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.
14/100,717	11/25/2014	8895612	30015730-0065	2813

26263 7590 11/05/2014

DENTONS US LLP
P.O. BOX 061080
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 0 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):

Luitpold Pharmaceuticals, Inc., Shirley, NY, Assignee (with 37 CFR 1.172 Interest);
Mary Jane Helenek, Brookville, NY;
Marc L. Tokars, Douglassville, PA;
Richard P. Lawrence, Calverton, NY;

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 09/22/2014
DENTONS US LLP
P.O. BOX 061080
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.
14/100,717	12/09/2013	Mary Jane Helenek	30015730-0065	2813

TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	12/22/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
LAU, JONATHAN S	1673	514-502000

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 DENTONS US 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): SHIRLEY, NY

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. via EFS.
- ☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 19-3140 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Kathleen E. Chaffee/ Date 20 October 2014

Typed or printed name Kathleen E. Chaffee Registration No. 69,903

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal	
Application Number:	14100717
Filing Date:	09-Dec-2013
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Filer:	Kathleen E. Chaffee/Connie Payne
Attorney Docket Number:	30015730-0065
Filed as Large 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	1501	1	960	960
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt	
EFS ID:	20456035
Application Number:	14100717
International Application Number:	
Confirmation Number:	2813
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	Kathleen E. Chaffee/Connie Payne
Filer Authorized By:	Kathleen E. Chaffee
Attorney Docket Number:	30015730-0065
Receipt Date:	20-OCT-2014
Filing Date:	09-DEC-2013
Time Stamp:	10:31:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$960
RAM confirmation Number	8401
Deposit Account	193140
Authorized User	CHAFFEE, KATHLEEN
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

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_30015730-0065.pdf	148470 2fb15a9b8b4a34e84196480cbd39f9ec50e31438	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30179 147a912fca0ec9adc2fbafadd5946a8086a6ff2a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	178649		

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 09/22/2014

DENTONS US LLP
P.O. BOX 061080
CHICAGO, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1673	

DATE MAILED: 09/22/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/100,717	12/09/2013	Mary Jane Helenek	30015730-0065	2813

TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	12/22/2014

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 ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

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. 02/11)

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 09/22/2014
DENTONS US LLP
P.O. BOX 061080
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.
14/100,717	12/09/2013	Mary Jane Helenek	30015730-0065	2813

TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	12/22/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
LAU, JONATHAN S	1673	514-502000

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 credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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.
14/100,717	12/09/2013	Mary Jane Helenek	30015730-0065	2813

26263 7590 09/22/2014

DENTONS US LLP
P.O. BOX 061080
CHICAGO, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1673	

DATE MAILED: 09/22/2014

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

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

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. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B 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.

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 disclosure of these records is required by the Freedom of Information Act.
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 inspection 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.

Notice of Allowability	Application No. 14/100,717	Applicant(s) HELENEK ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1673	AIA (First Inventor to File) Status No

-- 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 *9 Jun 2014*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1,3-10 and 12-22*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   Certified copies:
   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.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ 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. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 5 pgs
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/LAYLA BLAND/
Primary Examiner, Art Unit 1673

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 Kathleen Chaffee on 16 Sep 2014.

The application has been amended as follows:

Amendment to the Claims

- Claim 1 is 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 polyisomaltose complex, an iron polymaltose complex, an iron sorbitol complex, and an iron polyglucose sorbitol carboxymethyl ether complex~~, and an iron hydrogenated dextran complex~~;

the single dosage unit of elemental iron is administered in about 15 minutes or less; and

the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

This Office Action is responsive to Applicant's Amendment and Remarks, filed 9 Jun 2014, in which claim 1 is amended to change the scope and breadth of the claim, claims 2 and 11 are canceled, and new claims 21 and 22 are added.

This application is a domestic application, filed 9 Dec 2013; and claims benefit as a CON of 13/847,254, filed 19 Mar 2013; which claims benefit as a CON of 12/787,283, issued as Patent 8,431,549, filed 25 May 2010; which claims benefit as a CON of 11/620,986, issued as Patent 7,754,702, filed 8 Jan 2007; which claims benefit of provisional application 60/757,119, filed 6 Jan 2006.

This application is a domestic application, filed 9 Dec 2013; and claims benefit as a CON of 13/847,254, filed 19 Mar 2013; which claims benefit as a CON of 12/787,283, issued as Patent 8,431,549, filed 25 May 2010; which claims benefit as a CON of 11/620,986, issued as Patent 7,754,702, filed 8 Jan 2007; which claims benefit of provisional application 60/757,119, filed 6 Jan 2006.

Claims 1, 3-10 and 12-22 are pending in the current application and are allowed in view of the examiner's amendment herein.

Terminal Disclaimer

The terminal disclaimer filed on 9 Jun 2014 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of Patent 8,431,549 and Patent 7,754,702 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Reasons for Allowance

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

Rejections Withdrawn

Applicant's Amendment, filed 9 Jun 2014, with respect that claims 1, 3-5, 8, 13, 14 and 18 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Geisser et al. (WIPO Publication WO 2004/037865 A1, published 6 May 2004, of record, English language equivalent US Patent 7,612,109 provided, of record) has been fully considered and is persuasive, as amended claim 1 requires the single dosage unit of elemental iron administered in about 15 minutes or less and Geisser et al. discloses the dose applied, for example, during the course of one hour.

This rejection has been **withdrawn**.

Applicant's Remarks, filed 9 Jun 2014, with respect that claims 1-3, 7-12 and 18-20 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Helenek et al. (US Patent Application Publication 2004/0180849 A1, published 16 Sep 2004, of

record) has been fully considered and is persuasive, as Applicant's remarks and the evidence made of record in the Declaration of Lawrence filed 26 Aug 2009 in parent application 11/620,986 are persuasive that Helenek et al. discloses the selection of the iron complex in terms of iron release rate, that disclosure of a single dosage unit of at least about 0.6 grams of elemental iron is limited to the embodiment of iron sucrose, and that the disclosure of Helenek et al. acknowledges that the per unit dose limited by maximal tolerated dose for the iron complex known in the prior art at the time of the invention. Therefore Applicant's remarks are persuasive that Helenek et al. does not explicitly or implicitly disclose all limitations of the instant invention as claimed, and the known maximal tolerated dose for iron complexes other than iron sucrose or iron dextran teaches away from the instant invention as claimed.

This rejection has been **withdrawn**.

Applicant's Amendment and Remarks, filed 9 Jun 2014, with respect that claims 1, 4-6, 8-12 and 18-20 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Hamstra et al. (JAMA, 1980, 243(17), p1726-1731, of record) in view of Muller et al. (US Patent 3,100,202, issued 6 Aug 1963, of record) has been fully considered and is persuasive, as amended claim 1 requires the single dosage unit of at least about 0.6 grams of elemental iron administered in about 15 minutes or less and Applicant's remarks are persuasive that the prior art at the time of the invention suggested the maximal tolerated dose for iron dextran complexes was not predictable for different iron complexes and that differences in toxicity and proinflammatory effect

for different iron complexes was expected, and that the prior art suggests decreasing the dose to minimize adverse reactions.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 9 Jun 2014, with respect that claim 17 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Hamstra et al. (JAMA, 1980, 243(17), p1726-1731, of record) in view of Muller et al. (US Patent 3,100,202, issued 6 Aug 1963, of record) as applied to claims 1, 4-6, 8-12 and 18-20, and further in view of Lawrence et al. (US Patent 5,624,668, issued 29 Apr 1997, provided by Applicant in IDS mailed 17 Jun 2010) has been fully considered and is persuasive, as amended claim 1 requires the single dosage unit of at least about 0.6 grams of elemental iron administered in about 15 minutes or less and Applicant's remarks are persuasive regarding Hamstra et al. in view of Muller et al., and Lawrence et al. does not remedy the teaching with regard to the single dosage unit administered.

This rejection has been **withdrawn**.

The terminal disclaimer, filed 9 Jun 2014, with respect that claims 1-20 are rejected on the ground of nonstatutory double patenting over claims 1-57 of U.S. Patent No. 7,754,702 has been fully considered and is persuasive, as the terminal disclaimer is recorded.

This rejection has been **withdrawn**.

The terminal disclaimer, filed 9 Jun 2014, with respect that claims 1-12 and 15-20 are rejected on the ground of nonstatutory double patenting over claims 1-23 of U.S. Patent No. 8,431,549 has been fully considered and is persuasive, as the terminal disclaimer is recorded.

This rejection has been **withdrawn**.

Regarding amended claim 1, Kabat et al. (Journal of Immunology, 1953, 70, p514-532, cited in PTO-892) teaches hydrogenated dextran is not substantially different in its reactive with antidextran from clinical dextrans (page 524, left column, paragraph 2) and both clinically used dextran and hydrogenated dextran are antigenic in man (page 531, left column, paragraph 2-3). Amended claim 1 specifically encompasses the combination of an iron hydrogenated dextran complex and a substantially non-immunogenic carbohydrate component and raises issues of enablement for the species of hydrogenated dextran complex in view of Kabat et al. In a telephonic interview with Kathleen Chaffee, agreement was reached on an examiner's amendment in order to facilitate placing the claims in condition for allowance.

Regarding amended claims 1 and 22, Kabat et al. teaches the clinical use of antigenic dextrans as above. Helenek et al. at page 3, paragraph 0021 suggests iron dextran and iron polyisomaltose are used synonymously in the art of iron carbohydrate complexes. Applicant's remarks note evidence made of record in the Declaration of Lawrence filed 26 Aug 2009 in parent application 11/620,986 that the subgenus of

polyisomaltose being substantially non-immunogenic is known in the prior art. Therefore the prior art does not teach or fairly suggest selecting the subgenus of iron polyisomaltose wherein the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component because the prior art suggests the clinical use of antigenic dextrans. See MPEP 2143 I.A. example 3 citing the case of *In re Omeprazole Patent Litigation*, 536 F.3d 1361, 87 USPQ2d 1865 (Fed. Cir. 2008) in which an extra process step that added an additional component to a known, successfully marketed formulation was found not to be obvious because the proposed modification thus amounted to extra work and greater expense for no apparent reason.

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, 3-10 and 12-22 are pending in the current application and are allowed in view of the examiner’s amendment 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 S Lau/
Examiner, Art Unit 1673

/LAYLA BLAND/
Primary Examiner, Art Unit 1673

Notice of References Cited	Application/Control No. 14/100,717	Applicant(s)/Patent Under Reexamination HELENEK ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1673	Page 1 of 1

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	Kabat et al., Journal of Immunology, 1953, 70, p514-532.
	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.

PTO/SB/08A (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	14/100,717
Filing Date	09 December 2014
First Named Inventor	Mary Jane Helenek
Art Unit	1673
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0065

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
	1.	US-6599498	07-29-2003	Groman et al.	
	2.	US-6960571	11-01-2005	Helenek et al.	
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		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Number 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]
	3.	CA 2493806	05-06-2004	Vifor (International) AG		☐
	4.	KR 10-2005-0070014	07-05-2005	Vifor Int. AG		☐
	5.	#WO 1997/011711	04-03-1997	Luitpold Pharmaceuticals, Inc.		☐
	6.	#WO 2007/023154	03-01-2007	Vifor (International) AG		☐

Examiner Signature		Date Considered	

#EXAMINER: Reference cited in parent (Application Serial Nos. 13/847,254, 12/787,283, and 11/620,986) and are not provided herewith.

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Art Unit	1673
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0065

OTHER ITEMS – 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]
	7.	#ANDERSSON, Clinical investigations on a new intramuscular haematinic, British Medical Journal, 1961, pp. 275-279, Vol. 2.	
	8.	#Australian Office Action dated 15 September 2011 in related Australian Application No. AU2007205167 filed 08 January 2007, 3 pages.	
	9.	#BAILIE et al., Hypersensitivity reactions and deaths associated with intravenous iron preparations, Nephrol Dial Transplant, 2005, pp. 1443-1449, Vol. 20.	
	10.	#BESHARA et al., Pharmacokinetics and red cell utilization of $^{52}Fe/^{59}Fe$-labelled iron polymaltose in anaemic patients using positron emission tomography, Br J of Haematol, 2003, pp. 853-859, Vol. 120.	
	11.	Canadian Office Action dated 4 January 2013 in related Canadian Application No. CA 2,635,894 filed 08 January 2007, 4 pages.	
	12.	Canadian Office Action dated 17 October 2013 in related Canadian Application No. CA 2,635,894 filed 08 January 2007, 4 pages.	
	13.	#Chinese Office Action dated 30 April 2010 in related Chinese Application No. CN 200780002006 filed 08 January 2007, English translation, 7 pages.	
	14.	#CISAR et al., Binding Properties of Immunoglobulin Combining Sites Specific for Terminal or Nonterminal Antigenic Determinants in Dextran, J Exp. Med,1975, pp. 435-459, Vol. 142.	
	15.	#ESCHBACH et al., NKF-K/DOQI clinical practice guidelines for anemia of chronic kidney disease: update 2000, Am J Kidney Dis, 2001, pp. S182-238, Vol. 37 (Supp 1).	
	16.	European Supplementary Search Report issued 21 October 2009 in related European Application No. EP 07716309.5, 9 pages.	
	17.	European Official Communication dated 10 May 2011 in related European Application No. EP 07716309.5 filed 08 January 2007, 6 pages.	
	18.	#European Official Communication dated 04 June 2012 in related European Application No. EP 07716309.5 filed 08 January 2007, 5 pages.	
	19.	European Office Action dated 5 July 2013 in related European Application No. EP 07716309.5 filed on 8 January 2007, 5 pages.	

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Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0065

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	20.	European Search Report dated 08 July 2013 in related European Application No. EP 13166988.9 filed 08 May 2013, 8 pages.	
	21.	#FIELDING, Intravenous iron-dextrin in iron-deficiency anaemia, British Medical Journal, 1961, pp. 279-283, Vol. 2.	
	22.	#FISHBANE, Safety in iron management, Am J Kidney Dis, 2003, S18-S26, Vol. 41, No. 6 (Suppl 5).	
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	27.	#KUDASHEVA et al., Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanoparticles in parenteral formulations, Journal of Inorganic Biochemistry, 2004, pp. 1757-1769, Vol. 98.	
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	30.	MARCHASIN et al., The Treatment of Iron-Deficiency Anemia with Intravenous Iron Dextran, Blood, 1964, pp. 354-358, Vol. 23, No. 3.	
	31.	#NEWNHAM et al., Safety of iron polymaltose given as a total dose iron infusion, Internal Medicine Journal, 2006, pp. 672-674, Vol. 36, No. 10.	
	32.	#NISSENSON et al., Controversies in iron management, Kidney International, 2003, pp. S64-S71, Vol. 64 (Supp 87).	

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Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0065

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	33.	#SIPE et al., Brain iron metabolism and neurodegenerative disorders, Dev Neurosci, 2002, pp. 188-196, Vol. 24, No. 2-3.	
	34.	#SOFIC et al., Increased iron (III) and total iron content in post mortem substantia nigra of parkinsonian brain, J. Neural Transm, 1988, pp.199-205, Vol. 74.	
	35.	#SPINOWITZ et al., The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients, Kidney International, 2005, pp. 1801-1807, Vol. 68.	
	36.	#VAN WYCK et al., Making sense: a scientific approach to intravenous iron therapy, J Am Soc Nephrol, 2004, pp. S91-S92, Vol. 15 (Supp.2).	
	37.	#VAN WYCK, Labile iron: manifestations and clinical implications, J Am Soc Nephrol, 2004, pp. S107-S111, Vol. 15 (Supp. 2).	

Examiner Signature	/Jonathan Lau/	Date Considered	09/16/2014

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14100717	HELENEK ET AL.
	Examiner	**Art Unit**
	JONATHAN S LAU	1673

CPC							
Symbol						**Type**	**Version**
C07H		23	/	00		F	2013-01-01
A61K		31	/	715		I	2013-01-01
A61K		31	/	721		I	2013-01-01
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CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

/JONATHAN S LAU/ Examiner.Art Unit 1673 (Assistant Examiner)	09/16/2014 (Date)	**Total Claims Allowed:** 20	
/LAYLA BLAND/ Primary Examiner.Art Unit 1673 (Primary Examiner)	09/17/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14100717	HELENEK ET AL.
	Examiner	**Art Unit**
	JONATHAN S LAU	1673

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
514	502	A 6 1 K 31 / 295 (2006.0)	
		A 6 1 K 31 / 7016 (2006.0)	
CROSS REFERENCE(S)		A 6 1 K 31 / 715 (2006.0)	
		A 6 1 K 31 / 721 (2006.0)	

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	53	54	58	59	

/JONATHAN S LAU/ Examiner.Art Unit 1673	09/16/2014	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	20	
/LAYLA BLAND/ Primary Examiner.Art Unit 1673	09/17/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

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Part of Paper No. 20140916

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14100717	HELENEK ET AL.
	Examiner	**Art Unit**
	JONATHAN S LAU	1673

☒ 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	15	17												
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/JONATHAN S LAU/ Examiner.Art Unit 1673 (Assistant Examiner)	09/16/2014 (Date)	**Total Claims Allowed:** 20	
/LAYLA BLAND/ Primary Examiner.Art Unit 1673 (Primary Examiner)	09/17/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

PTO/SB/08a (07-09)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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	14/100,717
Filing Date	09 December 2013
First Named Inventor	Mary Jane Helenek et al.
Art Unit	1673
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0065

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
	1.	US- 7,871,597	01-18-2011	Groman et al.	
	2.	US- 2003/0232084 A1	12-18-2003	Groman et al.	
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Number 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	09/16/2014

*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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14100717	HELENEK ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1673

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	53, 54, 58, 59, 502	9/16/2014	JSL

SEARCH NOTES		
Search Notes	Date	Examiner
EAST - see attached notes	2/6/2014	JSL
EAST - inventor name search (Mary Helenek, Marc Tokars, Richard Lawrence)	2/6/2014	JSL
Google Scholar - see attached notes	2/6/2014	JSL
EAST - inventor name search (Mary Helenek, Marc Tokars, Richard Lawrence) - updated	9/16/2014	JSL
Google Scholar - see attached notes	9/16/2014	JSL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	53, 54, 58, 59, 502	9/16/2014	JSL

Risks of parenteral deferoxamine for acute **iron** poisoning
MA Howland - Clinical Toxicology, 1996 - informahealthcare.com
... iisultant to New York City Poison Center and Department of **Emergency** Medicine, Bellevue ... deferoxamine by other routes without difficulty and then developed ARDS with IV **infusion**. ... proposed that deferoxamine chelates intracellular **iron** making it unavailable for the synthesis ...
Cited by 56 Related articles All 4 versions Cite Save

Is there a difference between the allergic potencies of the **iron** sucrose and low molecular weight **iron** dextran?
T Sav, B Tokgoz, MH Sipahioglu, M Deveci... - Renal ..., 2007 - informahealthcare.com
... mg of **iron** diluted in 100 mL of normal saline was administered over 30 minutes. Adverse reactions were recorded. The **infusion** was considered to be discontinued if any serious adverse effects are occurred. Materials and drugs to be used in case of an **emergency** intervention ...
Cited by 50 Related articles All 5 versions Cite Save

Iron toxicity in **emergency** medicine
CS Spanierman, A Tarabar - 2011 - medisuite.ir
... Provide oxygen to patients in shock. References. **Emergency** Department Care. ... Excreted in urine and bile and gives urine a red discoloration. Readily chelates **iron** from ferritin and hemosiderin but not transferrin. Most effective when administered continuously by **infusion**. ...
Cited by 2 Related articles All 11 versions Cite Save More

A hospital-based cost minimization study of the potential financial impact on the UK health care system of introduction of **iron** isomaltoside 1000
S Bhandari - Therapeutics and clinical risk management, 2011 - ncbi.nlm.nih.gov
... body weight and to a ceiling of 1000 mg per **infusion**, limited to once a week. **Iron** isomaltoside 1000, whilst also administered rapidly, allows for 20 mg of **iron** per kg of body weight. This range of dosing offers a broader spectrum of treatment, including total dose **infusions**, for a ...
Cited by 9 Related articles All 6 versions Cite Save

Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine **infusions**
NF Olivieri, JR Buncic, E Chew, T Gallant... - ... England Journal of ..., 1986 - Mass Medical Soc
... A second patient reported a hearing loss during the continuous intravenous **infusion** of deferoxamine (10 mg per ... (2001) Optic neuropathy in uremia: An interdisciplinary **emergency**. ... (2001) Noninvasive methods for quantitative assessment of transfusional **iron** overload in sickle ...
Cited by 414 Related articles All 7 versions Cite Save

P374 Fecal transplantation in patients with moderately to severely chronic active ulcerative colitis (UC)
S Angelberger, C Lichtenberger, C Gratzer... - Journal of Crohn's and ..., 2012 - Elsevier
Cited by 4 Related articles All 3 versions Cite Save

Iron poisoning: Report of three cases and a review of therapeutic intervention
JL Schauben, WL Augenstein, J Cox, R Sato - The Journal of **emergency** ..., 1990 - Elsevier
... In the **emergency** department, an IV line was established and he received an IV **infusion** of deferoxamine, delivered at 13 mg/kg/hr. An abdominal x-ray study (Figure 3) revealed one intact pill fragment in the stomach and some amorphous radiopaque debris, consistent with **iron** ...
Cited by 29 Related articles All 4 versions Cite Save

Hydroxyurea use in patients with sickle cell disease in a Medicaid population
J Ritho, H Liu, AG Hartzema... - American journal of ..., 2011 - Wiley Online Library
... cell transfusions (OR = 1.62, 95% CI = [1.15, 2.27]), **iron** chelation (OR = 2.25, 95% CI = [1.23, 4.12]), long-acting opioids (OR = 2.43, 95% CI = [1.96, 3.03]) had higher odds of using HU. Patient demographics (race, age, and gender), and use of **emergency** department medical ...
Cited by 3 Related articles All 4 versions Cite Save

The rise in the TIBC after **iron** overdose
K Burkhart, K Kulig, BH Rumack, KB Hammond... - Annals of **Emergency** ..., 1990 - Mosby
Cited by 2 Related articles All 2 versions Cite Save

Acute **iron** ingestion in a 2-year-old child

D Danis, JG Deason - Journal of **Emergency** Nursing, 1995 - Elsevier

... set of tests were obtained at 5:30 PM (Table 1). Results of the follow-up **iron** studies were even more abnormal than the first test results. An IV Ms. Deason is a staff nurse, **Emergency** Department, Saint Mary Corwin Regienal Medical Center, Pueblo, Colorado **infusion** of normal ...

