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P.O. Box 1450
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/787,283	04/30/2013	8431549	30015730-0053	4251

26263 7590 04/10/2013

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 47 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

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

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

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

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

Mary Jane Helenek, Brookville, NY;
Marc L. Tokars, Douglassville, PA;
Richard P. Lawrence, Southold, 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 02/28/2013
SNR DENTON 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.
12/787,283	05/25/2010	Mary Jane Heimek	30015730-0053	4251

TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$885	$300	$0	$1185	05/28/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
LAU, JONATHAN S	1623	514-058000

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

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

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

Authorized Signature: Kathleen E. Chaffee
Date: 20 March 2013
Typed or printed name: Kathleen E. Chaffee
Registration No.: 69,903

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

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Mary Jane Helenek et al.	Confirmation No:	4251
Serial No:	12/787,283	Customer No:	26263
Filed:	25 May 2010	Docket No:	30015730-0053
Examiner:	Jonathan S. Lau		
Art Unit:	1623		
Title:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON		

FILED VIA EFS WEB
MAIL STOP ISSUE FEE
Commission for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NOTIFICATION OF LOSS OF ENTITLEMENT TO SMALL ENTITY STATUS

Dear Sir:

In accordance with 37 C.F.R. 1.27(g)(2), Applicants hereby notify the U.S. Patent and Trademark Office that they are no longer eligible to claim Small Entity Status in the above referenced application.

It is believed that no fees are due with filing this Notification. However, the Commissioner is herby authorized to charge any fees that may be required or credit any overpayments to SNR Denton US LLP Deposit Account No. 19-3140.

Respectfully Submitted,

20 March 2013
Date

/Kathleen E. Chaffee/
Kathleen E. Chaffee, Reg. No. 69,903
Agent for Applicant(s)

SNR Denton US LLP
P.O. Box 061080
Wacker Drive Station, Willis Tower
Chicago, IL 60606-1080
Phone: 973-912-7174
Fax: 973-912-7199

Electronic Patent Application Fee Transmittal	
Application Number:	12787283
Filing Date:	25-May-2010
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Filer:	Kathleen E. Chaffee/Drenda Nemeth
Attorney Docket Number:	30015730-0053
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	1780	1780
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2080**

Electronic Acknowledgement Receipt	
EFS ID:	15305812
Application Number:	12787283
International Application Number:	
Confirmation Number:	4251
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/Drenda Nemeth
Filer Authorized By:	Kathleen E. Chaffee
Attorney Docket Number:	30015730-0053
Receipt Date:	20-MAR-2013
Filing Date:	25-MAY-2010
Time Stamp:	11:28:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2080
RAM confirmation Number	30493
Deposit Account	
Authorized User	

File Listing:

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

1	Issue Fee Payment (PTO-85B)	Issue_fee_transmittal_correcting_small_entity_status_executed.pdf	1822305 95d9ee8f462988373a1191e5e3223608715 5768f	no	1
Warnings:					
Information:					
2	Notification of loss of entitlement to small entity status	Notification_Of_Loss_Of_Entitlement_To_Small_Entity_Status_20_March_2013.pdf	58748 030a2974be5387bdd1bf5ef12c71b07d388 fc132	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	31760 62142d1baa823cf9f50bf317e5b81435b4ea 6495	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1912813		

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

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

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

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

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUPPLEMENTARY **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	30015730-0053
	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.)

Applicant Information:

Applicant 1

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

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

Citizenship under 37 CFR 1.41(b)[i] US

Mailing Address of Applicant:

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

Applicant 2

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

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

Citizenship under 37 CFR 1.41(b)[i] US

Mailing Address of Applicant:

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

Applicant 3

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

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

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

City	~~New York~~ Calverton	State/Province	NY	Country of Residence[i]	US

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0053
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

Citizenship under 37 CFR 1.41(b) [i]	US		
Mailing Address of Applicant:			
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@sonnenschein.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON		
Attorney Docket Number	30015730-0053	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
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).
Enter either 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/SB/14 (07-07)
Approved for use through 06/30/2010. 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	30015730-0053
	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(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	11620986	2007-01-08
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
11620986	non provisional of	60757119	2006-01-06

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

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. 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(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			(•) Yes ( ) No

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

Assignee Information:

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

Assignee 1

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

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

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

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0053
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.					
Signature	/Kathleen E. Chaffee/			Date (YYYY-MM-DD)	2013-03-19
First Name	Kathleen E.	Last Name	Chaffee	Registration Number	69903

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.

