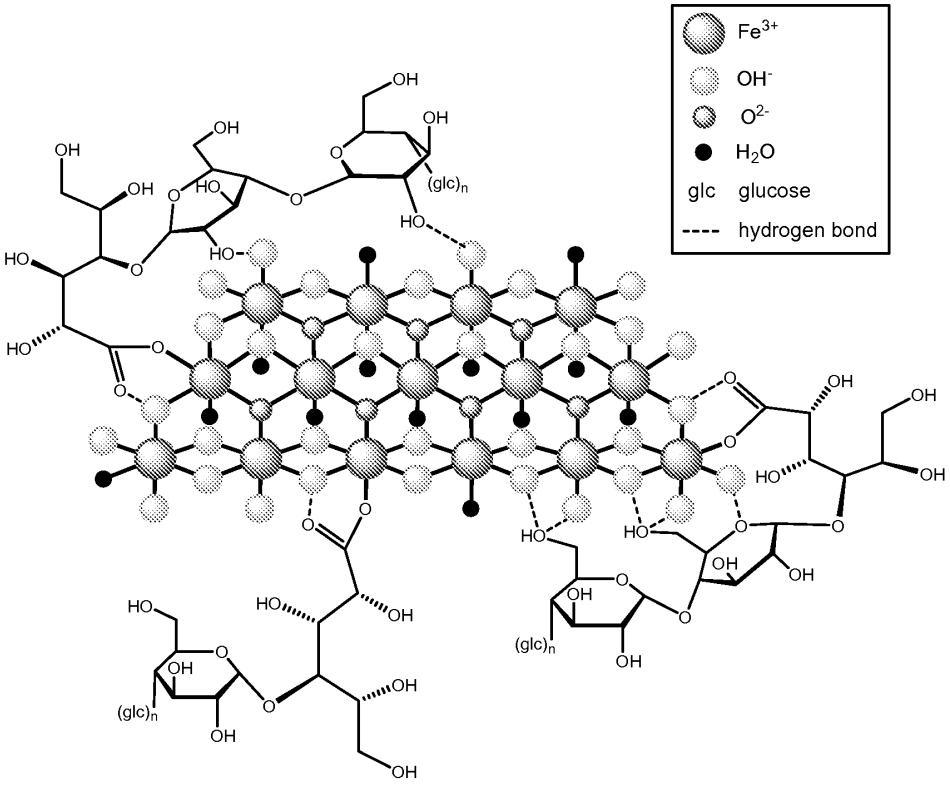


FIG. 1C

FIGURE 2



Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Filer:	George H. Blosser/Dennis Harney
Attorney Docket Number:	30015730-0043

Filed as Small Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	75	75
Utility Search Fee	2111	1	250	250
Utility Examination Fee	2311	1	100	100
Pages:				
Claims:				
Claims in excess of 20	2202	40	25	1000
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1425**

Electronic Acknowledgement Receipt	
EFS ID:	1424059
Application Number:	11620986
International Application Number:	
Confirmation Number:	1325
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	George H. Blosser/Dennis Harney
Filer Authorized By:	George H. Blosser
Attorney Docket Number:	30015730-0043
Receipt Date:	08-JAN-2007
Filing Date:	
Time Stamp:	17:30:50
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1425
RAM confirmation Number	668
Deposit Account	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)

1	Transmittal of New Application	Cover_NPA_30015730_0043.pdf	179657	no	1
Warnings:					
Information:					
2	Application Data Sheet	ADS_NPA_30015730_0043.pdf	451805	no	3
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3		NPA_30015730_0043.pdf	1488797	yes	52

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	41
	Claims	42	49
	Abstract	50	50
	Drawings	51	52

Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	8502	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2128761		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **11/620986**	Examiner:
Applicant: **Mary Jane HELENEK et al.**	Group Art Unit:
Filed: **January 8, 2007**	Confirmation No.: **1325**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	Customer No.: **26263**
Docket No.: **30015730-0043**	

January 8, 2006

FILED ELECTRONICALLY VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Sir:

Prior to substantive examination, please consider the following preliminary amendment and remarks.

IN THE SPECIFICATION

Please replace ¶0001 with the following:

[0001] This application claims priority from U.S. Provisional Application Serial No. 60/757,119 filed on January 6 [[1]], 2006, which is incorporated herein by reference in its entirety.

REMARKS

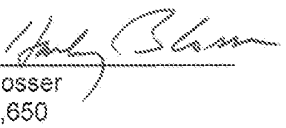
Paragraph 0001 has been amended so as to reflect the January 6, 2006 filing date for priority document U.S. Prov. App. No. 60/757,119 . No new matter has been added by way of this response.

CONCLUSION

Applicants respectfully request the Office to enter the preliminary amendment and believes that the claims as presented represent allowable subject matter. If the Examiner desires, Applicant welcomes a telephone interview to expedite prosecution. Applicant believes there is no fee due at this time. But the Commissioner is hereby authorized to deduct any deficiency or credit any overpayment to Deposit Account No. 19-3140.

Respectfully submitted,

SONNENSCHEIN NATH & ROSENTHAL LLP

By: 
G. Harley Blosser
Reg. No. 33,650
Telephone No. 314.259.5806

ATTORNEYS FOR APPLICANT

Electronic Acknowledgement Receipt	
EFS ID:	1424313
Application Number:	11620986
International Application Number:	
Confirmation Number:	1325
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	George H. Blosser/Dennis Harney
Filer Authorized By:	George H. Blosser
Attorney Docket Number:	30015730-0043
Receipt Date:	08-JAN-2007
Filing Date:	
Time Stamp:	18:21:44
Application Type:	Utility

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Preliminary Amendment	Prelim_Amd_30015730_0043.pdf	392359	no	3
Warnings:					

Information:	
Total Files Size (in bytes):	392359

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

PTO/SB/06 (12-04)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number: 11/620,986

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	75		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	250		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	100		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	60	* 40	X 25=	1,000	OR	X 50=	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2	*	X 100=			X 200=	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			180			N/A	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1,425		TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					180		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.