Cited by 2 Related articles All 5 versions Cite Save

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	14100717
Filing Date	09-Dec-2013
First Named Inventor	Mary Helenek
Attorney Docket Number	30015730-0065
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Luitpold Pharmaceuticals, Inc.	100%

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

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as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

(●) Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request. ( ) I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.	
Applicant claims the following fee status: ( ) Small Entity ( ) Micro Entity (●) Regular Undiscounted 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.	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: (●) An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number 69903 ( ) A sole inventor ( ) A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ( ) A joint inventor; all of whom are signing this request	
Signature	/Kathleen E. Chaffee/
Name	Kathleen E. Chaffee

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal	
Application Number:	14100717
Filing Date:	09-Dec-2013
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Filer:	Kathleen E. Chaffee
Attorney Docket Number:	30015730-0065
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Statutory or Terminal Disclaimer	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 14100717

Filing Date: 09-Dec-2013

Applicant/Patent under Reexamination: Helenek et al.

Electronic Terminal Disclaimer filed on June 9, 2014

☒ APPROVED

This patent is subject to a terminal disclaimer

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U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt	
EFS ID:	19252719
Application Number:	14100717
International Application Number:	
Confirmation Number:	2813
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	Kathleen E. Chaffee
Filer Authorized By:	
Attorney Docket Number:	30015730-0065
Receipt Date:	09-JUN-2014
Filing Date:	09-DEC-2013
Time Stamp:	18:05:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$160
RAM confirmation Number	5036
Deposit Account	
Authorized User	

File Listing:

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

1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	33468 41a9adcf454d79d29c7afbdff008c9cb9582af29c	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30110 7e21c581a2e450010b1828ea771ae5c4171df17d	no	2
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		Total Files Size (in bytes):	63578		

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.: **14/100,717**	Examiner: **LAU, JONATHAN S**
Applicant: **HELENEK, MARY JANE**	Group Art Unit: **1673**
Filed: **09 December 2013**	Confirmation No.: **2813**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	Customer No.: **26263**
Docket No.: **30015730-0065**	

09 June 2014

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 07 February 2014, Applicants request the Office to enter the following amendments and consider the remarks set forth below.

Because 07 June 2014, falls on a weekend, this Response is being filed on the next following business day, 09 June 2014, and is, therefore, timely filed as of the four month date.

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,~~ an iron sorbitol complex, an iron polyglucose sorbitol carboxymethyl ether complex, and an iron hydrogenated dextran complex;

the single dosage unit of elemental iron is administered in about 15 minutes or less; and

the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component.

2. (canceled)

3. (original) The method of claim 1, wherein the iron carbohydrate complex has substantially no cross reactivity with anti-dextran antibodies.

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

5. (original) The method of claim 4, wherein the anemia comprises iron deficiency anemia.

6. (original) The method of claim 4, wherein:

(i) the anemia comprises an iron deficiency anemia 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-steroidal anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents;

(ii) the anemia is of a chronic disease 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;

(iii) the anemia is due to impaired iron absorption or poor nutrition;

(iv) the anemia is associated with Crohn's Disease; gastric surgery; ingestion of drug products that inhibit iron absorption; or chronic use of calcium.

7. (original) 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.

8. (original) The method of claim 1 wherein the single dosage unit of elemental iron is at least about 1.0 grams.

9. (original) The method of claim 1 wherein the single dosage unit of elemental iron is at least about 1.5 grams.

10. (original) The method of claim 1 wherein the single dosage unit of elemental iron is at least about 2.0 grams.

11. (canceled)

12. (original) The method of claim 1 wherein the single dosage unit of elemental iron is administered in about 5 minutes or less.

13. (original) The method of claim 1 wherein the iron carbohydrate complex is an iron carboxymaltose complex.

14. (original) The method of claim 13, wherein

(i) 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; or

(ii) the iron carboxymaltose complex is a polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

15. (original) The method of claim 1, wherein the iron carbohydrate complex is an iron polyglucose sorbitol carboxymethyl ether complex.

16. (original) The method of claim 15, wherein the iron polyglucose sorbitol carboxymethyl ether complex is a polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite complex.

17. (original) The method of claim 1, wherein

mean iron core size is at least about 1 nm but no greater than about 9 nm; or

mean size of a particle of the iron carbohydrate complex is no greater than about 35 nm.

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

19. (original) The method of claim 18, wherein

(i) parenteral administration comprises intravenous infusion and the single unit dose of iron carbohydrate complex is administered at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent;

(ii) parenteral administration comprises bolus injection and the single unit dose of iron carbohydrate complex is administered at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent; or

(iii) parenteral administration comprises intramuscular injection and the single unit dose of iron carbohydrate complex is administered at a concentration of about 500 mg elemental iron in less than about 10 ml diluent.

20. (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.

21. (new) The method of claim 1, wherein iron carbohydrate complex does not have an iron release rate of 115 µg/dl at a concentration of 2,000 µg/dl.

22. (new) The method of claim 1, wherein the iron carbohydrate complex is an iron polyisomaltose complex.

REMARKS

Upon entry of this amendment, claims 1-22 are pending. Claim 1 has been amended. Claim 21 and 22 have been added. No claims have been withdrawn. Claims 2 and 11 have been canceled.

Support for the amendment to claim 1 appears at least at claim 2, claim 11, and claim 15. Support for new claim 21 appears at least at page 13, ¶0045, which incorporates by reference U.S. Patent Pub. No. 2004/0180849 (see page 3, ¶0026 of U.S. Patent Pub. No. 2004/0180849). Support for new claim 22 appears at least at claim 1.

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

Restriction Status

There has been no Invention Restriction or Species Restriction in the present application. Applicants understand the Office to be examining the full scope of all claims.

Examination Status

Applicants note the absence of any analysis or rejection over 35 U.S.C. § 112. The Office has an administrative burden "to clearly articulate any rejection early in the prosecution process so that the applicant has the opportunity to provide evidence of patentability and otherwise reply completely at the earliest opportunity." MPEP § 706 (emphasis added). If the Office subsequently presents a rejection under 35 U.S.C. § 112 in a subsequent Office Action, Applicants respectfully request the Office to provide a basis as to why such rejection was not addressed in the first Action.

Claim Rejections under 35 U.S.C. § 102 over Geisser

Applicants respectfully traverse and, for the following reasons, request reconsideration and withdrawal of the rejection of claims 1, 3-5, 8, 13, 14, and 18 under pre-AIA 35 U.S.C. §102(b) as being anticipated by Geisser et al., WO 2004/037865, evidenced by English language equivalent US 7,612,109 ("Geisser").

Anticipation under 35 U.S.C. §102 can be found only when the reference discloses exactly what is claimed. MPEP §2131.03(III). For anticipation, the cited reference must teach every aspect of the claimed invention either explicitly or impliedly, and any feature not directly taught must be inherently present. MPEP §706.02(V).

Claim 11 is not rejected as anticipated by Geisser. In the interest of furthering prosecution, claim 1 has been amended to recite "the single dosage unit of elemental iron is administered in about 15 minutes or less". As such, all features of canceled claim 11 have been incorporated into claim 1.

For at least the above reasons, claim 1 is not *prima facie* anticipated by Geisser. The above argument applies equally to claim 1 and claims dependent thereon or featuring pertinent elements thereof, such as claims 3-5, 8, 13, 14, and 18.

Claim Rejections under 35 U.S.C. § 102 over Helenek

Applicants respectfully traverse and, for the following reasons, request reconsideration and withdrawal of the rejection of claims 1-3, 7-12, and 18-20 under pre-AIA 35 U.S.C. §102(b) as being anticipated by Helenek et al., US 2004/0180849 ("Helenek"). Claims 2 and 11 have been canceled, making the above rejection moot as to these claims.

Standards of novelty are as discussed above.

Helenek discloses treatment of Restless Leg Syndrome (RLS) with an iron complex having an iron release rate greater than iron dextran (IDI). Specifically, Helenek discloses 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, page 3, ¶0026).

The Office asserts that Helenek discloses 1,000 mg elemental iron single dose of iron polyisomaltose (wrongfully equated with iron dextran), iron polymaltose, iron gluconate, iron sorbitol, and iron hydrogenated dextran as direct injections administered from 2 to 5 minutes (citing page 3, ¶0021; page 5, ¶¶0051-0052; page 7, ¶0097). As shown below, these assertions are incorrect at least because methods of Helenek apply only to iron carbohydrate complexes having an iron release rate greater than IDI.

(1) Helenek methods are limited to iron carbohydrates with iron release rates greater than IDI.

Helenek discloses treatment of Restless Leg Syndrome (RLS) with an iron complex having an iron release rate greater than iron dextran (IDI) (see Abstract; page 2, ¶¶0012-0015; page 3, ¶0018). Helenek defines IDI as iron dextran solutions, such as INFeD® and Dexferrum® (page 2, ¶0011). Helenek discloses IDI has a release rate of 69.5-113.5 µg/dl and, accordingly, sets a cutoff of a release rate greater than 115 µg/dl for any iron carbohydrate to be used in the disclosed methods (see page 3, ¶0026).

Helenek only recites iron polyisomaltose, iron polymaltose, iron sorbitol, and iron hydrogenated dextran in a generic listing of examples of iron carbohydrate complexes but does not assert that all such examples can be used in that invention (page 3, ¶0021). In fact, immediately thereafter, Helenek makes clear that "[i]n the present 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, page 3, ¶0026, emphasis added; see Abstract; page 2, ¶¶0012-0015; page 5, ¶¶0049, 0050). Similarly, Helenek recites that "any iron complex that has a release rate greater than that of IDI is an effective RLS therapeutic" (page 3, ¶0018).

Helenek does not disclose 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 (set at 115 µg/dl) 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, i.e., both examples of IDI) (see FIG. 1, Table 2).

The Declaration of Lawrence (filed 26 August 2009 in US App Ser No. 11/620,986) evidences that methods disclosed in Helenek include only those iron carbohydrate complexes having an iron release rate greater than IDI (see ¶5).

(2) Iron Carbohydrates of Claim 1 have Release Rates Lower Than IDI.

(A) Iron Carboxymaltose.

As further evidenced in the Declaration of Lawrence (filed 26 August 2009 in US App Ser No. 11/620,986), VIT-45, an iron carboxymaltose complex, has an iron release rate less than IDI (see TABLE A; ¶¶6-7). Because an iron carboxymaltose complex has an iron release rate less than IDI, methods of Helenek cannot be applied thereto (see ¶7).

(B) Iron polyglucose sorbitol carboxymethyl ether.

Jahn et al. 2011 Eur J Pharma and Biopharma 78, 480-491, evidences that ferumoxytol has an iron release rate much lower than iron dextran (see page 489, Section 4.3; FIG. 7; FIG. 9). Feraheme® (ferumoxytol) is described by Jahn et al. 2011 as an iron carboxymethyl dextran. As discussed on page 22, ¶¶0075-0076 of the present application, ferumoxytol (i.e. an iron polyglucose sorbitol carboxymethyl ether; more specifically, a polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite) is a preferred complex for use methods of the present disclosure and falls within the scope of claim 1 (see also claims 15-16). Because the iron polyglucose sorbitol carboxymethyl ether has an iron release rate less than IDI, methods of Helenek cannot be applied thereto.

(C) Iron Polyisomaltose.

Helenek does not disclose administration of "an iron polyisomaltose [having] a substantially non-immunogenic carbohydrate component", as recited in claim 1.

The Office equates administration of an iron polyisomaltose with administration of an iron dextran (Action of 07 February 2014, page 4, lines 8-9).

First, claim 1 recites "an iron polyisomaltose [having] a substantially non-immunogenic carbohydrate component". It was understood in the art that the dextran carbohydrate component is immunogenic. Thus, iron dextran does not read on "an iron polyisomaltose [having] a substantially non-immunogenic carbohydrate component", as recited in claim 1.

Second, at the time of filing, and as acknowledged by the Office (in US App Ser No., 12/787,283, Action of June 6, 2012, page 4, lines 8-11), an iron polyisomaltose is understood as a type of iron carbohydrate complex that includes isomaltose units in the carbohydrate component. An isomaltose is a disaccharide similar to maltose, but with a α-(1-6)-linkage between two glucose units instead of an α-(1-4)-linkage (see Lawrence Declaration, ¶4, filed 06 December 2012, in US App Ser No., 12/787,283). One example of an iron polyisomaltose complex is an iron isomaltoside (e.g., Monofer®), where the carbohydrate component is a pure linear chemical structure of repeating α1-6 linked glucose units (Id. at ¶4). In contrast, a dextran is a branched glucan with straight chains having α1-6 glycosidic linkages and branches beginning from α1-3 linkages.

It was understood at the time of filing that isomaltose oligomers prevent or block anaphylaxis to dextrans (Coulson and Stevens 1961 J Immun 86, 241; evidenced by Jahn et al. 2011 Eur J Pharma and Biopharma 78, 480-491, at 489, column 1, lines 53-58; see Lawrence Declaration, ¶5). It was also understood at the time of filing that isomaltose oligomers acted as haptens against circulating anti-dextran antibodies (retrospective summary in Jahn et al. 2011 Eur J Pharma and Biopharma 78, 480-491, at 489, column 1, lines 58-60; see Lawrence Declaration, ¶5). A hapten can bind an antibody without inducing anaphylaxis or an immune response (see term definition in retrospective summary of Jahn et al. 2011 Eur J Pharma and Biopharma 78, 480-491, at 489, column 2, lines 3-5; see Lawrence Declaration, ¶5).

For at least the above reasons, the Office is incorrect in equating an iron dextran to "an iron polyisomaltose [having] a substantially non-immunogenic carbohydrate component", as recited in claim 1.

Third, Jahn et al. 2011 Eur J Pharma and Biopharma 78, 480-491, evidences that iron "isomaltoside" (i.e., an iron polyisomaltose) does not have an iron release rate higher than iron dextran (page 489, Section 4.3; FIG. 7; FIG. 9).

Thus, Helenek does not disclose administration of "an iron polyisomaltose [having] a substantially non-immunogenic carbohydrate component", as recited in claim 1. Because an iron polyisomaltose has an iron release rate less than IDI, methods of Helenek cannot be applied thereto.

(3) Single High Dose in Helenek Applies Only to Iron Sucrose.

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, page 5, ¶0052; page 7, ¶0095), which is an iron carbohydrate not recited in claim 1.

Conclusion

For at least the above reasons, claim 1 is not prima facie anticipated by Helenek. The above argument applies equally to claim 1 and claims dependent thereon or featuring pertinent elements thereof, such as claims 3, 7-10, 12, and 18-20.

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, 4-6, 8-12, and 18-20 under 35 U.S.C. §103(a) as being unpatentable over Hamstra et al. 1980 JAMA 243(17),

1726-1731 ("Hamstra") in view of Muller et al., US 3,100,202 ("Muller"). Claim 11 has been canceled, making the above rejection moot as to this claim.

To establish obviousness of a claim, the prior art must disclose or suggest each element of the claim; there must be some apparent 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 all 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. 398, 418 (2007).

Claim 1 recites:

> 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 sorbitol complex, and an iron hydrogenated dextran complex; the single dosage unit of elemental iron is administered in about 15 minutes or less; and the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component.

Cited References Fail to Disclose All Claim Elements

Neither Hamstra nor Muller disclose all features of the claims.

The Office asserts that Hamstra discloses intravenous injection of iron dextran 1,000 mg or >1,000 mg of elemental iron per injection. But iron dextran is not recited as an iron carbohydrate complex in claim 1; and Hamstra does not disclose such dosage for any other iron carbohydrate.

To overcome the inadequacies of Hamstra, the Office cites Muller. But Muller fails to overcome the inadequacies of Hamstra. While Muller discloses a method for making an iron polyisomaltose, Muller fails to provide any information concerning dosage or administration protocol.

Insufficient Reason to Modify Cited References to Reach All Claim Features

The present inventors have found that, in spite of the teachings of the prior art, it is possible to administer the combination of high single dose (e.g., at least 0.6 g iron) and short administration time (e.g., 15 minutes or less) for those iron carbohydrate complexes recited in claim 1 without causing significant adverse side effects in a patient.

Applicants have discovered that certain characteristics of iron carbohydrate complexes make them amenable to administration at dosages higher than contemplated by conventional administration protocols at the time of filing (see page 17, ¶0060). As described in the application, an iron carbohydrate complex of the claims can 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 (page 17, ¶0060). For example, the effect of iron core size and/or molecular weight is discussed at page 23, ¶0079 - page 24, ¶0082. The application also provides guidance as to measuring or determining the presence of such features in an iron carbohydrate complex (see page 18, ¶0061). As disclosed in the application, the iron carbohydrate complexes recited in claim 1 have one or more of the above described features.