Electronic Acknowledgement Receipt	
EFS ID:	15299849
Application Number:	12787283
International Application Number:	
Confirmation Number:	4251
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:	30015730-0053
Receipt Date:	19-MAR-2013
Filing Date:	25-MAY-2010
Time Stamp:	16:04:56
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	Application Data Sheet	Supp_ADS_30015730-0053_uspto.pdf	567466 3ef47301476b05f56ef25c61fc153fe833c00e14	no	5
Warnings:					
Information:					

This is not an USPTO supplied ADS fillable form	
Total Files Size (in bytes):	567466

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 02/28/2013

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

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 02/28/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/787,283	05/25/2010	Mary Jane Helenek	30015730-0053	4251

TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$885	$300	$0	$1185	05/28/2013

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

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

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

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

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

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

If the SMALL ENTITY is shown as NO:

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

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

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

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

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

PTOL-85 (Rev. 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 02/28/2013
SNR DENTON 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.
12/787,283	05/25/2010	Mary Jane Helenek	30015730-0053	4251

TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$885	$300	$0	$1185	05/28/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
LAU, JONATHAN S	1623	514-058000

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

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

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

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

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

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

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

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

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

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/787,283	05/25/2010	Mary Jane Helenek	30015730-0053	4251

26263 7590 02/28/2013

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

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 02/28/2013

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

The Patent Term Adjustment to date is 90 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 90 day(s).

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

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

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

PTOL-85 (Rev. 02/11)

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. 12/787,283	Applicant(s) HELENEK ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	

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

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

1. ☒ This communication is responsive to *Applicant's Amendment and Remarks, filed 6 Dec 2012*.

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 *1,3-12 and 15-26*. 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).
   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 2 Oct 2012, 14 Jan 2013
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 _____.

/SHAOJIA ANNA JIANG/
Supervisory Patent Examiner, Art Unit 1623

EXAMINER'S AMENDMENT

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

Authorization for this examiner's amendment was given in a telephone interview with Kathleen Chaffee on 7 Feb 2013.

The application has been amended as follows:

Amendment to the Claims

- Claims 13, 14 and 27 are canceled.
- Claims 1 and 7 are amended as follows:

1. (currently amended) A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism resulting in reduced bioavailability of dietary iron, comprising administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron,

wherein,

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

the iron carbohydrate complex has a substantially non-immunogenic

carbohydrate component, and

the disease, disorder or condition is not Restless Leg Syndrome.

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

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 6 Dec 2012, in which claim 1 is amended to change the scope and breadth of the claim, claim 2 is canceled, and new claims 21-27 are added.

The declaration of Richard P. Lawrence (inventor), submitted by Applicants on 6 Dec 2012 under 37 CFR § 1.132, is acknowledged and will be further discussed below.

This application is a domestic application, filed 25 May 2010; and claims benefit as a CON of 11/620,986, filed 8 Jan 2007, issued as PAT 7,754,702, which claims benefit of provisional application 60/757,119, filed 6 Jan 2006.

Claims 1 and 3-27 are pending in the current application. Claims 7 and 13-16, drawn to non-elected species, are rejoined herein. Claims 13, 14 and 27 are canceled by examiner's amendment herein. Claims 1, 3-12 and 15-26 are allowed in view of the examiner's amendment herein.

Terminal Disclaimer

The terminal disclaimer filed on 5 Feb 2013 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent 7,754,702 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Election/Restrictions

Claims 1-6, 8-12 and 17-20 are drawn to allowable subject matter. The election of species requirement amount First species of disease, disorder or condition treated, Second species of iron carbohydrate complex, and Third species of route of administration, as set forth in the Office action mailed on 23 Mar 2012, has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction/election of species requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.** Claims 7 and 13-16, directed to non-elected species are no longer withdrawn from consideration because the claim(s) requires all the limitations of an allowable claim.