The present application thus 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 of at least 0.6 g iron and in 15 minutes or less, thereby providing a safe and efficient means for delivery of a total dose of iron in fewer sessions and less time per session over the course of therapeutic treatment (see Application, page 3, ¶0008; page 8, ¶0026). The present claims recite use of an iron carbohydrate complex (selected from an iron carboxymaltose complex,

an iron mannitol complex, an iron polyisomaltose complex, an iron polymaltose complex, an iron sorbitol complex, an iron polyglucose sorbitol carboxymethyl ether complex, and an iron hydrogenated dextran complex) in a single dosage unit of at least about 0.6 grams of elemental iron administered in 15 minutes or less.

The reduced administration time has considerable advantages as it is less unpleasant for the patient and less time consuming for the medical staff supervising the treatment. In view of this it is submitted that the amended claims are nonobvious over the cited prior art.

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 protocols using iron carbohydrate complex so as to reach the single unit dosage and timing requirements for particular iron carbohydrate compounds recited in claim 1 (*see KSR Int'l Co.*, at 424). The mere fact that references can be combined or modified does not render the resultant combination obvious unless there is some apparent reason that suggests the desirability of the combination. MPEP §2143.01(III).

The Office has failed to provide sufficient reason to modify Muller and/or Hamstra so as to reach all features of claim 1.

First, the prior art evidences that disclosure related to iron dextran cannot necessarily be extrapolated to other iron carbohydrate complexes. For example, 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, page 64, column 2, emphasis added). 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, page S26, column 2) and various iron carbohydrate complexes differentially exert acute toxicity and a proinflammatory effect (see Zager, page S29, column 1). Thus, disclosure related to the dosage of iron dextran cannot be extrapolated to other iron carbohydrate complexes.

Second, the prior art teaches away (i.e., criticizes, discredits, or otherwise discourages, *see* MPEP §2141.02(VI)) from high doses of iron carbohydrate complexes. The present Application discloses that while iron dextran compositions can be given at

high dose, the prior art recognizes that the immune response and risk of anaphylaxis limits use of iron dextran. To achieve iron repletion under conventional therapy models, a total dose of 1 g of elemental iron typically required 5 to 10 sessions over an extended period of time, incurring significant expense for supplies, nursing time, and patient inconvenience (see Application, ¶0007).

Macdougall (1999) Kidney International 55(69), 61-66 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, page 64, column 2). 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. Further, Macdougall discloses 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, page 64, column 1).

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, page 73, column 3; citing Chandler et al. 2001 Am J Kidney Dis 38, 988-991). Such references demonstrate that from around 2001 and continuing through at least 2008, elevated dosages of ferric gluconate were strongly discouraged for intravenous administration.

The present Application, citing Geisser at al. 1992 Arnzneimittelforschung 42, 1439-1452 at page 2-3, ¶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, page 2-3, ¶0007).

Helenek, US 2004/0180849 discloses the use of a lower dosage of iron complex and/or slow infusion of iron complexes to avoid risk of anaphylaxis and toxicity (see e.g., ¶0017, ¶[0097], Table 4).

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, page 22, ¶0076).

Spinowitz (2005) Kidney International 68, 1801-1807 discloses parenteral iron preparations require multiple and/or time-consuming administration regimens (page 1801, ¶ 8). Spinowitz et al. (2005) Kidney Int. discloses administration of ferumoxytol in 4 doses of 255 mg iron in four weeks or 2 doses of 510 mg iron in 2 weeks.

Furthermore, in the Notice of Allowance dated 05 April 2010, in parent US App Ser No. 11/620,986 (issued as US Pat No. 7,754,702), the Office acknowledges that "Nissenson et al. (Kidney International, 2003, 64(Supplement 87), pS64-S71 [ ] teaches optimizing the maximum amount of iron carbohydrate complex to minimize adverse events" (page S67, emphasis added).

Even Hamstra discourages high doses of iron dextran by reciting: "[t]he severe delayed reactions (Table 6) were usually associated with large doses of iron dextran given to relatively small patients" and "[d]ecreasing the dose to 250 mg or less per injection … resulted in a decrease in incidence and severity of this type of reaction" (page 1730, column 3, ¶2, emphasis added). Hamstra also recites "anaphylactoid reactions [from iron dextran] are serious and unpredictable" (Abstract, emphasis added). Thus, Hamstra recognizes the inherent risk of high dose iron dextran and recommends decreasing the dose to 250 mg or less per injection.

As shown above, the prior art at the time of filing discouraged a skilled person from the combination of high single dose and low administration time for iron carbohydrate complexes and demonstrates repeated doses of low-concentration iron-carbohydrate complexes due to perceived risk of anaphylaxis. The presently claimed subject matter safely and effectively overcomes the need for repeated low-dose, slow introductions of an iron carbohydrate complex.

Conclusion

For at least the above reasons, claim 1 is not obvious over Hamstra and Muller. The above argument applies equally to claim 1 and claims dependent thereon or featuring pertinent elements thereof, such as claims 4-6, 8-10, 12, and 18-20.

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 claim 17 under 35 U.S.C. §103(a) as being unpatentable over Hamstra et al. 1980 JAMA 243(17), 1726-1731 ("Hamstra") in view of Muller et al., US 3,100,202 ("Muller") and Lawrence et al., US 6,624,668 ("Lawrence").

Standards of obviousness are as discussed above. Claim 17 depends from claim 1.

As discussed above, neither Hamstra nor Muller disclose all features of claim 1 and the Office fails to provide sufficient motivation to modify these references so as to reach all features of claim 1.

To overcome the inadequacies of Hamstra and Muller, the Office cites Lawrence. The Office relies on Lawrence for disclosure of Dexferrum particle sizes. Lawrence is a generic reference directed to treatment of iron deficiency anemia with a ferric oxyhydroxide-dextran composition (i.e., Dexferrum). The maximum disclosed single unit dosage in Lawrence is 100 mg (see column 10., lines 27-31; column 12, lines 33-36).

But the Office fails to show that Lawrence in any way discloses "a single dosage unit of at least about 0.6 grams of elemental iron" or administration "in about 15 minutes or less", as recited in claim 1, and by way of dependency claim 17. Nor does the Office show that Lawrence in any way provides a reason to modify cited references so as to reach all features of claim 1, and by way of dependency claim 17.

For at least the above reasons, claim 17 is not obvious over Hamstra, Muller, and Lawrence.

Nonstatutory Double Patenting Rejection over US 7,754,702

Claims 1-20 are provisional rejected as being unpatentable over claims 1-57 of US Pat No 7,754,702 (Docket No. 30015730-0043). In the interest of furthering prosecution, a terminal disclaimer is filed herewith in the present application over US Pat No 7,754,702. It is noted that filing of the terminal disclaimer is not an admission of the propriety of the rejection and raises neither a presumption nor estoppel on the merits of the rejection. *See Quad Envi-ronmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991).

Nonstatutory Double Patenting Rejection over US 8,431,549

Claims 1-12 and 15-20 are provisional rejected as being unpatentable over claims 1-23 of US Pat No 8,431,549 (Docket No. 30015730-0053). In the interest of furthering prosecution, a terminal disclaimer is filed herewith in the present application over US Pat No 8,431,549 . It is noted that filing of the terminal disclaimer is not an admission of the propriety of the rejection and raises neither a presumption nor estoppel on the merits of the rejection. *See Quad Envi-ronmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991).

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 petition the Office for a one (1) month extension of time and submit herewith the requisite extension fee paid by credit card via EFS-Web. The Commissioner is hereby authorized to deduct any deficiency not covered by this credit card payment or credit any overpayment to Deposit Account No. 19-3140.

Respectfully submitted,

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ATTORNEYS FOR APPLICANT

Electronic Patent Application Fee Transmittal

Application Number:	14100717
Filing Date:	09-Dec-2013
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Filer:	Kathleen E. Chaffee
Attorney Docket Number:	30015730-0065

Filed as Large 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:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	200	200

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**200**

Electronic Acknowledgement Receipt	
EFS ID:	19252849
Application Number:	14100717
International Application Number:	
Confirmation Number:	2813
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	Kathleen E. Chaffee
Filer Authorized By:	
Attorney Docket Number:	30015730-0065
Receipt Date:	09-JUN-2014
Filing Date:	09-DEC-2013
Time Stamp:	18:10:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$200
RAM confirmation Number	5129
Deposit Account	
Authorized User	

File Listing:

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

1		ROA_to_OA_07Feb2014_30015730-0065.pdf	190644 2ecb116c1dcea3d4a7917f5212a0046f18d06e65	yes	19

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	19

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30261 eee26771910e6aa8a6000d2f0741ec75b284fac8	no	2

Warnings:

Information:

Total Files Size (in bytes):	220905

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<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/100,717	Filing Date 12/09/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 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	

APPLICATION AS AMENDED – PART II

AMENDMENT	06/09/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

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

LIE
/CAROL BARNES/

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

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	14/100,717
Filing Date	09 December 2013
First Named Inventor	Mary Jane Helenek et al.
Art Unit	1673
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0065

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
	1.	US- 7,871,597	01-18-2011	Groman et al.	
	2.	US- 2003/0232084 A1	12-18-2003	Groman et al.	
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Number 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, 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.**

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Electronic Patent Application Fee Transmittal	
Application Number:	14100717
Filing Date:	09-Dec-2013
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Filer:	Christopher Lee Marion/Connie Payne
Attorney Docket Number:	30015730-0065
Filed as Large 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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

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EFS ID:	18875508
Application Number:	14100717
International Application Number:	
Confirmation Number:	2813
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	Christopher Lee Marion/Connie Payne
Filer Authorized By:	Christopher Lee Marion
Attorney Docket Number:	30015730-0065
Receipt Date:	28-APR-2014
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1	Transmittal Letter	IDS_Transmittal_30015730-0065_filed_28APR14.pdf	118786 6a71b2f0c56b7bbf7d471209fea8c8a25731f791	no	2
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2	Information Disclosure Statement (IDS) Form (SB08)	SB08_30015730-0065_filed_28APR14.pdf	217853 04c7ad8bc83d9ab26fc862930883b716a4d36c2c	no	1
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **14/100,717**	Examiner: **Jonathan S. Lau**
Applicant: **Luitpold Pharmaceuticals, Inc.**	Group Art Unit: **1673**
Filed: **9 December 2013**	Confirmation No.: **2813**
Docket No.: **30015730-0065**	Customer No.: **26263**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	

28 April 2014

FILED VIA EFS WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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UNDER 37 C.F.R. § 1.97(c)

Sir:

In accordance with the provisions of 37 C.F.R. § 1.56, Applicant requests citation and examination of the references identified on the attached PTO-SB08A form, 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 the mailing of a first Office action on the merits.

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statement under § 1.97(c). The Commissioner is hereby authorized to charge any additional fees that may be required or credit any overpayments to Dentons US LLP Deposit Account No. 19-3140.

Respectfully submitted,

28 April 2014
Date

/Chris L. Marion/
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/100,717	12/09/2013	Mary Jane Helenek	30015730-0065

CONFIRMATION NO. 2813

26263
DENTONS US LLP
P.O. BOX 061080
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Title:METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

Publication No.US-2014-0099381-A1
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 4

Complete if Known	
Application Number	14/100,717
Filing Date	09 December 2014
First Named Inventor	Mary Jane Helenek
Art Unit	1673
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0065

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
	1.	US-6599498	07-29-2003	Groman et al.	
	2.	US-6960571	11-01-2005	Helenek et al.	
		US-			
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Number 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]
	3.	CA 2493806	05-06-2004	Vifor (International) AG		☐
	4.	KR 10-2005-0070014	07-05-2005	Vifor Int. AG		☐
	5.	#WO 1997/011711	04-03-1997	Luitpold Pharmaceuticals, Inc.		☐
	6.	#WO 2007/023154	03-01-2007	Vifor (International) AG		☐

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Art Unit	1673
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0065

OTHER ITEMS – 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]
	7.	#ANDERSSON, Clinical investigations on a new intramuscular haematinic, British Medical Journal, 1961, pp. 275-279, Vol. 2.	
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Art Unit	1673
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0065

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	20.	European Search Report dated 08 July 2013 in related European Application No. EP 13166988.9 filed 08 May 2013, 8 pages.	
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	33.	#SIPE et al., Brain iron metabolism and neurodegenerative disorders, Dev Neurosci, 2002, pp. 188-196, Vol. 24, No. 2-3.	
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(30) **102 49 552.1 DE 23.10.2002**

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(54) COMPLEXES FER/HYDRATE DE CARBONE HYDROSOLUBLES, LEUR PRODUCTION ET MEDICAMENTS CONTENANT CES COMPLEXES

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

(57)

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.

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(71) Demandeur/Applicant:
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(54) Titre : COMPLEXES FER/HYDRATE DE CARBONE HYDROSOLUBLES, LEUR PRODUCTION ET MEDICAMENTS CONTENANT CES COMPLEXES

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

(57) Abrégé/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.

Abstract

Water soluble iron carbohydrate complex obtainable from an aqueous solution of iron(III) salt and an aqueous solution of the oxidation product of one or more maltrodextrins using an aqueous hypochlorite solution at a pH-value within the alkaline range, where, 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 of the mixture lies between 5 and 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between 2 and 40, process for its production and medicament for the treatment and prophylaxis of iron deficiency conditions.

Vifor (International) AG

Aqueous iron carbohydrate complexes, their production and medicaments containing them

The present invention concerns water-soluble iron carbohydrate complexes which are used for the treatment of iron deficiency anaemia, their preparation, medicaments containing them and their use for the prophylaxis or treatment of iron deficiency anaemia. The medicaments are especially useful for parenteral application.

Iron deficiency anaemia can be treated or prophylactically treated by the application of medicaments containing iron. In this respect the use of iron carbohydrate complexes is known. A water soluble iron (III) hydroxide sucrose complex is a frequently and successfully used preparation (Danielson, Salmonson, Derendorf, Geisser, Drug Res., Vol. 46: 615 – 621, 1996). It is also known in the art to use, for parenteral application, iron dextran complexes as well as complexes based on pullulans (WO 02/46241), which are difficult to obtain and have to be produced under pressure at high temperatures and involving hydrogenating steps. Other iron carbohydrate complexes are also known for oral application.

The problem to be solved by the present invention is to provide an iron preparation which is especially to be applied parenterally and which can easily be sterilized; the known parenterally applicable preparations on the basis of sucrose and dextran were only stable at temperatures up to 100 °C, which made sterilisation difficult. Further, the preparation to be provided by the invention shall have reduced toxicity and shall avoid dangerous anaphylactic shocks which can be induced by dextran. Also, the stability of the complexes of the preparation shall be high in order to enable a high applicable dosage and a high rate of application. Furthermore, the iron preparation is to be producible from easily obtainable starting products and without great effort.

In accordance with the present invention the problem can be solved by providing iron (III) carbohydrate complexes on the basis of the oxidation products of maltodextrins. Therefore, an object of the present invention are water soluble iron carbohydrate complexes which are obtainable from an aqueous solution of an iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins, using an aqueous hypochlorite solution at an alkaline pH-value of e.g. 8 to 12 where, 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 of the mixture lies between 5 and 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between 2 and 40.

A further object of the present invention is a process for producing the iron carbohydrate complexes according to the invention wherein one or more maltodextrins are oxidized in an aqueous solution at an alkaline pH-value of e.g. 8 to 12 using an aqueous hypochlorite solution and reacting the obtained solution with an aqueous solution of an iron (III) salt where, 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 of the mixture lies between 5 and 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between 2 and 40.

The usable maltodextrins are easily obtainable starting products, and they are commercially available.

In order to prepare the ligands of the complexes of the invention, the maltodextrins are oxidized in an aqueous solution with a hypochlorite solution. Suitable examples are solutions of alkali hypochlorites such as a solution of sodium hypochlorite. Commercially available solutions can be used. The concentration of the hypochlorite solution is, e.g. at least 13 % by weight, preferably in the order of 13 to 16 % by weight, calculated as active chlorine. Preferably the solutions are used in such an amount that

about 80 to 100 %, preferably about 90 % of one aldehyde group per molecule of maltodextrin is oxidized. In this manner, the reactivity caused by the glucose content of the maltodextrin molecules is lowered to 20% or less, preferably to 10% or less.

The oxidation is carried out in an alkaline solution, e.g. at a pH of 8 to 12, for example 9 to 11. As an example, oxidation can be carried out at temperatures in the order of 15 to 40 °C, preferably of 25 to 35 °C. The reaction times are, e.g. in the order of 10 minutes to 4 hours, e.g. 1 to 1.5 hours.

By this procedure the degree of depolymerisation of the starting maltodextrins is kept at a minimum. Only theoretically it is assumed that the oxidation occurs mainly at the terminal aldehyde group (acetal or semiacetal group respectively) of the maltodextrin molecules.

It is also possible to catalyse the oxidation reaction of the maltodextrins. The addition of bromide ions is suitable, e.g. in the form of alkali bromides, for example sodium bromide. The added amount of bromide is not critical. The amount is kept as low as possible in order to achieve an end product (Fe-complex) which can easily be purified. Catalytic amounts are sufficient. As stated above, the addition of bromide is possible, however, not necessary.

Further, it is also possible to use other oxidation systems, such as e.g. the known ternary oxidation system hypochlorite/alkali bromide/2,2,6,6,-tetramethypiperidine-1-oxyl (TEMPO) for the oxidation of the maltodextrins. The process to oxidize maltodextrins catalytically with alkali bromides or with the ternary TEMPO system is described e.g. by Thaburet et al in Carbohydrate Research 330 (2001) 21 – 29, which method can be used for the present invention.

In order to prepare the complexes of the invention the obtained oxidized maltodextrins are reacted with an iron (III) salt in an aqueous solution. In order to do so, the oxidized maltodextrins can be isolated and

redissolved; however, it is also possible to use the obtained aqueous solutions of the oxidized maltodextrins directly for the further reaction with the aqueous iron (III) solutions.

Water soluble salts of inorganic or organic acids, or mixtures thereof, such as halides, e.g. chloride and bromide or sulfates can be used as iron (III) salts. It is preferred to use physiologically acceptable salts. It is especially preferred to use an aqueous solution of iron (III) chloride.

It has been found that the presence of chloride ions favours the formation of the complexes. The chloride ions can be used in the form of water soluble chlorides such as alkali metal chlorides, e.g. sodium chloride, potassium chloride or ammonium chloride. As stated, the iron (III) is preferably used in the form of the chloride.

For instance, the aqueous solution of the oxidized maltodextrin can be mixed with an aqueous solution of the iron (III) salt in order to carry out the reaction. Here, it is preferred to proceed in a manner so that during and immediately after mixing of the oxidized maltodextrin and the iron (III) salt, the pH is strongly acid or so low that no hydrolysis of the iron (III) salt occurs, e.g. 2 or less, in order to avoid an undesired precipitation of iron hydroxides. In general, it is not necessary to add an acid, if iron (III) chloride is used, since aqueous solutions of iron (III) chloride can be sufficiently acid. Only after mixing, the pH is raised to values of e.g. in the order of at least 5, for example up to 11, 12, 13 or 14. The pH is preferably raised slowly or gradually which, for example, can be achieved by first adding a weak base, for example, up to a pH of about 3, and then neutralizing further using a stronger base. Examples of weak bases are alkali – or alkaline earth - carbonates, bicarbonates, such as sodium and potassium carbonate or bicarbonate, or ammonia. Examples of strong bases are alkali – or alkaline earth - hydroxides such as sodium, potassium, calcium or magnesium hydroxide.

The reaction can be improved by heating. For example, temperatures in the order of 15 °C up to boiling point can be used. It is preferred to raise

the temperature gradually. Thus, for example, it is possible to heat to about 15 to 70 °C and then raise the temperature gradually up to boiling point.

The reaction times are, for example, in the order of 15 minutes up to several hours, e.g. 20 minutes to 4 hours, such as 25 to 70 minutes, e.g. 30 to 60 minutes.

The reaction can be carried out in a weakly acid range, for example, at a pH in the order of 5 to 6. However, it has been found, that it is useful, but not necessary, to raise the pH during the formation of the complexes to higher values of up to 11, 12, 13 or 14. In order to complete the reaction, the pH can be lowered then by addition of an acid, for example, to the order of 5 to 6. It is possible to use inorganic or organic acids or mixture thereof, especially hydrogen halide acids such as hydrogen chloride or aqueous hydrochloric acid respectively.

As stated above, the formation of the complexes is usually improved by heating. Thus, at the preferred embodiment of the invention, wherein the pH is raised during the reaction to ranges of at least 5 and above up to 11 or 14, it is, for instance, possible to work at first at lower temperatures in the order of 15 to 70°C, such as 40 to 60°C, e.g. about 50 °C, whereafter the pH is reduced to values in the order of at least 5 and the temperature is gradually raised over 50 °C up to boiling point.

The reaction times are in the order of 15 minutes up to several hours and they can vary depending on the reaction temperature. If the process is carried out with an intermediate pH of more than 5, it is, for example, possible to work 15 to 70 minutes, e.g. 30 to 60 minutes, at the enhanced pH, for example at temperatures of up to 70°C, whereafter the pH is lowered to a range in the order of at least 5 and the reaction is carried out for a further 15 to 70 minutes, e.g. 30 to 60 minutes, at temperatures e.g. up to 70°C, and optionally a further 15 to 70 minutes, e.g. 30 to 60 minutes, at higher temperatures up to boiling point.

After the reaction the obtained solution can be cooled to e.g. room temperature and can optionally be diluted and optionally be filtered. After cooling, the pH can be adjusted to the neutral point or a little below, for example, to values of 5 to 7, by the addition of an acid or base. It is possible to use e.g. the acids and bases which have been mentioned for carrying out the reaction. The solutions obtained are purified and can directly be used for the production of medicaments. However, it is also possible to isolate the iron (III) complexes from the solution e.g. by precipitation with an alcohol such as an alkanol, for example, ethanol. Isolation can also be effected by spray-drying. Purification can take place in the usual way, especially in order to remove salts. This can, for example, be carried out by reverse osmosis. It is, for example, possible to carry out the reverse osmosis before spray-drying or before a direct application in medicaments.

The iron content of the obtained iron (III) carbohydrate complexes is, for example, 10 to 40 % weight/weight, especially, 20 to 35 % weight/weight. They can easily be dissolved in water. It is possible to prepare neutral aqueous solutions which, e.g. have an iron content of 1 % weight/vol. to 20 % weight/vol. Such solutions can be sterilised thermically. The weight average molecular weight mw of the obtained complexes, is, for example, 80 kDa to 400 kDa, preferably 80 kDa to 350 kDa, especially preferred up to 300 kDa (measured by gel permeation chromatography, e.g. as described by Geisser et al, in Arzneim. Forsch/Drug Res. 42(II), 12, 1439-1452 (1992), paragraph 2.2.5).

As stated above, it is possible to provide aqueous solutions from the complexes of the invention. These solutions are especially useful for parenteral application. However, it is also possible to apply them orally or topically. Contrary to the known parenterally applicable iron preparations they can be sterilized at high temperatures, e.g. at 121 °C and above, at short contact times of, e.g. 15 minutes, by acquiring $F_0 \geq 15$. The contact times are correspondingly shorter at higher temperatures. Preparations hitherto known had to be sterilely filtrated and mixed with preservatives, such as benzyl alcohol or phenol. Such

additives are not necessary in the invention. Hence, it is possible to fill the solutions of the complexes, for example, into ampoules. It is, for example, possible, to fill solutions having a content of 1 to 20 % by weight, e.g. 5 % by weight, into vessels such as ampoules or phials of e.g. 2 to 100 ml, e.g., up to 50 ml. The preparation of the parenterally applicable solutions can be carried out as known in the art, optionally using additives which are normally used for parenteral solutions. The solutions can be formulated in such a way that they can be administered by injection or in the form of an infusion, e.g., in brine solution. For the oral or topical application it is possible to formulate preparations with usual excipients and additives.

Thus, a further object of the invention are aqueous medicaments which are especially useful for the parenteral, intravenous but also intramuscular application as well as for the oral or topical application; they are especially useful for the treatment of iron deficiency anaemia. A further object of the invention is also the use of the iron (III) carbohydrate complexes according to the invention for the treatment and prophylaxis of iron deficiency anaemia or the production of medicaments especially for the parenteral treatment iron deficiency anaemia. The medicaments can be used in human and veterinary medicine.

The advantages which are achieved with the iron (III) carbohydrate complexes of the invention are the above-mentioned high sterilisation temperatures as well as the low toxicity and the reduced danger of anaphylactic shock. The toxicity of the complexes according to the invention is very low. The LD_{50} lies at over 2000 mg Fe/kg, compared to the LD_{50} of the known pullulan complexes, which lies at 1400 mg Fe/kg. In view of the high stability of the complexes of the invention, it is possible to enhance the rates of application as well as the dosages. Thus, it is possible to apply the medicaments of the invention parenterally in the form of a single dose. Such a single dose is, for example, 500 to 1000 mg iron; it can be applied, for example, during the course of one hour. A further advantage lies in the high degree of

availability of the maltodextrins used as starting products, which are, e.g., commercially available additives in the food processing industry.

In the present description, as well as in the following examples, the dextrose equivalents are measured gravimetrically. In order to do so, the maltodextrins are reacted in a boiling aqueous solution with Fehling's solution. The reaction is carried out quantitatively, i.e. until the Fehling's solution is no longer discoloured. The precipitated copper (I) oxide is dried at 105°C until a constant weight is achieved and measured gravimetrically. The glucose content (dextrose equivalent) is calculated from the obtained results as % weight/weight of the maltodextrin dry substance. It is, for example, possible to use the following solutions: 25 ml Fehling's solution I, mixed with 25 ml Fehling's solution II; 10 ml aqueous maltodextrin solution (10 % mol/vol) (Fehling's solution I: 34.6 g copper (II) sulfate dissolved in 500 ml water; Fehling's solution II: 173 g potassium sodium tartrate and 50 g sodium hydroxide dissolved in 400 ml water).

Example 1

100 g maltodextrin (9.6 dextrose equivalent measured gravimetrically) are dissolved by stirring in 300 ml water at 25 °C and oxidized by addition of 30 g sodium hypochlorite solution (13 to 16 weight percent active chlorine) at pH 10.

At first, the oxidized maltodextrin solution and then 554 g sodium carbonate solution (17.3 % weight/weight) are added at room temperature to 352 g of a stirred iron (III) chloride solution (12 % weight by weight Fe).

Then, the pH is adjusted to 11 by addition of sodium hydroxide and the solution is heated to 50 °C and kept at 50 °C for 30 minutes. Then, acidification to a pH of 5 to 6 is effected by addition of hydrochloric acid, the solution is kept at 50 °C for a further 30 minutes and then heated to 97 - 98 °C and the temperature is kept for 30 minutes at this

range. After cooling the solution to room temperature, the pH is adjusted to 6 - 7 by the addition of sodium hydroxide.

The solution is then filtered through a sterilisation filter and then examined for sediments. Thereafter, the complex is isolated by precipitation with ethanol in a range of 1 : 0.85 and then dried in vacuum at 50 °C.

The yield is 125 g (corresponding to 87 % of the theoretical value) of a brown amorphic powder having an iron content of 29.3 % weight/weight (measured complexometrically).

Molecular weight mw 271 kDa.

Example 2

200 g maltodextrin (9.6 dextrose equivalent measured gravimetrically) are dissolved by stirring in 300 ml water at 25 °C and oxidized by addition of 30 g sodium hypochlorite solution (13 to 16 weight percent active chlorine) at pH 10.

At first the oxidized maltodextrin solution and then 554 g sodium carbonate solution (17.3 % weight/weight) are added at room temperature to 352 g of a stirred iron (III) chloride solution (12 % weight by weight Fe).

Then the pH is adjusted to 11 by addition of sodium hydroxide and the solution is heated to 50 °C and kept for 30 minutes at 50 °C. Then, acidification to a pH of 5 to 6 is effected by addition of hydrochloric acid, the solution is kept at 50 °C for a further 30 minutes and then heated to 97 - 98 °C and the temperature is kept for 30 minutes at this range. After cooling the solution to room temperature the pH is adjusted to 6 - 7 by the addition of sodium hydroxide.

The solution is then filtered through a sterilisation filter and then examined for sediments. Thereafter, the complex is isolated by precipitation with ethanol in a range of 1 : 0.85 and then dried in vacuum at 50 °C.

The yield is 123 g (corresponding to 65 % of the theoretical value) of a brown amorphic powder having an iron content of 22.5 % weight/weight (measured complexometrically).

Molecular weight mw 141 kDa.

Example 3

100 g maltodextrin (9.6 dextrose equivalent measured gravimetrically) are dissolved by stirring in 300 ml water at 25 °C and oxidized by addition of 30 g sodium hypochlorite solution (13 to 16 weight percent active chlorine) and 0.7 g sodium bromide at pH 10.

At first the oxidized maltodextrin solution and then 554 g sodium carbonate solution (17.3 % weight/weight) are added at room temperature to 352 g of a stirred iron (III) chloride solution (12 % weight by weight Fe).

Then the pH is adjusted to 6.5 by addition of sodium hydroxide and the solution is heated to 50 °C and kept for 60 minutes at 50 °C. Then, acidification to a pH of 5 to 6 is effected by addition of hydrochloric acid, the solution is kept at 50 °C for a further 30 minutes and then heated to 97 - 98 °C and the temperature is kept for 30 minutes at this range. After cooling the solution to room temperature the pH is adjusted to 6 - 7 by the addition of sodium hydroxide.

The solution is then filtered through a sterilisation filter and then examined for sediments. Thereafter, the complex is isolated by precipitation with ethanol in a range of 1 : 0.85 and then dried in vacuum at 50 °C.

The yield is 139 g (corresponding to 88 % of the theoretical value) of a brown amorphic powder having an iron content of 26.8 % weight/weight (measured complexometrically).

Molecular weight mw 140 kDa.

Example 4

A mixture of 45 g maltodextrin (6.6 dextrose equivalent measured gravimetrically) and 45 g maltodextrin (14.0 dextrose equivalent measured gravimetrically) is dissolved by stirring in 300 ml water at 25 °C and oxidized by addition of 25 g sodium hypochlorite solution (13 to 16 weight percent active chlorine) and 0.6 g sodium bromide at pH 10.

At first the oxidized maltodextrin solution and then 554 g sodium carbonate solution (17.3 % weight/weight) are added at room temperature to 352 g of a stirred iron (III) chloride solution (12 % weight by weight Fe).

Then the pH is adjusted to 11 by addition of sodium hydroxide and the solution is heated to 50 °C and kept for 30 minutes at 50 °C. Then, acidification to a pH of 5 to 6 is effected by addition of hydrochloric acid, the solution is kept at 50 °C for a further 30 minutes and then heated to 97 - 98 °C and the temperature is kept for 30 minutes at this range. After cooling the solution to room temperature the pH is adjusted to 6 - 7 by the addition of sodium hydroxide.

The solution is then filtered through a sterilisation filter and then examined for sediments. Thereafter, the complex is isolated by precipitation with ethanol in a range of 1 : 0.85 and then dried in vacuum at 50 °C.

The yield is 143 g (corresponding to 90 % of the theoretical value) of a brown amorphic powder having an iron content of 26.5 % weight/weight (measured complexometrically).

Molecular weight mw 189 kDa.

Example 5

90 g maltodextrin (14.0 dextrose equivalent measured gravimetrically) are dissolved by stirring in 300 ml water at 25 °C and oxidized by addition of 35 g sodium hypochlorite solution (13 to 16 weight percent active chlorine) and 0.6 g sodium bromide at pH 10.

At first, the oxidized maltodextrin solution and then 554 g sodium carbonate solution (17.3 % weight/weight) are added at room temperature to 352 g of a stirred iron (III) chloride solution (12 % weight by weight Fe).

Then the pH is adjusted to 11 by addition of sodium hydroxide and the solution is heated to 50 °C and kept for 30 minutes at 50 °C. Then, acidification to a pH of 5 to 6 is effected by addition of hydrochloric acid, the solution is kept at 50 °C for a further 30 minutes and then heated to 97 - 98 °C and the temperature is kept for 30 minutes at this range. After cooling the solution to room temperature the pH is adjusted to 6 - 7 by the addition of sodium hydroxide.

The solution is then filtered through a sterilisation filter and then examined for sediments. Thereafter, the complex is isolated by precipitation with ethanol in a range of 1 : 0.85 and then dried in vacuum at 50 °C.

The yield is 131 g (corresponding to 93 % of the theoretical value) of a brown amorphic powder having an iron content of 29.9 % weight/weight (measured complexometrically).

Molecular weight mw 118 kDa.

Example 6

A mixture of 45 g maltodextrin (5.4 dextrose equivalent measured gravimetrically) and 45 g maltodextrin (18.1 dextrose equivalent measured gravimetrically) is dissolved by stirring in 300 ml water at 25 °C and oxidized by addition of 31 g sodium hypochlorite solution (13 to 16 weight percent active chlorine) and 0.7 g sodium bromide at pH 10.

At first the oxidized maltodextrin solution and then 554 g sodium carbonate solution (17.3 % weight/weight) are added at room temperature to 352 g of a stirred iron (III) chloride solution (12 % weight by weight Fe).

Then the pH is adjusted to 11 by addition of sodium hydroxide and the solution is heated to 50 °C and kept for 30 minutes at 50 °C Then, acidification to a pH of 5 to 6 is effected by addition of hydrochloric acid, the solution is kept at 50 °C for a further 30 minutes and then heated to 97 - 98 °C and the temperature is kept for 30 minutes at this range. After cooling the solution to room temperature the pH is adjusted to 6 - 7 by the addition of sodium hydroxide.

The solution is then filtered through a sterilisation filter and then examined for sediments. Thereafter, the complex is isolated by precipitation with ethanol in a range of 1 : 0.85 and then dried in vacuum at 50 °C.

The yield is 134 g (corresponding to 88 % of the theoretical value) of a brown amorphic powder having an iron content of 27.9 % weight/weight (measured complexometrically).

Molecular weight mw 178 kDa.

Example 7

100 g maltodextrin (9.6 dextrose equivalent measured gravimetrically) are dissolved by stirring in 300 ml water at 25 °C and oxidized by addition of 29 g sodium hypochlorite solution (13 to 16 weight percent active chlorine) and 0.7 g sodium bromide at pH 10.

At first the oxidized maltodextrin solution and then 554 g sodium carbonate solution (17.3 % weight/weight) are added at room temperature to 352 g of a stirred iron (III) chloride solution (12 % weight by weight Fe).

Then the pH is adjusted to 11 by addition of sodium hydroxide and the solution is heated to 50 °C and kept for 30 minutes at 50 °C. Then, acidification to a pH of 5 to 6 is effected by addition of hydrochloric acid, the solution is kept at 50 °C for a further 70 minutes. After cooling the solution to room temperature the pH is adjusted to 6 - 7 by the addition of sodium hydroxide.

The solution is then filtered through a sterilisation filter and then examined for sediments. Thereafter, the complex is isolated by precipitation with ethanol in a range of 1 : 0.85 and then dried in vacuum at 50 °C.

The yield is 155 g (corresponding to 90 % of the theoretical value) of a brown amorphic powder having an iron content of 24.5 % weight/weight (measured complexometrically).

Molecular weight mw 137 kDa.

Example 8

126 g maltodextrin (6.6 dextrose equivalent measured gravimetrically) are dissolved by stirring in 300 ml water at 25 °C and oxidized by

addition of 24 g sodium hypochlorite solution (13 to 16 weight percent active chlorine) and 0.7 g sodium bromide at pH 10.

At first the oxidized maltodextrin solution and then 554 g sodium carbonate solution (17.3 % weight/weight) are added at room temperature to 352 g of a stirred iron (III) chloride solution (12 % weight by weight Fe).

Then the pH is adjusted to 11 by addition of sodium hydroxide and the solution is heated to 50 °C and kept for 30 minutes at 50 °C. Then, acidification to a pH of 5 to 6 is effected by addition of hydrochloric acid, the solution is kept at 50 °C for a further 70 minutes. After cooling the solution to room temperature the pH is adjusted to 6 - 7 by the addition of sodium hydroxide.

The solution is then filtered through a sterilisation filter and then examined for sediments. Thereafter, the complex is isolated by precipitation with ethanol in a range of 1 : 0.85 and then dried in vacuum at 50 °C.

The yield is 171 g (corresponding to 86 % of the theoretical value) of a brown amorphic powder having an iron content of 21.35 % weight/weight (measured complexometrically).

Molecular weight mw 170 kDa.

Comparative test

In the following the characteristics of the iron carbohydrate complexes are compared with a commercially available iron sucrose complex. It can be seen that the iron content can be enhanced, the thermal treatment can be carried out at higher temperatures and the toxicity (LD_{50}) can be lowered in accordance with the invention.

	According to the invention	Iron hydroxide/sucrose complex
Fe content [%]	5.0	2.0
pH	5 - 7	10.5 – 11.0
mw [kDa][1]	80 - 350	34 - 54
Thermal treatment	121 °C/15'	100 °C/35'
LD_{50} i.v., w.m. [mg Fe/kg body weight]	> 2000	> 200

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Claims

1. Water soluble iron carbohydrate complex obtainable from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltrodextrins using an aqueous hypochlorite solution at a pH-value within the alkaline range, where, 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 of the mixture lies between 5 and 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between 2 and 40.

2. A process for producing an iron carbohydrate complex according to claim 1, wherein one or more maltrodextrins are oxidized in an aqueous solution at an alkaline pH-value using an aqueous hyprochlorite solution and the obtained solution is reacted with an aqueous solution of an iron (III) salt, where, 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 of the mixture lies between 5 and 20 and the dextrose equivalent of each individual maltodextrins contained in the mixture lies between 2 and 40.

3. A process according to claim 2, characterized in that the oxidation of the maltodextrin or the maltodextrins is carried out in the presence of bromide ions.

4. A process according to claim 2 or 3, characterized in that the iron (III) chloride is used as the iron (III) salt.

5. A process according to claims 2, 3 or 4, characterized in that the oxidized maltrodextrin and the iron (III) salt are mixed to form an aqueous solution having a pH-value so low that no hydrolysis of the iron (III) salt occurs, whereafter the pH is raised to 5 to 12 by the

addition of a base.

6. A process according to any of claims 3 to 5, characterized in that the reaction is carried out at a temperature of 15 °C up to boiling point for 15 minutes up to several hours.

7. A medicament containing an aqueous solution of an iron carbohydrate complex according to claim 1 or 2 or obtained in accordance with any of claims 3 to 6.

8. A medicament according to claim 7 formulated for parenteral or oral application.

9. Use of the iron carbohydrate complexes according to claim 1, or obtained in accordance with any of claims 2 to 6, for the therapy or prophylaxis of iron deficiency.

10. Use of the iron carbohydrate complexes according to claim 1, or obtained in accordance with any of claims 2 to 6, for the production of a medicament for therapy or prophylaxis of iron deficiency.