In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

REASONS FOR ALLOWANCE

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

Rejections Withdrawn

Applicant's Remarks, filed 6 Dec 2012, and the declaration of Richard P. Lawrence (inventor), submitted by Applicants on 6 Dec 2012 under 37 CFR § 1.132 with respect that claims 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for iron polyisomaltose complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies has been fully considered and is persuasive, as Applicant's Remarks and declaration of Richard P. Lawrence regarding the state of the art at the time of the instant invention as presented in post art Jahn et al. are perusiave that one of ordinary skill in the art at the time of the instant invention would have been able to practice the invention for iron polyisomaltose complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies. Post art Jahn et al. at page 489, left column, paragraph 5 provides evidence that at the time of the instant invention one of ordinary skill in the art would have been able to select isomaltose oligomers to block anaphlaxis to dextrans and that selection of isomaltose oligomers that were nonanaphylactogenic and desensitizing in animals sensitized against dextran. MPEP 2164.08(b) provides that "The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." In the instant case, post art Jahn et al. provides evidence that at the time of the

instant invention was made a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Therefore the presence of any embodiments taught to be inoperative by Cisar et al. does not render the instant claims nonenabled.

This rejection has been **withdrawn**.

Applicant's Remarks, filed 6 Dec 2012, and examiner's amendment detailed herein with respect that claims 1, 4-6, 8-12 and 18-20 are rejected under 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) has been fully considered and is persuasive, as Applicant's Remarks are persuasive that one of ordinary skill in the art would not have been motivated to combine the teaching of Hamstra et al. in view of Muller et al. to substitute iron polyisomaltose taught by Muller et al. in the method of Hamstra et al. at the dosage taught by Hamstra et al. Applicant provides evidence of the understanding of one of ordinary skill in the art at the time of the invention regarding suggested doses for different iron carbohydrate complexes as taught within Macdougall et al. In view of the withdrawal of the election of species herein, Applicant's remarks are also persuasive for the full scope of the claim as amended herein. See also, MPEP 2145 X.D.3. providing "The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." and "[k]nown disadvantages in old

devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." Therefore the instant invention is not taught or fairly suggested by the prior art in view of the totality of the prior art.

This rejection has been **withdrawn**.

Applicant's Remarks, filed 6 Dec 2012, and examiner's amendment detailed herein with respect that claims 17 is rejected under 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, 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 Applicant's Remarks are persuasive as detailed above with respect to Hamstra et al. in view of Muller et al.

This rejection has been **withdrawn**.

In the telephonic interview with Kathleen Chaffee and Dennis Harney on 4 Feb 2013 indicated allowable subject matter was discussed as detailed in the Interview Summary mailed 6 Feb 2013. In order to facilitate allowance of the indicated allowable subject matter, the terminal disclaimer was filed and agreement was reached on the examiner's amendment detailed herein.

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, 3-12 and15-26 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.

/SHAOJIA ANNA JIANG/
Supervisory Patent Examiner, Art Unit 1623

/Jonathan S Lau/
Examiner, Art Unit 1623

PTO/SB/08A (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	12/787,283
Filing Date	25 May 2010
First Named Inventor	Mary Jane Helenek
Art Unit	1623
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0053

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/J.L./	1.	US-7612109	11-03-2009	Geisser et al.	
		US-			
		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]
						☐
						☐
						☐
						☐
						☐

Examiner Signature	/Jonathan Lau/	Date Considered	02/08/2013

*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.

PTO/SB/08B (01-08)
Approved for use through 03/31/2008. OMB 0651-0031
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	12/787,283
Filing Date	25 May 2010
First Named Inventor	Mary Jane Helenek
Art Unit	1623
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0053

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]
/J.L./	2.	European Official Communication dated 04 June 2012 in related Application No. EP 07716309.5 filed 08 January 2007, 5 pages.	