11. Water-soluble iron carbohydrate complex according to claim 1 for therapy or prophylaxis of iron deficiency.

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(54) 수용성 철-탄수화물 복합체, 그의 제조 방법 및 상기복합체를 함유하는 약제

요약

알칼리성 pH 값 범위의 차아염소산염 수용액을 사용하여 철(III)염 수용액 및 1종 이상의 말토덱스트린 산화 생성물로부터 얻을 수 있는 수용성 철-탄수화물 복합체가 개시되는데, 상기 말토덱스트린의 덱스트로스 당량 범위는 1종의 말토덱스트린이 이용되는 경우 5 내지 20이며, 한편 수종의 말토덱스트린으로 이루어진 혼합물의 덱스트로스 당량 범위는 5 내지 20이고, 상기 수종의 말토덱스트린 혼합물이 이용되는 경우, 상기 혼합물 중에 함유된 각각의 말토덱스트린의 덱스트로스 당량 범위는 2 내지 40이다. 또한, 철분 결핍증의 치료 및 예방을 위한 상기 복합체 및 약제의 제조 방법도 개시되어 있다.

색인어

철-탄수화물 복합체

명세서

기술분야

본 발명은 철분 결핍성 빈혈 치료용 수용성 철 탄수화물 복합체, 이것의 제조 방법, 이를 함유하는 약제 및 철분 결핍성 빈혈의 예방 또는 치료를 위한 그의 용도에 관한 것이다. 상기 약제는 특히 비경구성 투여에 유용하다.

배경기술

철분 결핍성 빈혈은 철분 함유 약제를 투여함으로써 치료되거나 또는 예방 치료될 수 있다. 이에 관해서는 철 탄수화물 복합체를 사용하는 것이 알려져 있다. 수용성 수산화철[III]-수크로스 복합체가 흔히 성공적으로 이용되고 있는 제제이다(Danielson, Salmonson, Derendorf, Geisser, Drug Res., Vol. 46:615-621, 1995). 또한, 이 기술 분야에서는 비경구 투여용으로 철-덱스트란 복합체는 물론 푸루란계 복합체(WO 제02/46241호)를 사용하는 것도 익시 알려져 있는데, 이들은 얻기가 어려우며 수소 첨가 공정을 비롯한 고온 가압하에서 생성시켜야 한다. 또한, 기타 철 탄수화물 복합체들도 경구 투여용으로 알려져 있다.

본 발명이 해결하고자 하는 할 문제점은 특히 비경구 투여되어야 하고 열균이 용이한 철분 제제를 제공하기 위한 것이다. 기존의 비경구 투여 가능한 수크로스 및 덱스트란계 제제는 100℃ 이하의 온도에서만 안정하므로 멸균시키기가 어려웠다. 나아가, 본 발명이 제공하고자 하는 제제는 독성이 감소되고, 덱스트란에 의하여 유도될 수 있는 위험한 과민성 쇼크를 방지하는 것이어야 한다. 또한, 상기 제제의 복합체의 안정도를 높여서 적용 가능한 투여량을 높이고 투여율을 높일 수 있도록 하여야 한다. 나아가, 상기 철분 제제는 큰 노력을 들이지 않고 용이하게 구득할 수 있는 출발 물질로부터 제조될 수 있어야 한다.

발명의 상세한 설명

본 발명에 따르면 상기 문제점은 말토덱스트린의 산화 생성물에 기초한 철 [III]-탄수화물 복합체를 제공함으로써 해결될 수 있다. 따라서, 본 발명의 목적은알칼리성, 예컨대 pH 8 내지 12의 차아염소산염 수용액을 사용하여, 철[III]염 수용액 및 1종 이상의 말토덱스트란 산화 생성물 수용액으로부터 생성될 수 있는 수용성 철[III]-탄수화물 복합체인데, 1종의 말토덱스트린이 사용되는 경우, 그의 덱스트로스 당량은 5 내지 20 이고, 수종의 말토덱스트린의 혼합물이 사용되는 경우, 그 혼합물의 덱스트로스 당량은 5 내지 20 이며, 상기 혼합물 중에 함유된 각각의 말토덱스트린의 덱스트로스 당량은 2 내지 40 이다.

본 발명의 또 한 가지 목적은 1종 이상의 말토덱스트린을 알칼리성 pH 값, 예컨대 pH 8 내지 12의 차아염소산 수용액 중에서 산화시켜 본 발명에 따른 상기 철-탄수화물 복합체의 제조 방법을 제공하는 것이며, 이 때 1종의 말토덱스트린이 사용되는 경우, 그의 덱스트로스 당량은 5 내지 20이고, 수종의 말토덱스트린의 혼합물이 사용되는 경우, 그 혼합물의 덱스트로스 당량은 5 내지 20이며, 상기 혼합물 중에 함유된 각각의 말토덱스트린의 덱스트로스 당량은 2 내지 40이다._

상기 이용 가능한 말토덱스트린은 용이하게 구득할 수 있는 출발 물질이며, 이들은 시판 중에 있다.

본 발명에 의한 복합체의 리간드를 제조하기 위하여, 상기 말토덱스트린을 차아염소산 용액에 의하여 수용액 중에서 산화시킨다. 적절한 예로서는 차아염소산나트륨 용액 등의 차아염소산의 알칼리 금속염 용액이 있다. 시판되는 용액을 사용할 수 있다. 차아염소산 용액의 농도는 활성 염소로 환산시, 예컨대 적어도 13 중량%, 종기로는 13 내지 16 중량%이다. 상기 용액은 말토덱스트린의 분자당 1개의 알데히드기의 약 80 내지 100%, 종기로는 약 90%가 산화되기 위한 양으로 사용되는 것이 좋다. 이러한 방식으로, 상기 말토덱스트린 분자의 글루코스 함량에 의하여 발생되는 반응도는 20% 또는 그 미만, 종기로는 10% 또는 그 미만까지 저하된다.

상기 산화는 예컨대 pH 8 내지 12, 예컨대 9 내지 11의 알칼리성 용액 중에서 수행된다. 예컨대, 산화는 15 내지 40℃, 종기로는 25 내지 35℃의 온도에서 수행될 수 있다. 상기 반응 시간은 예컨대 10분 내지 4시간, 예컨대 1 시간 내지 1.5 시간이다.

이러한 방법에 의하여, 상기 출발 물질인 말토덱스트린의 해중합도(解重合度)는 최소로 유지된다. 이론적으로만 보면, 상기 산화는 주로 말토덱스트린 분자의 말단 알데히드기(각각의 아세탈기 또는 쥰아세탈기)에서 일어나는 것으로 추정된다.

또한, 상기 말토덱스트린의 산화 반응을 촉매시키는 것도 가능하다. 브롬화물 이온을, 예컨대 브롬화나트륨 등의 알칼리 브롬화물 형태로 첨가하는 것이 좋다. 브롬화물의 첨가량은 중요하지 않다. 상기 양은 용이하게 정제될 수 있는 최종 생성물(Fe-목합체)을 얻기 위하여 가능한 한 적게 유지시킨다. 촉매량(접촉량)이 충분한 양이다. 전술한 바와 같이, 브롬화물을 첨가하는 것이 가능하지만 필요한 것은 아니다.

나아가, 상기 말토덱스트린을 산화시키기 위하여, 기타의 산화 반응계, 예컨대 차아염소산염/알칼리 브롬화물/2,2,6,6-테트라메틸피페리딘-1-옥실(TEMPO)으로 된 기지의 삼성분 산화 반응계 등을 사용하는 것도 가능하다. 알칼리 브롬화물 또는 삼성분 TEMPO계를 사용하는 말토덱스트린의 촉매 접촉식 산화 방법은, 예컨대 문헌(Thaburet *et al.*, Carbohydrate Research 330 [2001] 21-29)에 설명되어 있으며, 이 방법은 본 발명에 사용될 수 있다.

상기 생성된 말토덱스트린 산화 생성물을 수용액 중에서 철[III]염과 반응시키면 본 발명의 복합체가 제조된다. 이를 위해서는, 상기 산화 말토덱스트린을 단리시켜 재용해시킬 수도 있으나, 상기 철[III] 수용액과의 후속 반응을 위하여 상기 생성된 말토덱스트린 산화 생성물의 수용액을 직접 사용하는 것도 가능하다.

수용성 무기산염 또는 유기산염, 또는 이들의 혼합물, 예컨대 염화물 및 브롬화물 등의 할로겐화물 또는 황산염이 철[III]염으로서 사용될 수 있다. 생리학적으로 허용되는 염을 사용하는 것이 좋다. 특히 염화철[III]의 수용액을 사용하는 것이 좋다.

염화물 이온의 존재로 상기 복합체의 생성이 조장된다는 사실을 알게 되었다. 상기 염화물 이온은 알칼리 금속 염화물, 예컨대 염화나트륨, 염화칼륨 또는 염화암모늄 등의 수용성 염화물 형태로 사용될 수 있다. 전술한 바와 같이, 상기 철[III]은 염화물 형태로 사용되는 것이 좋다.

예컨대, 상기 말토덱스트린 산화 생성물의 수용액을 상기 철[III]염 수용액과 혼합하여 상기 반응을 수행할 수 있다. 이 때, 상기 말토덱스트린 산화 생성물 및 상기 철[III]염의 혼합 도중 및 혼합 직후, 원하지

양은 철 수산화물의 침전 발생을 방지하기 위하여 철[III]염의 가수 분해가 일어나지 않도록 pH는 강산성으로 하거나 또는 낮은 pH, 예컨대 pH 2 또는 그 이하로 하여 진행시키는 것이 좋다. 일반적으로, 염화철[III]이 이용되는 경우에는, 염화철[III]의 수용액이 충분히 산성일 수 있으므로, 산을 첨가할 필요는 없다. 혼합한 후에만, pH는 예컨대 적어도 5, 예컨대 최대 11, 12, 13 또는 14까지 상승된다. 상기 pH는 서서히 또는 점진적으로 상승되는 것이 좋은데, 이는 우선 약염기를 예컨대 최대 약 3의 pH까지 첨가한 다음, 보다 강한 염기를 더 사용하여 중화시킴으로써 달성될 수 있다. 약염기의 예로서는, 탄산나트륨 및 탄산칼륨 또는 중탄산나트륨 및 중탄산칼륨 등의 알칼리(또는 알칼리토류) 탄산염, 중탄산염, 또는 암모니아를 들 수 있다. 강염기의 예로서는, 수산화나트륨, 수산화칼륨, 수산화칼슘 또는 수산화마그네슘 등의 알칼리(또는 알칼리토류) 수산화물을 들 수 있다.

상기 반응은 가열에 의하여 촉진될 수 있다. 예컨대, 15℃ 내지 최대 비등점까지의 온도가 사용될 수 있다. 온도는 점진적으로 상승시키는 것이 좋다. 따라서, 예컨대 약 15 내지 70℃까지 가열한 다음, 온도를 비등점까지 점진적으로 상승시키는 것이 가능하다.

상기 반응 시간은 예컨대 15분 내지 수 시간 이하, 예컨대 20분 내지 4 시간, 25분 내지 70분, 예컨대 30분 내지 60분이다.

상기 반응은 약한 산성 범위, 예컨대 pH 5 내지 6에서 수행될 수 있다. 그러나, 상기 복합체의 생성 도중에 pH를 보다 높은 값인 최대 11, 12, 13 또는 14까지 상승시키는 것이 유용하지만 필요한 것은 아니라는 사실을 알게 되었다. 상기 반응을 종결시키려면, 이어서 산을 첨가하여 pH를 예컨대 5 내지 6까지 낮출 수 있다. 무기산 또는 유기산 또는 이들의 혼합물, 특히 염화수소 또는 염산 수용액 등의 할로겐화수소산을 사용하는 것이 가능하다.

전술한 바와 같이, 상기 복합체의 생성은 일반적으로 가열에 의하여 촉진된다. 따라서, 반응 중에 pH가 적어도 5 이상 최대 11 또는 14까지 상승하는 본 발명의 양호한 실시 상태에 있어서, 우선 예를 들면 15 내지 70℃의 범위의 저온, 즉 40 내지 60℃, 예컨대 약 50℃에서 수행하는 것이 가능하고, 이 후에 상기 pH는 적어도 5까지 감소되며, 상기 온도는 50℃ 이상 비등점까지 점진적으로 상승된다.

상기 반응 시간은 15분 내지 최대 수 시간이며, 이는 반응 온도에 따라 달라질 수 있다. 상기 방법을 pH 5 이상인 중간 pH에서 수행되는 경우에는, 15분 내지 70분간, 예컨대 30분 내지 60분간 수행하는 것이 가능하며, 높은 pH에서는 예컨대 70℃ 이하의 온도에서 수행하는 것이 가능하고, 이 후에 상기 pH는 적어도 5의 범위로 내려가고, 상기 반응은 예컨대 70℃이하의 온도에서 15분 내지 70분간, 예컨대 30분 내지 60분간 더 수행되며, 필요에 따라 최대 비등점까지의 고온에서 15분 내지 70 분간, 예컨대 30분 내지 60분간 더 수행된다.

상기 반응 후에, 생성된 용액은 예컨대 실온으로 냉각시킬 수 있으며, 필요에 따라 희석 및 여과될 수 있다. 냉각 후에, 산 또는 염기를 첨가하여 pH를 중화점(中和点) 또는 중화점의 다소 아래, 예컨대 5 내지 7까지 조절될 수 있다. 예컨대, 상기 반응을 수행하기 위하여 앞에서 언급하였던 산 및 염기를 사용하는 것이 가능하다. 생성된 용액은 정제 후 약제를 제조하는 데 직접 사용될 수 있다. 그러나, 상기 철[III]-탄수화물 복합체를 알카놀, 예컨대 에탄올 등의 알콜로 침전시켜 그 용액으로부터 단리시키는 것도 역시 가능하다. 또한, 분무 건조에 의하여 단리시킬 수도 있다. 정제는 특히 염류를 제거하기 위하여 통상의 방법으로 수행될 수 있다. 이는 예컨대 역삼투법에 의하여 수행될 수 있다. 예컨대, 분무 건조 전 또는 약제에 직접 적용하기 전에 역삼투법을 수행하는 것이 가능하다.

생성된 철[III]-탄수화물 복합체의 철 함량은 예컨대 10 내지 40 % 중량/중량, 특히 20 내지 35 % 중량/중량이다. 이들은 물 중에 용이하게 용해될 수 있다. 예컨대 철 함량이 1 % 중량/체적 내지 20 % 중량/체적인 중성의 수용액을 제조하는 것이 가능하다. 이러한 용액은 가열에 의하여 멸균 처리될 수 있다. 상기 생성된 복합체의 중량 평균 분자량(mw)은, 예컨대 80 kDa 내지 400 kDa, 좋기로는 80 kDa 내지 350 kDa이며, 특히 300 kDa 이하인 것이 좋다[상기 분자량은, 예컨대 문헌 (Geisser *et al*., Arzneim. Forsch/Drug Res. 42[II], 12, 1439-1452 [1992], paragraph 2.2.5)에 설명되어 있는 겔 투과 크로마토그라피법에 의하여 측정된다].

전술한 바와 같이, 본 발명의 복합체의 수용액을 제공하는 것이 가능하다. 이들 수용액은 특히 비경구 투여에 유용하다. 그러나, 이들을 경구 또는 국부 투여하는 것도 가능하다. 기지의 비경구 투여 가능한 철분 제제와는 달리, F_0 ≥15를 달성함으로써, 단시간의 접촉 시간, 예컨대 15분으로, 고온 예컨대 121℃ 및 그 이상에서 멸균 처리될 수 있다. 이에 따라, 상기 접촉 시간은 더 고온에서는 더 단축된다. 종전에 알려져 있었던 제제는 멸균 여과시켜서 벤질 알콜 또는 페놀 등의 보존제와 함께 혼합시켜야 하였다. 본 발명에서는 이러한 첨가제들이 필요하지 않다. 따라서, 상기 복합체의 용액을 예컨대 앰플에 충입(充入)시키는 것이 가능하다. 예컨대, 함량이 1 내지 20 중량%, 예를 들면 함량이 5 중량%인 용액을 앰플 또는 약병에, 예컨대 2 내지 100 ml, 이르테면 최대 50 ml까지 충입시키는 것이 가능하다. 비경구 투여 가능한 용액의 제조는, 필요에 따라 비경구 용액에 대하여 통상 사용되는 첨가제를 사용하여 이 기술 분야에 알려진 방법으로 수행할 수 있다. 상기 용액은 이들을 주사에 의하여 또는 주입형, 예컨대 염수 용액의 형태로 투여될 수 있도록 제제될 수 있다. 경구 또는 국부 투여를 위하여, 이들 제제는 통상의 부형제 및 첨가제와 함께 제제하는 것이 가능하다.

따라서, 본 발명의 또 다른 목적은 경구 또는 국부 투여 뿐만 아니라, 비경구 정맥내 및 근육내 투여에 특히 유용한 수용성 약제를 제공하는 것으로서, 이들은 특히 철분 결핍성 빈혈의 치료에 유용하다. 또한, 본 발명의 추가의 목적은 철 분 결핍성 빈혈의 치료 및 예방을 위한 본 발명에 따른 철[III]-탄수화물 복합체의 용도, 또는 특히 철분 결핍성 빈혈의 비경구 치료용 약제의 제조 방법을 제공하는 것이다. 상기 약제는 인간 및 수의학 약제로 사용될 수 있다.

본 발명의 철[III]-탄수화물 복합체에 의하여 달성되는 장점으로서는, 전술한 바와 같은 저독성 뿐만 아니라 고온 멸균화 온도 및 과민성 쇼크의 위험 감소를 들 수 있다. 본 발명에 따른 상기 복합체의 독성은 매우 낮다. LD_{50}이 체중 Kg당 철분이 1400 mg인 기지의 풀루란 복합체에 비하여, 본 발명의 LD_{50}은 체중 Kg당 철분이 2000 mg 이상이다. 본 발명의 복합체의 높은 안정성의 관점에서 보면, 투여량 뿐만 아니라 투여율

을 향상시키는 것이 가능하다. 따라서, 본 발명의 약제를 단일 투여형으로 하여 비경구 투여하는 것이 가능하다. 이러한 단일 투여형은 예컨대 철분이 500 내지 1000 mg인데, 이는 예를 들면 1 시간의 기간 중에 투여될 수 있다. 추가의 장점으로서는, 출발 물질로 이용된 말토덱스트린류의 입수 가능성이 높다는 점을 들 수 있는데, 이들은 예컨대 식품 가공업계에서 사판 중인 첨가제이다.

본 명세서 뿐만 아니라 후술하는 실시예에 있어서, 상기 덱스트로스의 당량은 중량 기준으로 측정된다. 이를 위해서는, 상기 말토덱스트린을 비등 중인 수용액 중에서 펠링(Fehling) 용액과 반응시킨다. 이 반응은 정량적으로, 즉 상기 펠링 용액이 더 이상 변색되지 않을 때까지 수행된다. 침전된 산화구리[I]은 일정한 중량에 도달하여 중량이 측정될 때까지 105℃에서 건조시킨다. 얻은 결과로부터, 글루코스의 함량(덱스트로스 당량)은 상기 말토덱스트린 건조 물질의 %중량/중량으로서 산출된다. 이를테면, 다음의 용액, 즉 펠링 용액 I 25 ml와 혼합시킨 펠링 용액 I 25 ml; 말토덱스트린 수용액 10 ml(10 % 본/체적)(펠링 용액 I: 500 ml 물에 용해된 황산구리[II] 34.6 g; 펠링 용액 II: 주석산나트륨칼륨 173 g 및 물 400 ml에 용해된 수산화나트륨 50 g)을 사용하는 것이 가능하다.

실시예

실시예 1

말토덱스트린 100 g(중량 기준 덱스트로스 당량 9.6)을 25℃에서 300 ml 물에 교반하여 용해시킨 다음, pH 10의 차아염소산나트륨 용액 30 g(활성 염소 13 내지 16 중량%)을 가하여 산화시킨다.