Examiner Signature	/Jonathan Lau/	Date Considered	02/08/2013

*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.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12787283	HELENEK ET AL.
	Examiner	**Art Unit**
	JONATHAN S LAU	1623

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets			
Symbol	**Type**	**Set**	**Ranking**	**Version**

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION	
CLASS	**SUBCLASS**	**CLAIMED**	**NON-CLAIMED**
514	58	A 6 1 K 31 / 721 (2006.01.01)	
CROSS REFERENCE(S)		A 6 1 K 31 / 718 (2006.01.01)	
		A 6 1 K 31 / 295 (2006.01.01)	
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**		
514	54 502		
536	113		

/JONATHAN S LAU/ Examiner.Art Unit 1623 (Assistant Examiner)	2/8/2013 (Date)	**Total Claims Allowed:** 23
/SHAOJIA ANNA JIANG/ Supervisory Patent Examiner, Art Unit 1623 (Primary Examiner)	(Date)	O.G. Print Claim(s) 1 / O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12787283	HELENEK ET AL.
	Examiner	**Art Unit**
	JONATHAN S LAU	1623

/JONATHAN S LAU/ Examiner.Art Unit 1623	2/8/2013	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	23	
/SHAOJIA ANNA JIANG/ Supervisory Patent Examiner, Art Unit 1623		O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12787283	HELENEK ET AL.
	Examiner	**Art Unit**
	JONATHAN S LAU	1623

☒ 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	14	17												
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2	3	16	19												
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10	11		27												
11	12														
	13														
	14														
12	15														
13	16														

/JONATHAN S LAU/ Examiner.Art Unit 1623 (Assistant Examiner)	2/8/2013 (Date)	**Total Claims Allowed:** 23	
/SHAOJIA ANNA JIANG/ Supervisory Patent Examiner, Art Unit 1623 (Primary Examiner)	(Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12787283	HELENEK ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1623

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	54, 58, 502	2/8/2013	JSL

SEARCH NOTES		
Search Notes	Date	Examiner
EAST - inventor name search (Mary Helenek, Marc Tokars, Richard Lawrence)	6/1/2012	JSL
EAST - see attached notes	6/1/2012	JSL
Google Scholar - see attached notes	6/1/2012	JSL
EAST - inventor name search (Mary Helenek, Marc Tokars, Richard Lawrence) - updated	2/8/2013	JSL
Review parent application 11/620,986	2/8/2013	JSL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	54, 58, 502	2/8/2013	JSL

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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	12/787,283
Filing Date	25 May 2010
First Named Inventor	Mary Jane Helenek
Art Unit	1623
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0053

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.L./	1.	European Official Communication dated 04 June 2012 in related Application No. EP 07716309.5 filed 08 January 2007, 4 pages.	

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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.
12/787,283	05/25/2010	Mary Jane Helenek	30015730-0053	4251

26263 7590 02/06/2013

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

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
02/06/2013	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.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	12/787,283	HELENEK ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Jonathan S. Lau*.

(2) *Shaojia Anna Jiang*.

(3) *Kathleen Chaffee*.

(4) *Dennis Harney*.

Date of Interview: *04 February 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☒ Yes ☐ No.
If Yes, brief description: *response of record, filed 6 Dec 2012, and IDS filed 14 Jan 2013*.

Issues Discussed ☐101 ☒112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1,3 and 7*.

Identification of prior art discussed: *Helenek et al. (US 6,960,571), parent patent US 7,754,702*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/SHAOJIA ANNA JIANG/
Supervisory Patent Examiner, Art Unit 1623

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: The response of record was discussed and found to be persuasive regarding the rejections under 112 and 103 of record.

The rationale behind the election of species requirement being based on the record at the time the requirement was originally made was discussed, and the withdrawal of the election of species requirement in view of allowable subject matter was discussed. The obviousness of different species was discussed in view of the updated record which can change the determination of what species are independent and distinct.

It was discussed that upon withdrawal of the election of species requirement, the Hamstra reference may be applicable against the species of iron hydrogenated dextran complex. This species would require further search and examination.