우선, 상기 말토덱스트린 산화 생성물 용액에 이어서 탄산나트륨 용액 554 g(17.3 % 중량/중량)을 실온에서 교반된 염화철[III] 용액 352 g(Fe 12 중량%)에 첨가한다.

이어서, 수산화나트륨을 첨가하여 pH 11까지 조절하고, 용액을 50℃까지 가열한 다음 50℃에서 30분간 유지시킨다. 이어서, 염산을 가하여 pH 5 내지 6까지 산성화시키고, 용액을 50℃에서 30분간 더 유지한 다음, 97 내지 98℃까지 가열하고, 상기 온도를 이 범위에서 30분간 유지한다. 상기 용액을 실온까지 냉각한 후, 수산화나트륨을 첨가하여 pH 6 내지 7까지 조절한다.

이어서, 상기 용액을 멸균 필터를 통하여 여과한 다음, 침전물 검사를 행하였다. 이 후, 1:0.85 범위의 에탄올로 침전시켜 복합체를 단리시킨 다음, 50℃에서 진공 건조시킨다.

수득량은 철분 함량이 중량당 29.3 %중량/중량(착물 측정법으로 측정)인 갈색 비결정성 분말 125 g(이론값의 87%에 해당)이다.

분자량(mw)은 271 kDa이다.

실시예 2

말토덱스트린 200 g(중량기준 덱스트로스 당량 9.6)을 25℃에서 300 ml 물에 교반하여 용해시킨 다음, pH 10의 차아염소산나트륨 용액 30 g(활성 염소 13 내지 16 중량%)을 가하여 산화시킨다.

우선, 상기 말토덱스트린 산화 생성물 용액에 이어서 탄산나트륨 용액 554 g(17.3 % 중량/중량)을 실온에서 교반된 염화철[III] 용액 352 g(Fe 12 중량%)에 첨가한다.

이어서, 수산화나트륨을 첨가하여 pH 11까지 조절하고, 용액을 50℃까지 가열한 다음 50℃에서 30분간 유지시킨다. 이어서, 염산을 가하여 pH 5 내지 6까지 산성화 시키고, 용액을 50℃에서 30 분간 더 유지한 다음, 97 내지 98℃까지 가열하고, 상기 온도를 이 범위에서 30분간 유지한다. 상기 용액을 실온까지 냉각한 후, 수산화나트륨을 첨가하여 pH 6 내지 7까지 조절한다.

이어서, 상기 용액을 멸균 필터를 통하여 여과한 다음 침전물 검사를 행하였

다. 이후, 1:0.85 범위의 에탄올로 침전시켜 복합체를 단리시킨 다음, 50℃에서 진공 건조시킨다.

수득량은 철분 함량이 중량당 22.5 % 중량/중량(착물측정법으로 측정)인 갈색 비결정성 분말 123g(이론 값의 65%에 해당)이다.

분자량(mw)은 141 kDa이다.

실시예 3

말토덱스트린 100 g(중량 기준 덱스트로스 당량 9.6)을 25℃에서 300 ml 물에 교반하여 용해시킨 다음, pH 10의 차아염소산나트륨 용액 30 g(활성 염소 13 내지 16 중량%)및 브롬화나트륨 0.7g을 가하여 산화시킨다.

우선, 상기 말토덱스트린 산화 생성물 용액에 이어서 탄산나트륨 용액 554 g(17.3 % 중량/중량)을 실온에서 교반된 염화철[III] 용액 352 g(Fe 12 중량%)에 첨가한다.

이어서, 수산화나트륨을 첨가하여 pH 11까지 조절하고, 용액을 50℃까지 가열한 다음 50℃에서 60분간 유지시킨다. 이어서, 염산을 가하여 pH 5 내지 6까지 산성화 시키고, 용액을 50℃에서 30 분간 더 유지한 다음, 97 내지 98℃까지 가열하고, 상기 온도를 이 범위에서 30분간 유지한다. 상기 용액을 실온까지 냉각한 후, 수산화나트륨을 첨가하여 pH 6 내지 7까지 조절한다.

이어서, 상기 용액을 멸균 필터를 통하여 여과한 다음, 침전물 검사를 행하였다. 이 후, 1:0.85 범위의 에탄올로 침전시켜 복합체를 단리시킨 다음, 50℃에서 진공 건조시킨다.

수득량은 철분 함량이 26.8 % 중량/중량(착물 측정법으로 측정)인 갈색 비결정성 분말 139g(이론 값의 88%에 해당)이다.

분자량(mw)은 140 kDa이다.

실시예 4

말토덱스트린 45 g(중량 기준 덱스트로스 당량 6.6)및 말토덱스트린 45 g(중량 기준 덱스트로스 당량 14.0)의 혼합물을 25℃에서 300 ml 물에 교반하여 용해시킨 다음, pH 10의 차아염소산나트륨 용액 25 g(활성 염소 13 내지 16 중량%)및 브롬화나트륨 0.6 g을 가하여 산화시킨다.

우선, 상기 말토덱스트린 산화 생성물 용액에 이어서 탄산나트륨 용액 554 g(17.3 % 중량/중량)을 실온에서 교반된 염화철[III] 용액 352 g(Fe 12 중량%)에 첨가한다.

이어서, 수산화나트륨을 첨가하여 pH 11까지 조절하고, 용액을 50℃까지 가열한 다음 50℃에서 30분간 유지시킨다. 이어서, 염산을 가하여 pH 5 내지 6까지 산성화 시키고, 상기 용액을 50℃에서 30 분간 더 유지한 다음, 97 내지 98℃까지 가열하고, 상기 온도를 이 범위에서 30분간 유지한다. 상기 용액을 실온까지 냉각한 후, 수산화나트륨을 첨가하여 pH 6 내지 7까지 조절한다.

이어서, 상기 용액을 멸균 필터를 통하여 여과한 다음, 침전물 검사를 행하였다. 이후, 1:0.85 범위의 에탄올로 침전시켜 복합체를 단리시킨 다음, 50℃에서 진공 건조시킨다.

수득량은 철분 함량이 26.5 % 중량/중량(착물 측정법으로 측정)인 갈색 비결정성 분말 143g(이론값의 90%에 해당)이다.

분자량(mw)은 189 kDa이다.

실시예 5

말토덱스트린 90 g(중량 기준 덱스트로스 당량 14.0)을 25℃에서 300 ml 물에 교반하여 용해시킨 다음, pH 10의 차아염소산나트륨 용액 35 g(활성 염소 13 내지 16 중량%)및 브롬화나트륨 0.6 g을 가하여 산화시킨다.

우선, 상기 말토덱스트린 산화 생성물 용액에 이어서 탄산나트륨 용액 554 g(17.3 % 중량/중량)을 실온에서 교반된 염화철[III] 용액 352 g(Fe 12 중량%)에 첨가한다.

이어서, 수산화나트륨을 첨가하여 pH 11까지 조절하고, 용액을 50℃까지 가열한 다음 50℃에서 30분간 유지시킨다. 이어서, 염산을 가하여 pH 5 내지 6까지 산성화 시키고, 상기 용액을 50℃에서 30 분간 더 유지한 다음, 97 내지 98℃까지 가열하고, 상기 온도를 이 범위에서 30분간 유지한다. 상기 용액을 실온까지 냉각한 후, 상기 pH를 수산화나트륨을 첨가하여 6 내지 7까지 조절한다.

이어서, 상기 용액을 멸균 필터를 통하여 여과한 다음, 침전물 검사를 행하였다. 이후, 1:0.85 범위의 에탄올로 침전시켜 상기 복합체를 단리시킨 다음, 50℃에서 진공 건조시킨다.

수득량은 철분 함량이 29.9 % 중량/중량(착물 측정법으로 측정)인 갈색 비결정성 분말 131g(이론 값의 93%에 해당)이다.

분자량(mw)은 118 kDa이다.

실시예 6

말토덱스트린 45 g(중량 기준 덱스트로스 당량 5.4)및 말토덱스트린 45 g(중량 기준 덱스트로스 당량 18.1)의 혼합물을 25℃에서 300 ml 물에 교반하여 용해시킨 다음, pH 10의 차아염소산나트륨 용액 30 g(활성 염소 13 내지 16 중량%)및 브롬화나트륨 0.7 g을 가하여 산화시킨다.

우선, 상기 말토덱스트린 산화 생성물 용액에 이어서 탄산나트륨 용액 554 g(17.3 % 중량/중량)을 실온에서 교반된 염화철[III] 용액 352 g(Fe 12 중량%)에 첨가한다.

이어서, 수산화나트륨을 첨가하여 pH 11까지 조절하고, 상기 용액을 50℃까지 가열한 다음 50℃에서 30분간 유지시킨다. 이어서, 염산을 가하여 pH 5 내지 6까지 산성화 시키고, 용액을 50℃에서 30 분간 더 유지한 다음, 97 내지 98℃까지 가열하고, 상기 온도를 이 범위에서 30분간 유지한다. 상기 용액을 실온까지 냉각한 후, 수산화나트륨을 첨가하여 pH 6 내지 7까지 조절한다.

이어서, 상기 용액을 멸균 필터를 통하여 여과한 다음, 침전물 검사를 행하였다. 이후, 1:0.85 범위의 에탄올로 침전시켜 복합체를 단리시킨 다음, 50℃에서 진공 건조시킨다.

수득량은 철분 함량이 27.9 % 중량/중량(착물 측정법으로 측정)인 갈색 비결정성 분말 134g(이론값의 88%에 해당)이다.

분자량(mw)은 178 kDa이다.

실시예 7

말토덱스트린 100 g(중량 기준 덱스트로스 당량 9.6)을 25℃에서 300 ml 물에 교반하여 용해시킨 다음, pH 10의 차아염소산나트륨 용액 29 g(활성 염소 13 내지 16 중량%)및 브롬화나트륨 0.7 g을 가하여 산화시킨다.

우선, 상기 말토덱스트린 산화 생성물 용액에 이어서 탄산나트륨 용액 554 g(17.3 % 중량/중량)을 실온에서 교반된 염화철[III] 용액 352 g(Fe 중량의 12 중량%)에 첨가한다.

이어서, 수산화나트륨을 첨가하여 pH 11까지 조절하고, 용액을 50℃까지 가열한 다음 50℃에서 30분간 유지시킨다. 이어서, 염산을 가하여 pH 5 내지 6까지 산성화 시키고, 상기 용액을 50℃에서 70 분간 더 유지한다, 상기 용액을 실온까지 냉각한 후, 수산화나트륨을 첨가하여 pH 6 내지 7까지 조절한다.

이어서, 상기 용액을 멸균 필터를 통하여 여과한 다음, 침전물 검사를 행하였다. 이후, 1:0.85 범위의 에탄올로 침전시켜 복합체를 단리시킨 다음, 50℃에서 진공 건조시킨다.

수득량은 철분 함량이 중량당 24.5 % 중량/중량(착물 측정법으로 측정)인 갈색 비결정성 분말 155g(이론값의 90%에 해당)이다.

분자량(mw)은 137 kDa이다.

실시예 8

말토덱스트린 126 g(중량 기준 덱스트로스 당량 6.6)을 25℃에서 300 ml 물에 교반하여 용해시킨 다음, pH 10의 차아염소산나트륨 용액 24 g(활성 염소 13 내지 16 중량%)및 브롬화나트륨 0.7 g을 가하여 산화시킨다.

우선, 상기 말토덱스트린 산화 생성물 용액에 이어서 탄산나트륨 용액 554 g(17.3 % 중량/중량)을 실온에서 교반된 염화철[III] 용액 352 g(Fe 12 중량%)에 첨가한다.

이어서, 수산화나트륨을 첨가하여 pH 11까지 조절하고, 상기 용액을 50℃까지 가열한 다음 50℃에서 30분간 유지시킨다. 이어서, 염산을 가하여 pH 5 내지 6까지 산성화 시키고, 용액을 50℃에서 70 분간 더 유지한다. 상기 용액을 실온까지 냉각한 후, 수산화나트륨을 첨가하여 pH 6 내지 7까지 조절한다.

이어서, 상기 용액을 멸균 필터를 통하여 여과한 다음, 침전물 검사를 행하였다. 이후, 1:0.85 범위의 에탄올로 침전시켜 복합체를 단리시킨 다음, 50℃에서 진공 건조시킨다.

수득량은 철분 함량이 21.35 % 중량/중량(착물 측정법으로 측정)인 갈색 비결정성 분말 171g(이론 값의 86%에 해당)이다.

분자량(mw)은 170 kDa이다.

비교 실험

이하에서는 상기 철 탄수화물 복합체의 특성을 시판되는 철 수크로스 복합체와 비교하고 있다. 본 발명에 따라 철분 함량이 증가될 수 있고, 열처리가 더 고 온도에서 수행될 수 있으며, 독성(LD_{50})이 저하될 수 있다는 사실을 알 수 있다.

	본 발명의 복합체	수산화철/수크로스 복합체
철분 함량 (%)	5.0	2.0
pH	5 - 7	10.5 - 11.0
분자량 (kDa)	80 - 350	34 - 54
열처리	121℃/15	100℃/35
LD_{50} i.v. w.m.(mg Fe/Kg-체중)	>2000	>200

청구의 범위

청구항 1

pH 값 범위가 알칼리성인 차아염소산염 수용액을 사용하여 철[III]염 수용액 및 1종 이상의 말토덱스트린 산화 생성물로 이루어진 수용액으로부터 제조될 수 있고, 1종의 말토덱스트린이 사용되는 경우, 그의 덱스트로스 당량은 5 내지 20이고, 1종 이상의 말토덱스트린의 혼합물이 이용되는 경우, 그 혼합물의 덱스트로스 당량은 5 내지 20이며, 상기 혼합물 중에 함유된 각각의 말토덱스트린의 덱스트로스 당량은 2 내지 40인 것을 특징으로 하는 수용성 철-탄수화물 복합체.

청구항 2

제1항에 있어서, 1종 이상의 말토덱스트린을 차아염소산 수용액을 사용하여pH 값 범위가 알칼리성인 수용액 중에서 산화시키고, 생성된 용액을 철[III]염 수용액과 반응시키는 것을 포함하고, 1종의 말토덱스트린이 사용되는 경우, 그의 덱스트로스 당량은 5 내지 20이고, 수종의 말토덱스트린의 혼합물이 사용되는 경우, 그 혼합물의 덱스트로스 당량은 5 내지 20이며, 상기 혼합물 중에 함유된 각각의 말토덱스트린의 덱스트로스 당량은 2 내지 40인 것인 철-탄수화물 복합체의 제조 방법.

청구항 3

제2항에 있어서, 상기 말토덱스트린 또는 말토덱스트린류의 산화는 브롬화물 이온의 존재하에 수행되는 것을 특징으로 하는 것인 제조 방법.

청구항 4

제2항 또는 제3항에 있어서, 상기 염화철[III]은 철[III] 염으로서 사용되는 것을 특징으로 하는 것인 제조 방법.

청구항 5

제2항, 제3항 또는 제4항에 있어서, 상기 말토덱스트린 산화물 및 상기 철 [III]염은 서로 혼합되어 상기 철[III]염의 가수 분해가 발생하지 않도록 pH 값이 낮은 수용액을 생성하고, 이어서 상기 pH는 염기의 첨가에 의하여 5 내지 12까지 상승되는 것을 특징으로 하는 것인 제조 방법.

청구항 6

제3항 내지 제5항 중 어느 하나의 항에 있어서, 15℃ 내지 최대 비등점의 온도에서 15분 내지 최대 수 시간 동안 수행되는 것을 특징으로 하는 것인 제조 방법.

청구항 7

제1항 또는 제2항에 따르거나 또는 제3항 내지 제6항 중 어느 하나의 항에 따라 생성된 철-탄수화물 복합체의 수용액을 함유하는 것을 특징으로 하는 약제.

청구항 8

제7항에 있어서, 상기 철-탄수화물 복합체가 비경구 또는 경구 투여용으로 제제된 것인 약제.

청구항 9

제1항에 따르거나, 또는 제2항 내지 제6항 중 어느 하나의 항에 따라 생성된, 철분 결핍증의 치료 또는 예방을 위한 철-탄수화물 복합체의 용도.

청구항 10

제1항에 따르거나, 또는 제2항 내지 제6항 중 어느 하나의 항에 따라 생성된, 철분 결핍증의 치료 또는 예방용 약제를 제조하기 위한 철-탄수화물 복합체의 용도.

청구항 11

제1항에 있어서, 철분 결핍증의 치료 또는 예방을 위한 수용성 철-탄수화물 복합체.

Electronic Patent Application Fee Transmittal	
Application Number:	14100717
Filing Date:	09-Dec-2013
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Filer:	Kathleen E. Chaffee/Connie Payne
Attorney Docket Number:	30015730-0065
Filed as Large 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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	18276007
Application Number:	14100717
International Application Number:	
Confirmation Number:	2813
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	Kathleen E. Chaffee/Connie Payne
Filer Authorized By:	Kathleen E. Chaffee
Attorney Docket Number:	30015730-0065
Receipt Date:	24-FEB-2014
Filing Date:	09-DEC-2013
Time Stamp:	10:39:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	10190
Deposit Account	
Authorized User	

File Listing:

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

1	Transmittal Letter	IDS_Transmittal_3001530-0065_filed_24FEB14.pdf	90475 7e7ac954223601a11ec6cbbfbffe1aa9f6195253	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	SB08_IDS_30015730-0065_filed_24FEB14.pdf	277788 547be78237cedf9af142e140ed90f7600da5ca6c	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	CA2493806A1.pdf	642859 e7ce8f18829c5eb7eda91620e68e8dfd6583e8ec	no	21
Warnings:					
Information:					
4	Foreign Reference	KR1020050070014.pdf	269034 bbcee877df204affb2b998bf531ba6dc4cd9b543	no	7
Warnings:					
Information:					
5	Other Reference-Patent/App/Search documents	0048CA_OA_1-4-13.pdf	458510 bff0d1e68be2c20a6b28df6517bfc3c92bb57372	no	4
Warnings:					
Information:					
6	Other Reference-Patent/App/Search documents	0048CA_OA_10-17-13.pdf	580801 5d1805f0fd40aea38b1d779c4db56e5c4f3f7e1e	no	4
Warnings:					
Information:					
7	Other Reference-Patent/App/Search documents	0049KR_OA_in_Korean_and_English.pdf	339791 3aa73c43ea1030381141c527478ce62aad3104ce	no	13
Warnings:					
Information:					
8	Other Reference-Patent/App/Search documents	0051EP_ESR_10-21-09.pdf	222317 e0aade521abe6101eb187d6502f1c884e1b2c152	no	9
Warnings:					
Information:					
9	Other Reference-Patent/App/Search documents	0051EP_OA_05-10-11.pdf	673049 f531d93fbd846b57d1390c54fdab961f7eab4936	no	6

Warnings:					
Information:					
10	Other Reference-Patent/App/Search documents	0051EP_OA_07-05-13.pdf	236368 8b83f0e20319d6fa0fc790182529fc59af60115e	no	5
Warnings:					
Information:					
11	Other Reference-Patent/App/Search documents	0061EP_ESR_07-08-13.pdf	994948 7a810323d111009d62cad7a847d7883c95dbb333	no	8
Warnings:					
Information:					
12	Non Patent Literature	Marchasin_1964.pdf	601987 54ec766772264f6d68040ffa5903dc3be27de92b	no	6
Warnings:					
Information:					
13	Fee Worksheet (SB06)	fee-info.pdf	30276 501ebef5c3303344bfb6bc06e1b1fba1c483d363	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	5418203		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.: 14/100,717	Examiner: Jonathan S. Lau
Applicant: Mary Jane Helenek et al.	Group Art Unit: 1673
Filed: 09 December 2013	Confirmation No.: 2813
Docket No.: 30015730-0065	Customer No.: 26263
Title: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

24 February 2014

FILED VIA EFS WEB
Mail Stop Amendment
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 the mailing of a first Office action on the merits; 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. § 1.98(d), applicants are not providing copies of the references (marked with a #) made of record by the applicants or by the U.S. Patent

and Trademark Office in related Application Serial Numbers 13/847,254; 12/787,283; and 11/620,986.