It was discussed that upon withdrawal of the election of species requirement the Helenek et al. reference disclosing treatment of Restless Leg Syndrome with iron dosage two to ten times greater than the dosage for treating other conditions.

It was discussed that upon withdrawal of the election of species requirement would raise the issue of obviousness-type double patenting with the parent patent US 7,754,702 due to the overlapping scope of claimed subject matter.

The IDS filed 14 Jan 2013 was discussed and the references included did not raise further issues.

Examiner noted that cancelation of the species of iron hydrogenated dextran complex, excluding Restless Leg Syndrome, and filing a TD to the parent patent US 7,754,702 would place the instant application in condition for allowance. Agreement was not reached during the interview, however Applicant will consider the indicated allowable subject matter and follow up with the examiner.

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	12787283
Filing Date	25-May-2010
First Named Inventor	Mary Helenek
Attorney Docket Number	30015730-0053
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 Phamaceuticals, 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)

7754702

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 SMALL ENTITY status. See 37 CFR 1.27.

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

◉ Applicant(s) status remains as SMALL ENTITY.

○ Applicant(s) status remains as other than SMALL ENTITY.

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

○ A joint inventor; all of whom are signing this request

○ The assignee of record of the entire interest that has properly made itself of record pursuant to 37 CFR 3.71

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:	12787283
Filing Date:	25-May-2010
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:	30015730-0053
Filed as Small Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Statutory or terminal disclaimer	2814	1	80	80
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($)
Miscellaneous:				
		Total in USD ($)		**80**

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

Application No.: 12787283

Filing Date: 25-May-2010

Applicant/Patent under Reexamination: Helenek et al.

Electronic Terminal Disclaimer filed on February 5, 2013

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt	
EFS ID:	14883705
Application Number:	12787283
International Application Number:	
Confirmation Number:	4251
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:	30015730-0053
Receipt Date:	05-FEB-2013
Filing Date:	25-MAY-2010
Time Stamp:	18:18:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$80
RAM confirmation Number	5312
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	33647 1ed2d0f7b2f2ae0516530a85d275ed3caf3ce4b1	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	29749 6dbcaf20482030ca9e336c47d759616740cd75a6	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	63396		

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

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

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

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

PTO/SB/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 2

Complete if Known	
Application Number	12/787,283
Filing Date	25 May 2010
First Named Inventor	Mary Jane Helenek
Art Unit	1623
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0053

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-7612109	11-03-2009	Geisser et al.	
		US-			
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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]
						☐
						☐
						☐
						☐
						☐

Examiner Signature		Date Considered	

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PTO/SB/08B (01-08)
Approved for use through 03/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of info unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	12/787,283
Filing Date	25 May 2010
First Named Inventor	Mary Jane Helenek
Art Unit	1623
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0053

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]
	2.	European Official Communication dated 04 June 2012 in related Application No. EP 07716309.5 filed 08 January 2007, 5 pages.	

Examiner Signature		Date Considered	

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Filer:	David Richard Metzger/Kathleen Chaffee
Attorney Docket Number:	30015730-0053
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:				
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Submission- Information Disclosure Stmt	1806	1	180	180
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Confirmation Number:	4251
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	David Richard Metzger/Kathleen Chaffee
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal Letter	IDS_Transmittal_Luitpold_0053.pdf	92748 b25b9d5090709074077bdb7079147cf816f704d7	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	IDS_SB08_Luitpold_0053.pdf	208882 5bc301b70bea0f090ec0ed1ba7458dda5eb0a31f	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	0051EP_OA_06-04-12.pdf	463152 1c0d5a647069afd1321dd3088fd44a1d23aac182	no	5
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30183 f8f3c95c32afe0ca44086a98436eddd2bb4431cc	no	2
Warnings:					
Information:					
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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Mary Jane Helenek et al.	Confirmation No:	4251
Serial No:	12/787,283	Customer No:	26263
Filed:	25 May 2010	Docket No:	30015730-0053
Examiner:	Johnathan S. Lau		
Art Unit:	1623		
Title:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON		

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-SB08B 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; 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).

The IDS filed 02 October 2012 inadvertently omitted page 3 of the EP Official Communication in corresponding European Application No. EP 077163093.5. A replacement copy, including the inadvertently omitted page, is supplied herewith. All references cited in the presently re-submitted European Official Communication are already of record and are not provided herewith.

Furthermore, the Australian Official Action dated 11 September 2011 in corresponding Australian Application No. AU 2007205167, citing WO2004/037865, was previously submitted in the 20 January 2012 IDS and considered by the Examiner on 01 June 2012. The Australian Official Action referenced US Pat. No. 7,612,109 as the English-language equivalent to WO2004/037865 and is provided herewith.

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

Applicants submit herewith a credit card payment via EFS-Web in the amount of $180.00, 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 SNR Denton US LLP Deposit Account No. 19-3140.

Respectfully Submitted,

January 14, 2013
Date

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **12/787,283**	Examiner: **Johnathan S. Lau**
Applicant: **Mary Jane Helenek**	Group Art Unit: **1623**
Filed: **May 25, 2010**	Confirmation No.: **4251**
Docket No.: **30015730-0053**	Customer No.: **26263**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	

December 6, 2012

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 June 6, 2012, Applicants request the Office consider the following amendments and remarks.

IN THE CLAIMS

1. (currently amended) A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism resulting in reduced bioavailability of dietary iron, comprising administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron**[[;]],**

wherein**,**

the iron carbohydrate complex is selected from the group consisting of ~~**an iron carboxymaltose complex,**~~ an iron mannitol complex, an iron polyisomaltose complex, an iron polymaltose complex, an iron gluconate complex, an iron sorbitol complex, and an iron hydrogenated dextran complex**,** **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. (withdrawn) 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. (original) The method of claim 1 wherein the single dosage unit of elemental iron is administered in about 15 minutes or less.

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

13-14. (canceled)

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

16. (withdrawn) 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 the single dosage unit of elemental iron is administered in about 2 minutes or less.

22. (new) The method of claim 1 wherein the single dosage unit of elemental iron is greater than 1.0 grams.

23. (new, withdrawn) The method of claim 1 wherein the iron carbohydrate complex is an iron mannitol complex.

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

25. (new, withdrawn) The method of claim 1 wherein the iron carbohydrate complex is an iron gluconate complex.

26. (new, withdrawn) The method of claim 1 wherein the iron carbohydrate complex is an iron sorbitol complex.

27. (new, withdrawn) The method of claim 1 wherein the iron carbohydrate complex is an iron hydrogenated dextran complex.

REMARKS

Upon entry of this amendment, claims 1, 3-12, 15-27 are pending. Claim 1 has been amended. Claims 21-27 have been added. Claims 7, 13-16, 23, 25-27 have been withdrawn. Claims 2, 13-14 have been canceled.

Support for the amendment to claim 1 appears at least at claim 1 and claim 2.

Support for new claim 21 appears at least at page 12, ¶0039. Support for new claim 22 appears at least at page 11, ¶0037. Support for new claims 23-27 appears at least in claim 1.

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

Restriction Status

Species Restriction

The Office is presently examining the claims with respect to the species of:

(i) disease, disorder or condition, **iron deficiency anemia associated with chronic blood loss or acute blood loss**, reading on claims 1, 3-6, 8-12, 15-27;

(ii) iron carbohydrate complex, **iron polyisomaltose**, reading on claims 1, 3-12, 15-20, 24.

(iii) route of administration, **intravenous infusion**, reading on claims 1, 3-12, 15-27.

By the Office's required species election, the Office acknowledges that each such specie is independent, distinct, and nonobvious over other species (MPEP 806.04; 37 CFR 1.146).

Applicants reserve the right to request REJOINDER, under MPEP § 821.04, and examination of non-elected species.