Applicants enclose a copy of the Korean Office Action for Application No. 10-2008-7016352, dated 28 May 2013, in Korean and English, and documents cited therein.

The following remarks are offered with respect to the non-English reference:

KR 10-2005-0070014 is in Korean. The English-language counterpart to KR 10-2005-0070014, WO 2004037865, is provided to serve as an English translation.

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.

Applicants submit herewith a credit card payment via EFS-Web in the amount of the fee set forth in 37 C.F.R. § 1.17(p) for submission of an information disclosure statement under § 1.97(c). The Commissioner is hereby authorized to charge any additional fees that may be required or credit any overpayments to Dentons US LLP Deposit Account No. 19-3140.

Respectfully Submitted,

24 February 2014
Date

/Kathleen E. Chaffee/
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/100,717	12/09/2013	Mary Jane Helenek	30015730-0065	2813

26263 7590 02/07/2014
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EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1673	
MAIL DATE	DELIVERY MODE
02/07/2014	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. 14/100,717	Applicant(s) HELENEK ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1673	AIA (First Inventor to File) Status No

-- 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 MONTHS 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 *9 Dec 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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*

5)☒ Claim(s) *1-20* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-20* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

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

11)☐ 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).

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).

Certified copies:

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)).

** 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) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

This application is made special as a Track I application.

This application is a domestic application, filed 9 Dec 2013; and claims benefit as a CON of 13/847,254, filed 19 Mar 2013; which claims benefit as a CON of 12/787,283, issued as Patent 8,431,549, filed 25 May 2010; which claims benefit as a CON of 11/620,986, issued as Patent 7,754,702, filed 8 Jan 2007; which claims benefit of provisional application 60/757,119, filed 6 Jan 2006.

Claims 1-20 are pending in the current application and are examined on the merits herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5, 8, 13, 14 and 18 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Geisser et al. (WIPO Publication WO 2004/037865 A1, published 6

May 2004, cited in PTO-892, English language equivalent US Patent 7,612,109 provided, cited in PTO-892). As WO 2004/037865 A1 is not in English, US Patent 7,612,109 is provided as an English language equivalent and is cited as Geisser et al. hereafter.

Geisser et al. discloses an iron carbohydrate complex of iron and the oxidation product of maltodextrins as a medicament for treatment of iron deficiency conditions (abstract). Geisser et al. discloses the iron carbohydrate complex for treatment of iron deficiency anemia and especially useful for parenteral application (column 1, lines 15-20), meeting limitations of instant claims 4, 5 and 18. Geisser et al. discloses the complexes shall have reduced toxicity and shall avoid dangerous anaphylactic shocks which can be induced by dextran (column 1, lines 35-40), meeting limitations of instant claim 3. Geisser et al. discloses in the complexes theoretically it is assumed that the oxidation occurs mainly at the terminal aldehyde group (acetal or semiacetal group respectively) of the maltodextrin molecules (column 2, lines 25-30), implying the iron carbohydrate complex is an iron carboxymaltose complex, meeting limitations of instant claim 13. Geisser et al. discloses the complexes are prepared from an iron (III) salt and a strong base such as a potassium, calcium or magnesium hydroxide (column 3, lines 1-15), implying the iron carbohydrate complex is a polynuclear iron (III)-hydroxide carboxymaltose complex and implicitly meeting limitations of instant claim 14. Geisser et al. discloses the advantage that the LD_{50} lies at over 2000 mg Fe/kg and it is possible to apply the medicaments of the invention parenterally in the form of a single dose of,

for example, 500 to 1000 mg iron; and it can be applied, for example, during the course of one hour (column 4, lines 50-65), meeting limitations of instant claim 1 and 8.

Claims 1-3, 7-12 and 18-20 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Helenek et al. (US Patent Application Publication 2004/0180849 A1, published 16 Sep 2004, cited in PTO-892).

Helenek et al. discloses a method of treating restless leg syndrome by administering to a subject an iron complex (abstract), meeting limitations of instant claim 7. Helenek et al. discloses the iron carbohydrate complexes administered include iron polyisomaltose (iron dextran), iron polymaltose (iron dextrin), iron gluconate, iron sorbital and iron hydrogenated dextran (page 3, paragraph 0021), meeting limitations of instant claim 1. Helenek et al. discloses the iron carbohydrate complexes avoid the risks of anaphylaxis associated with IDI when administered intravenously due to antibodies against the dextran moiety not being present in other iron complexes (page 3, paragraph 0017), meeting limitations of instant claims 2 and 3. Helenek et al. discloses the 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, for example particularly at least 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 (page 5, paragraph 0051), meeting limitations of instant claims 1 and 8-10. Helenek et al. discloses the embodiments of 1000 mg of elemental iron administered in an injectable

intravenous as a single dose as a 1.5-5 mg iron/ml in normal saline (page 5, paragraph 0052), implying a volume of 666 mL-200 mL normal saline, or diluent, meeting limitations of instant claim 18 and 19. Helenek et al. discloses the iron complexes may be administered ad hoc, that is, as symptoms reappear (page 5, paragraph 0053), meeting limitations of instant claim 20. Helenek et al. discloses embodiments of direct injection over 2 minutes and over 5 minutes (page 7, paragraph 0097), meeting limitations of instant claims 11 and 12.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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 pre-AIA 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 pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1, 4-6, 8-12 and 18-20 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Hamstra et al. (JAMA, 1980, 243(17), p1726-1731, cited in PTO-892) in view of Muller et al. (US Patent 3,100,202, issued 6 Aug 1963, cited in PTO-892).

Hamstra et al. teaches intravenous injection of iron dextran, usually 250 to 500 mg at less than 100 mg/min (page 1726, abstract), implying an intravenous infusion. Hamstra et al. teaches parenteral iron therapy in the treatment of iron deficiency anemia (page 1726, left column, paragraph 1), and teaches the patient population selected from patients having chronic and acute blood loss (page 1726, right column, paragraph 1). Hamstra et al. teaches injections wherein the iron content per injection includes 501-999 mg, 1,000 mg, and >1,000 mg (page 1726, Table 2 at bottom of right column). Hamstra et al. teaches the total amount of iron given ranges to >15,000 mg (page 1723, Table 3 at top of left column). Hamstra et al. teaches the intravenous injection diluted in 250 mL 5% dextrose in water or in normal saline and teaches optimizing the rate at which the injection is administered, such as 100 to 400 mL/hr or the undiluted drug at 1 to 5 mL/min (page 1727, left column, paragraph 1). Hamstra et al. teaches it is routine for one of ordinary skill in the art to perform treatment including subsequent iron dextran therapy as needed (page 1728, table 6 at top of page).

Hamstra et al. teaches does not specifically teach the iron carbohydrate complex is an iron polyisomaltose complex (instant claim 1). Hamstra et al. teaches does not specifically teach the single dosage unit of elemental iron is at least about 1.5 grams (instant claim 9) or 2.0 grams (instant claim 10).

Muller et al. teaches an iron-polyisomaltose complex which is parenterally injectible (column 1, lines 10-15). Muller et al. teaches a known treatment for iron deficiency anemia is the iron dextran complex (column 1, lines 45-50). Muller et al. teaches the improvement of the iron-polyisomaltose complex is more heterogeneous in particle size, surprisingly lower toxicity, better pharmacological properties, and higher therapeutic efficacy than the iron dextran complexes hitherto known (column 2, lines 25-30).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Hamstra et al. in view of Muller et al. Both Hamstra et al. and Muller et al. are drawn to iron carbohydrate complexes for treatment of iron deficiency anemia. One of ordinary skill in the art at the time of the invention would have been motivated to combine Hamstra et al. in view of Muller et al. with a reasonable expectation of success because Hamstra et al. teaches administration of iron dextran complexes to treat iron deficiency anemia and Muller et al. teaches improvements of the iron-polyisomaltose complex compared to iron dextran complexes. It would have been routine for one of ordinary skill in the art to optimize the iron dosage per injection and the rate of administration because Hamstra et al. teaches intravenous injection of iron dextran, usually 250 to 500 mg at less than 100 mg/min but also teaches embodiments wherein the iron content per injection includes 501-999 mg, 1,000 mg, and >1,000 mg, to a total amount of >15,000 mg iron given, as well as suggesting optimizing the rate at which the injection is administered.

Claim 17 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Hamstra et al. (JAMA, 1980, 243(17), p1726-1731, cited in PTO-892) in view of Muller et al. (US Patent 3,100,202, issued 6 Aug 1963, cited in PTO-892) as applied to claims 1, 4-6, 8-12 and 18-20 above, and further in view of Lawrence et al. (US Patent 5,624,668, issued 29 Apr 1997, provided by Applicant in IDS mailed 17 Jun 2010).

Hamstra et al. in view of Muller et al. teaches as above.

Hamstra et al. in view of Muller et al. does not specifically teach the method wherein the mean iron core size is at least about 1 nm but no greater than about 9 nm; or mean size of a particle of the iron carbohydrate complex is no greater than about 35 nm (instant claim 17).

Lawrence et al. teaches iron dextran composition for treating iron deficiency (abstract). Lawrence et al. teaches a greater degree of homogeneity is desired, such as a uniform molecular weight distribution (column 4, lines 45-55). Lawrence et al. teaches DEXFERRUM particles typically range in length from about 31.5 to about 36.5 nm and are approximately 4.5 nm in width (column 3, lines 60-65 and column 9, lines 10-15).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Hamstra et al. in view of Muller et al. further in view of Lawrence et al. All of Hamstra et al., Muller et al. and Lawrence et al. are drawn to iron carbohydrate complexes for treatment of iron deficiency. One of ordinary skill in the art would have been motivated to combine Hamstra et al. in view of Muller et al. further in view of Lawrence et al. because Lawrence et al. teaches the new improvment of a greater degree of homogeneity is desired, such as a uniform molecular weight distribution, and

suggests the improvement by optimizing the particle size of the iron carbohydrate complex.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-20 are rejected on the ground of nonstatutory double patenting over claims 1-57 of U.S. Patent No. 7,754,702 since the claims, if allowed, would improperly extend the “right to exclude” already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: Independent claim 1 of U.S. Patent No. 7,754,702 recites 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 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.

Independent claim 55 of U.S. Patent No. 7,754,702 recites 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 an iron carboxymaltose complex. Claims 2-9 of U.S. Patent No. 7,754,702 are drawn to the disease or conditions of instant claims 4-7. Claims 10-16 of U.S. Patent No. 7,754,702 are drawn to the dosage unit of elemental iron corresponding to instant claims 8-10. Claims 17-20 of U.S. Patent No. 7,754,702 are drawn to the duration of administration corresponding to instant claims 11 and 12. Claims 23, 26, 27 and 57 are drawn to the iron carboxymaltose complex corresponding to instant claims 13 and 14. Claims 28 and 29 are drawn to the iron carbohydrate complex corresponding to instant claims 15 and 16. Claims 30-40 of U.S. Patent No. 7,754,702 are drawn to the particle size corresponding to instant claim 17. Claims 41-52 of U.S. Patent No. 7,754,702 are drawn to the route of administration corresponding to instant claim 19. Claim 53 is drawn to a second administration corresponding to instant claim 20.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claims 1-12 and 15-20 are rejected on the ground of nonstatutory double patenting over claims 1-23 of U.S. Patent No. 8,431,549 since the claims, if allowed, would improperly extend the “right to exclude” already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: Independent claim 1 of U.S. Patent No. 8,431,549 is drawn to 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 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 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 wherein said disease, disorder or condition is not Restless Leg Syndrome. Claim 2 of U.S. Patent No. 8,431,549 is drawn to said complex having substantially no cross reactivity with anti-dextran antibodies corresponding to instant claim 3. Claims 3-6 of U.S. Patent No. 8,431,549 are drawn to the disease or conditions of instant claims 4-7. Claims 7-9 and 19 of U.S. Patent No. 8,431,549 are drawn to the dosage unit of elemental iron corresponding to instant claims 8-10. Claims 10, 11 and 18 of U.S. Patent No. 8,431,549 are drawn to the duration of administration corresponding to instant claims 11 and 12. Claims 12 and 13 are drawn to the iron carbohydrate complex corresponding to instant claims 15 and 16. Claim 14 of U.S. Patent No. 8,431,549 is drawn to the particle size corresponding to instant claim 17. Claims 15-16 of U.S. Patent No. 8,431,549 are drawn to the route of administration corresponding to instant claims

18 and 19. Claim 17 of U.S. Patent No. 8,431,549 is drawn to a second administration corresponding to instant claim 20.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

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 S Lau/
Examiner, Art Unit 1673

Notice of References Cited	Application/Control No. 14/100,717	Applicant(s)/Patent Under Reexamination HELENEK ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1673	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-7,612,109	11-2009	Geisser et al.	514/502
*	B	US-2004/0180849	09-2004	Helenek et al.	514/053
*	C	US-3,100,202	08-1963	ARTHUR MULLER et al.	536/113
*	D	US-5,624,668	04-1997	Lawrence et al.	424/78.17
	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	WO 2004037865 A1	05-2004	World Intellect	GEISSER et al.	C08B 31/18
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Hamstra et al., JAMA, 1980, 243(17), p1726-1731.
	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.

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

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102 49 552.1 23. Oktober 2002 (23.10.2002) DE

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(72) Erfinder; und
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(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.

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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

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

[X] Patent family members are listed in annex.

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"&" 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

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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	

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/11596

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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 :
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"&" 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

Internales 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

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14100717	HELENEK ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1673

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST - see attached notes	2/6/2014	JSL
EAST - inventor name search (Mary Helenek, Marc Tokars, Richard Lawrence)	2/6/2014	JSL
Google Scholar - see attached notes	2/6/2014	JSL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14100717	HELENEK ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1673

✓	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	02/06/2014								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
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	13	✓								
	14	✓								
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	16	✓								
	17	✓								
	18	✓								
	19	✓								
	20	✓								

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BIB DATA SHEET

CONFIRMATION NO. 2813

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/100,717	12/09/2013	514	1673	30015730-0065

APPLICANTS

Luitpold Pharmaceuticals, Inc., Shirley, NY, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

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

**** CONTINUING DATA ***************************

This application is a CON of 13/847,254 03/19/2013
which is a CON of 12/787,283 05/25/2010 PAT 8431549
which is a CON of 11/620,986 01/08/2007 PAT 7754702
which claims benefit of 60/757,119 01/06/2006

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

12/19/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged _____ Examiner's Signature	☐ Met after Allowance _____ Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NY	2	20	1

ADDRESS

DENTONS US LLP
P.O. BOX 061080
CHICAGO, IL 60606-1080
UNITED STATES

TITLE

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

FILING FEE RECEIVED		
1900	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

BIB (Rev. 05/07).

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	13	((MARY) near2 (HELENEK)).INV.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/03 09:32
S2	9	((MARC) near2 (TOKARS)).INV.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/03 09:32
S3	493	((RICHARD) near2 (LAWRENCE)).INV.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/03 09:32
S4	80	(LUITPOLD).INV,AN.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/03 09:32
S5	495	S1 or S2 or S3	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/03 09:32
S6	17	S5 and iron.clm.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/03 10:01
S7	1	"5624668".pn.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/05 09:40
S8	1	"20040180849".pn.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/05 09:41
S9	1	"20060116349"	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/05 10:02
S10	1	"6960571".pn.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/05 10:03
S11	72	LUITPOLD near9 PHARMACEUTICALS	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/05 10:37
S12	6	S11 and carboxymaltose	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/05 10:37
S13	19	(iron or ferric or ferrous) near9 carboxymaltose	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/05 10:39
S14	8	(iron or ferric or ferrous) near9 carboxymaltose	EPO; DERWENT	NEAR	ON	2014/02/05 10:41
S15	1	"20060205691".pn.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/05 10:42
S16	1	"7612109".pn.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/05 10:45
S17	4	"2004037865"	EPO; DERWENT	NEAR	ON	2014/02/05 10:48
S18	1	"20040180849".pn.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/05 11:27

EAST Search History (Interference)

<This search history is empty>

2/5/2014 3:10:20 PM
C:\Users\jlau1\Documents\EAST\Workspaces\14100717 - iron complex.wsp

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iron OR ferric OR ferrous carboxymaltose OR Injectafer OR vit-45

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[CITATION] Safety profile of **iron carboxymaltose**, a new high dose intravenous **iron** in patients with **iron** deficiency anemia.
MH Seid, A Mangione, TG Valaoras... - ..., 2006 - ... 1900 M STREET, NW SUITE 200, ...
Cited by 5 Related articles Cite Save

Treatment for women with postpartum **iron** deficiency anaemia [PDF] from update-software.com
J Dodd, MR Dare, P Middleton - Cochrane Database Syst Rev, 2004 - Wiley Online Library
Page 1. Treatment for women with postpartum **iron** deficiency anaemia (Review) Dodd JM, Dare MR, Middleton P ... Page 3. [Intervention Review] Treatment for women with postpartum **iron** deficiency anaemia Jodie M Dodd1, Marianna R Dare2, Philippa Middleton3 ...
Cited by 39 Related articles All 11 versions Cite Save

[PDF] Publication list [PDF] from uzh.ch
T Fehr - Nat. Med, 1998 - physiol.uzh.ch
... Grimmelt AC, Cohen CD, Fehr T, Serra AL, Wuethrich RP. Safety and tolerability of **ferric carboxymaltose** (FCM) for treatment of **iron** deficiency in patients with chronic kidney disease and in kidney transplant recipients. Clin Nephrol. 71:125-9 (2009). ...
Cited by 51 Related articles All 6 versions Cite Save More

Disorders of **iron** metabolism [PDF] from mcmaster.ca
NC Andrews - New England Journal of Medicine, 1999 - Mass Medical Soc
... This facilitates enzymatic reduction of **ferric iron** to its **ferrous** form by a brush-border ferrireductase.6 Divalent metal transporter 1 (DMT1; formerly called Nramp2 or DCT1) is a protein that transfers **iron** across the apical membrane and into the cell through a proton-coupled ...
Cited by 1234 Related articles All 9 versions Cite Save

Determination of **VIT 45** (IND# 63,243-American Regent) removal by closed loop in vitro hemodialysis system
HJ Manley, ML McClaran - International journal of artificial organs, 2006 - cat.inist.fr
... membranes at various ultrafiltration rates (UFR) is unknown. Methods: An in vitro HD system was constructed to determine the dialyzability of **iron** from a normal saline compartment (NSC) containing 1000 mg **iron** of **VIT 45**. ...
Cited by 2 Related articles All 2 versions Cite Save

[CITATION] Martindale: The Complete Drug Reference
A Acid, A Acid, A Acetylillinate, A Camphorate... - 2005 - Pharmaceutical Press, London
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[PDF] Panel Gives IV **Iron** Product Nod for Restricted Use [PDF] from oncologypractice.com
E MECHCATIE - JAMA, 2003 - oncologypractice.com
... SILVER SPRING , MD. — Concerns about off-label use and a mortality safety signal associated with treatment in clinical trials swayed a federal advisory panel against supporting the approval of **ferric carboxymaltose** injection (**Injectafer**), a new intravenous **iron** product, as a first ...
All 13 versions Cite Save More

Case for Diagnosis (**Ferrous** Iodide Rash)
M Morris - Proceedings of the Royal Society of Medicine, 1912 - ncbi.nlm.nih.gov
... PubMed related articles. Stability of salt double-fortified with **ferrous** fumarate and potassium iodate or iodide under storage and distribution conditions in Kenya. Food Nutr Bull. ... 2005]. Review**Ferric carboxymaltose**: a review of its use in **iron**-deficiency anaemia. Drugs. ...
All 3 versions Cite Save

IRON THERAPY IN THE ANAEMIA OF RHEUMATOID ARTHRITIS
EGL Bywaters - Annals of the Rheumatic Diseases, 1951 - ncbi.nlm.nih.gov
... 1951]. ReviewPrepartum anaemia: prevention and treatment. Ann Hematol. 2008 Dec; 87(12):949-59. Epub 2008 Jul 19. [Ann Hematol. 2008]. Review**Ferric carboxymaltose**: a review of its use in **iron**-deficiency anaemia. Drugs. 2009; 69(6):739-56. [Drugs. 2009]. ...
All 5 versions Cite Save

An unusual finding in a patient with **iron** deficiency anaemia [PDF] from bmj.com
J Leyden, C O'Shea, S Hegarty, P MacMathuna - Gut, 2005 - ncbi.nlm.nih.gov
... Pediatr Hematol Oncol. 2009 Jan; 26(1):57-61. [Pediatr Hematol Oncol. 2009]. Review**Ferric carboxymaltose**: a review of its use in **iron**-deficiency anaemia. Drugs. 2009; 69(6):739-56. [Drugs. 2009]. ReviewAn unusual case of severe **iron** deficiency anaemia. Gut. ...
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CHICAGO IL 60606-1080

MAILED
DEC 30 2013
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/100,717

1. THE REQUEST FILED December 9, 2013 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/100,717	12/09/2013	1623	1900	30015730-0065	20	1

CONFIRMATION NO. 2813

26263
DENTONS US LLP
P.O. BOX 061080
CHICAGO, IL 60606-1080

FILING RECEIPT

OC000000065664788

Date Mailed: 12/27/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. 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 submit a written request for a Filing Receipt Correction. 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**

Inventor(s)

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

Applicant(s)

Luitpold Pharmaceuticals, Inc., Shirley, 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 application is a CON of 13/847,254 03/19/2013
which is a CON of 12/787,283 05/25/2010 PAT 8431549
which is a CON of 11/620,986 01/08/2007 PAT 7754702
which claims benefit of 60/757,119 01/06/2006

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 12/19/2013
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/100,717**
Projected Publication Date: 04/10/2014

Non-Publication Request: No

Early Publication Request: No

Title

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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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 (1-866-999-4258).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/100,717	12/09/2013	Mary Jane Helenek	30015730-0065

CONFIRMATION NO. 2813

26263
DENTONS US LLP
P.O. BOX 061080
CHICAGO, IL 60606-1080

POA ACCEPTANCE LETTER

OC000000065664807

Date Mailed: 12/27/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/09/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/lnguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/100,717

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			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 420 =	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 $310 ($155 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
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

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))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(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 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))							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 found in the appropriate box in column 1.

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Form Revision Date: August 26, 2013

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-13)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Mary Jane Helenek	Nonprovisional Application Number (if known):	
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. The executed inventor's oath or declaration is filed with the application. (37 CFR 1.63 and 1.64)

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Kathleen E. Chaffee/	Date 09 December 2013
Name (Print/Typed) Kathleen E. Chaffee	Practitioner Registration Number 69,903

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

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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.

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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 inspection 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.

PTO/AIA/01 (06-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

As the below named inventor, I hereby declare that:

This declaration is directed to: ☒ The attached application, or

☐ United States application or PCT international application number _____

filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Mary Jane Helenek Date (Optional): 11-27-13

Signature: Mary Jane Helenek

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [x] The attached application, or
- [ ] United States application or PCT international application number _____

filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Richard P. Lawrence Date (Optional): 12/9/2013

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [■] The attached application, or
- [ ] United States application or PCT international application number _____

  filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Marc L. Tokars Date (Optional): Nov 21, 2013

Signature: /M. Tokars/

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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:	Kathleen E. Chaffee/Connie Payne
Attorney Docket Number:	30015730-0065
Filed as Large Entity	

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**6040**

Electronic Acknowledgement Receipt	
EFS ID:	17606298
Application Number:	14100717
International Application Number:	
Confirmation Number:	2813
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	Kathleen E. Chaffee/Connie Payne
Filer Authorized By:	Kathleen E. Chaffee
Attorney Docket Number:	30015730-0065
Receipt Date:	09-DEC-2013
Filing Date:	
Time Stamp:	16:41:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$6040
RAM confirmation Number	4083
Deposit Account	
Authorized User	

File Listing:

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

1	Application Data Sheet	ADS_30015730-0065_revised_form.pdf	1221754 6d5f10aeccb3ce6cc2d8045606cb42b1a88b15ae	no	7
Warnings:					
Information:					
2		CON3_30015730-0065.pdf	897820 04cc0adeb6672504e1b9b2c4c9a54f3847e6f140	yes	48
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	41	
	Claims		42	45	
	Abstract		46	46	
	Drawings-other than black and white line drawings		47	48	
Warnings:					
Information:					
3	TrackOne Request	Request_for_Prioritized_Exam_30015730-0065.pdf	156085 0df7a027640790e599a3bd67a84301167184feb7	no	2
Warnings:					
Information:					
4	Oath or Declaration filed	DEC_Helenek_30015730-0065.pdf	1262117 fe5196381b1b1e2c870afa58a3af2d43b27c627c	no	1
Warnings:					
Information:					
5	Oath or Declaration filed	DEC_Lawrence_30015730-0065.pdf	428573 d7ee5023c9e2f731987c99dac9baab303a47a5da	no	1
Warnings:					
Information:					
6	Oath or Declaration filed	DEC_Tokars_30015730-0065.pdf	1401997 a1370e78b6205ad8b06bbfecded6db3fbb7a930f	no	1
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	40158 c88b3cd23ff916553fe7db846ad63e0adefc4673	no	2
Warnings:					

Information:	
Total Files Size (in bytes):	5408504

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/AIA/14 (11-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0065
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mary	Jane	Helenek	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Brookville	State/Province	NY	Country of Residence i	US

Mailing Address of Inventor:

Address 1	13 Evans Drive		
Address 2			
City	Brookville	State/Province	NY
Postal Code	11545	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Marc	L.	Tokars	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Douglassville	State/Province	PA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	202 Farmingdale Drive		
Address 2			
City	Douglassville	State/Province	PA
Postal Code	19618	Country i	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Richard	P.	Lawrence	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

PTO/AIA/14 (11-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0065
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

City	Calverton	State/Province	NY	Country of Residence i	US

Mailing Address of Inventor:

Address 1	94 Young Avenue		
Address 2			
City	Calverton	State/Province	NY
Postal Code	11933	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	26263		
Email Address	patents.us@dentons.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON		
Attorney Docket Number	30015730-0065	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	2	Suggested Figure for Publication (if any)	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)

PTO/AIA/14 (11-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0065
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

Customer Number	26263

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13847254	2013-03-19

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13847254	Continuation of	12787283	2010-05-25	8431549	2013-04-30

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
12787283	Continuation of	11620986	2007-01-08	7754702	2010-07-13

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
11620986	Claims benefit of provisional	60757119	2006-01-06

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i]the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

PTO/AIA/14 (11-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0065
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☐ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (11-13)
Approved for use through 01/31/2014. 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 contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0065
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

(•) Assignee	( ) Legal Representative under 35 U.S.C. 117	( ) Joint Inventor
( ) Person to whom the inventor is obligated to assign.	( ) Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. [X]

Organization Name	Luitpold Pharmaceuticals, Inc.		
Mailing Address Information:			
Address 1	One Luitpold Drive		
Address 2	P.O. Box 9001		
City	Shirley	**State/Province**	NY
Country i	US	Postal Code	11967
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. [ ]

PTO/AIA/14 (11-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0065
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/Kathleen E. Chaffee/			Date (YYYY-MM-DD)	2013-12-09
First Name	Kathleen E.	Last Name	Chaffee	Registration Number	69903

Additional Signature may be generated within this form by selecting the Add button. Add

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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 records.

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.

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation Application that claims priority to U.S. Non-Provisional Application Serial No. 13/847,254, filed 19 March 2013; U.S. Non-Provisional Application Serial No. 12/787,283, filed 25 May 2010, issued as U.S. Patent No. 8,431,549 on 30 April 2013; and U.S. Non-Provisional Application Serial No. 11/620,986, filed 08 January 2007, issued as U.S. Patent No. 7,754,702 on 13 July 2010, both of which claim priority to U.S. Provisional Application Serial No. 60/757,119, filed 06 January 2006, each of which is incorporated herein by reference in their entireties.

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 T_{75} (min)	Size of the Particle (nm) +/- SEM 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 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, an iron sorbitol complex, and an iron hydrogenated dextran complex.

2. The method of claim 1, wherein the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component.

3. The method of claim 1, wherein the iron carbohydrate complex has substantially no cross reactivity with anti-dextran antibodies.

4. The method of claim 1, wherein the disease, disorder, or condition comprises anemia.

5. The method of claim 4, wherein the anemia comprises iron deficiency anemia.

6. The method of claim 4, wherein:

(i) the anemia comprises an iron deficiency anemia 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-steroidal anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents;

(ii) the anemia is of a chronic disease 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;

(iii) the anemia is due to impaired iron absorption or poor nutrition;

(iv) the anemia is associated with Crohn's Disease; gastric surgery; ingestion of drug products that inhibit iron absorption; or chronic use of calcium.

7. 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.

8. The method of claim 1 wherein the single dosage unit of elemental iron is at least about 1.0 grams.

9. The method of claim 1 wherein the single dosage unit of elemental iron is at least about 1.5 grams.

10. The method of claim 1 wherein the single dosage unit of elemental iron is at least about 2.0 grams.

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

12. The method of claim 1 wherein the single dosage unit of elemental iron is administered in about 5 minutes or less.

13. The method of claim 1 wherein the iron carbohydrate complex is an iron carboxymaltose complex.

14. The method of claim 13, wherein

(i) 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; or

(ii) the iron carboxymaltose complex is a polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

15. The method of claim 1, wherein the iron carbohydrate complex is an iron polyglucose sorbitol carboxymethyl ether complex.

16. The method of claim 15, wherein the iron polyglucose sorbitol carboxymethyl ether complex is a polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite complex.

17. The method of claim 1, wherein

mean iron core size is at least about 1 nm but no greater than about 9 nm; or

mean size of a particle of the iron carbohydrate complex is no greater than about 35 nm.

18. The method of claim 1, wherein the iron carbohydrate complex is administered parenterally.

19. The method of claim 18, wherein

(i) parenteral administration comprises intravenous infusion and the single unit dose of iron carbohydrate complex is administered at a concentration of

about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent;

(ii) parenteral administration comprises bolus injection and the single unit dose of iron carbohydrate complex is administered at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent; or

(iii) parenteral administration comprises intramuscular injection and the single unit dose of iron carbohydrate complex is administered at a concentration of about 500 mg elemental iron in less than about 10 ml diluent.

20. 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.

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

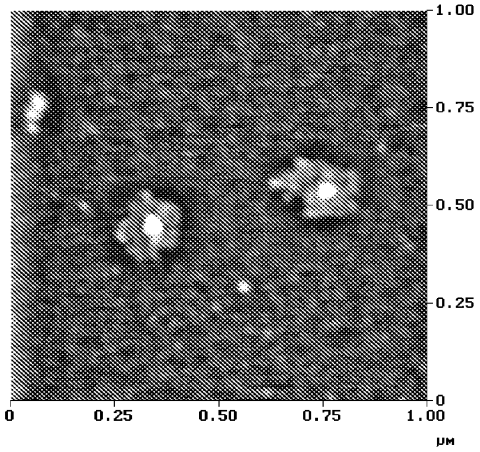


FIG. 1B

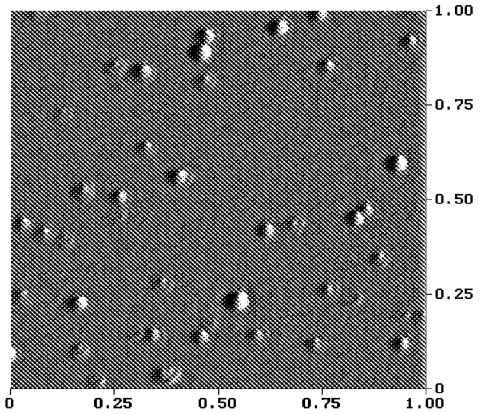


FIG. 1A

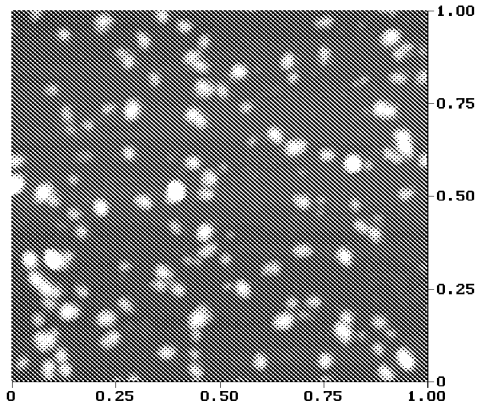
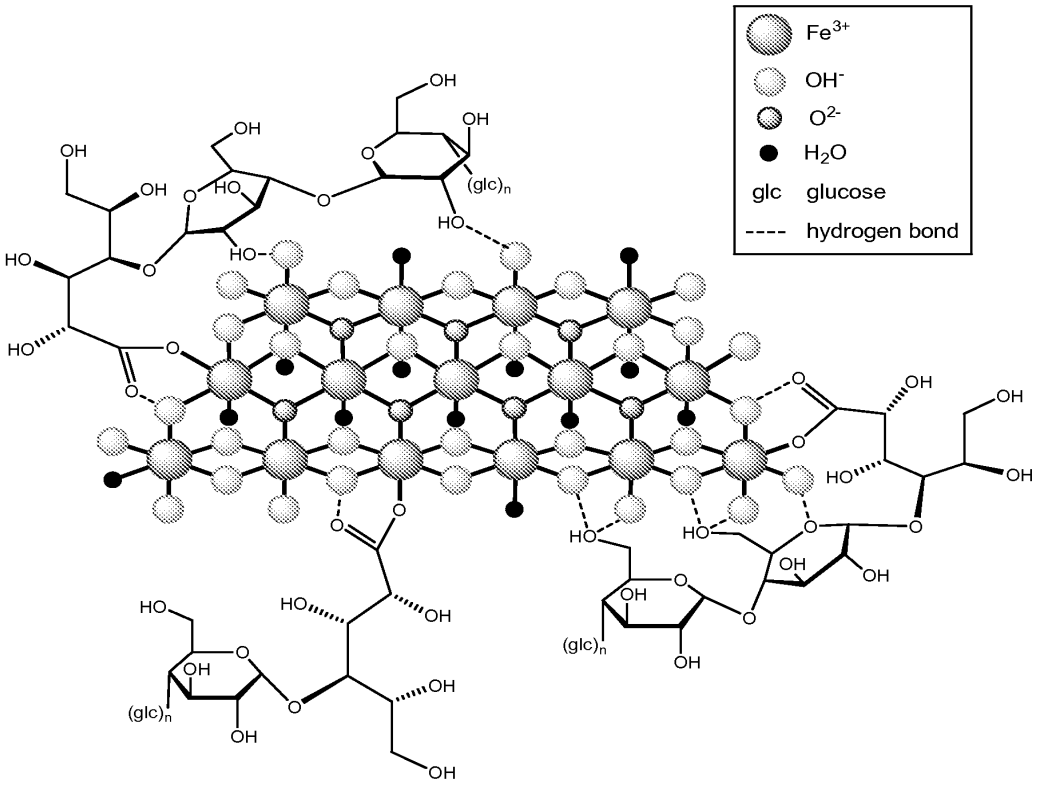


FIG. 1C

FIGURE 2



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Applicant/Patent Owner: Luitpold Pharmaceuticals, Inc.

Application No./Patent No.: 14/100,717 Filed/Issue Date: 09 December 2013

Titled: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

Luitpold Pharmaceuticals, Inc., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

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2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

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   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

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   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

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   2. From: _____ To: _____

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Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Kathleen E. Chaffee/	09 December 2013
Signature	Date
Kathleen E. Chaffee	69,903
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

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

The informationprovided 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 disclosure of these records is required by the Freedom of Information Act.
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 informationin 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 InternationalApplication 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, arecord 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 inspection or an issued patent.
9. A record from thissystem 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.

Docket Number: 30015730-0043

ASSIGNMENT

WHEREAS, Mary Jane Helenek, a citizen of the United States, residing at 13 Evans Drive, Brookville, New York 11545; Marc L. Tokars, a citizen of the United States, residing at 202 Farmingdale Drive, Douglassville, Pennsylvania 19618; and Richard P. Lawrence, a citizen of the United States, residing at 94 Youngs Avenue, Calverton, New York 11933; referred to as ASSIGNORS, have invented a certain invention entitled "METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON," and have executed an application for Letters Patent, entitled the same, having a filing date of January 8, 2007, and identified as United States Patent Application Serial No. 11/620,986; and

WHEREAS, Luitpold Pharmaceuticals, Inc., incorporated in the State of New York, with a principal place of business at One Luitpold Drive, Shirley, NY 11967, hereinafter referred to as ASSIGNEE, is desirous of acquiring the entire right, title and interest in, to and under said invention and the United States Letters Patent to be obtained therefor:

NOW THEREFORE, TO ALL WHOM IT MAY CONCERN:

Be it known that for good and valuable consideration, the receipt of which is hereby acknowledged, the ASSIGNORS hereby sell, assign and transfer to ASSIGNEE the full and exclusive right, title and interest to said invention and all Letters Patent of the United States to be obtained therefor on said applications or any non-provisional, continuation, division, renewal, substitute or reissue thereof for the full term or terms for which the same may be granted.

ASSIGNORS also assign all of its right, title and interest in and to said invention in all foreign countries, and all applications for Letters Patent which may evolve therefrom, including the right to claim International Convention priority.

ASSIGNORS hereby covenant that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale.

ASSIGNORS further covenant that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said applications, said invention and said Letters Patent as may be known and accessible to ASSIGNORS, and ASSIGNORS will testify as to the same in any interference or litigation related thereto and will promptly execute and deliver to ASSIGNEE or its legal representative

any and all papers, instruments or affidavits required to apply for obtain, maintain and enforce said applications, said invention and said Letters Patent which may be necessary or desirable to carry out the purposes hereof.

Date: Mar 2 2007

Mary Jane Helenek

Date: 3-1-2007

Marc L. Tokars

Date: 3/2/2007

Richard P. Lawrence

Electronic Acknowledgement Receipt

EFS ID:	17607847
Application Number:	14100717
International Application Number:	
Confirmation Number:	2813
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	Kathleen E. Chaffee/Connie Payne
Filer Authorized By:	Kathleen E. Chaffee
Attorney Docket Number:	30015730-0065
Receipt Date:	09-DEC-2013
Filing Date:	
Time Stamp:	17:37:55
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	Power of Attorney	US_General_POA_30015730.pdf	134172 31bf4b8ed0f65f063cbe5770d3c0bc39e487fe39	no	1
Warnings:					
Information:					

2	Assignee showing of ownership per 37 CFR 3.73.	37p3_Statement_executed.pdf	101562 8c756ea8f1ac0185621e7879bb710ac692e55c99	no	3
Warnings:					
Information:					
3	Assignee showing of ownership per 37 CFR 3.73.	Assignment_30015730-0043.pdf	97297 41c5affc9307b6888e6de47bdf5da285e8337141	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	333031		

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.