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

Applicants respectfully traverse and, for the following reasons, request reconsideration and withdrawal of the rejection of claims 2 and 3 under 35 U.S.C. §112, ¶1 as failing to comply with the enablement requirement. The Office asserts that the

specification does not provide enablement for iron polyisomaltose complex having substantially non-immunogenic carbohydrate component and substantially no cross-reactivity with anti-dextran antibodies, as recited in claims 2 and 3. Claim 2 has been canceled and features thereof incorporated into claim 1.

The specification meets the enablement requirement if, based on the disclosure in view of the state of the art, one of ordinary skilled in the art can make and use the entire scope of the claimed invention without undue experimentation. MPEP §2164.08.

Based upon the disclosure of the present application, undue experimentation would not be required for one skilled in the art to practice the invention. Analysis of the *Wands* factors (*see infra*) demonstrates that one skilled in the art would be enabled to make and use the invention from the disclosures in the present patent application coupled with information known in the art without undue experimentation. *See* MPEP §2164.01.

Nature of the invention—The present Application provides a method of treating iron associated diseases, disorders, or conditions with iron carbohydrate complexes, e.g., iron polyisomaltose, 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. The presently examined claimed subject matter

Skill in the Art—The Office acknowledges the level of one of ordinary skill in the art is high, with a practitioner of at least a Ph.D. researcher with several years of experience in the art. The high level of skill in the art supports that the claimed method could be practiced by one skilled in the art without undue experimentation.

Claim Scope—The claims are presently examined for the species of iron polyisomaltose from the genus of iron carbohydrate. Features pertinent to the above rejection include “a substantially non-immunogenic carbohydrate component” in claim 1 and “substantially no cross reactivity with anti-dextran antibodies” in claim 3.

Thus, the scope of the presently examined claimed subject matter is not overly broad, which supports that the claimed method could be practiced by one skilled in the art without undue experimentation.

State of the Art—The state of the art at the time of filing support that an iron polyisomaltose can be "substantially non-immunogenic" and have "substantially no cross reactivity with anti-dextran antibodies".

At the time of filing, and as acknowledged by the Office, an iron polyisomaltose is a type of iron carbohydrate complex that includes isomaltose units in the carbohydrate component (see Action of June 6, 2012, page 4, ln. 8-11). 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). 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. In fact, the Office acknowledges that a linear α-(1-6) chain of glucose is an example of a polymaltose (see Action of June 6, 2012, page 4, ln. 8-11)—thus the Office acknowledges that Monofer® is an example of an iron polyisomaltose. In contrast, a dextran is a branched glucan with straight chains having α1-6 glycosidic linkages and branches beginning from α1-3 linkages. Physiochemical properties of the iron isomaltoside Monofer® are described in Jahn et al. 2011 Eur J Pharma and Biopharma 78, 480-49 (Jahn et al.).

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, col. 1, ln. 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, col. 1, ln. 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, col. 2, ln. 3-5; see Lawrence Declaration, ¶5).

Cross-reactivity was understood at the time of filing as a reaction between an antibody and an antigen (that differs from an immunogen) resulting in an immune response (see Lawrence Declaration, ¶8). In other words, mere binding of an antibody and an antigen was not understood as "cross-reactivity" in the absence of an immune response (see Lawrence Declaration, ¶8).

Furthermore, it was within the skill of the art at the time of filing to test for immunogenicity and cross-reactivity to anti-dextran antibodies (see ¶0061 of the Application as filed, citing Bailie et al. (2005) Nephrol Dial Transplant, 20(7), 1443-1449, and Spinowitz et al. (2005) Kidney Intl 68, 1801-1807).

Thus, state of the art at the time of filing support that an iron polyisomaltose can be "substantially non-immunogenic" and have "substantially no cross reactivity with anti-dextran antibodies".

The Office asserts that Cisar discloses anti-dextran anti-bodies recognize both terminal and non terminal α(1-6) chains of dextran binding to a trisaccharide to hexasaccharide sized site. But the Office has failed to establish that any such binding results in an immune reaction and, as such, the Office has failed to show "cross-reactivity". Furthermore, assertions of the Office are rebutted by Jahn et al., which evidences that the iron isomaltoside Monofer® (i.e., one example of an iron polyisomaltose) is substantially non-immunogenic and has substantially no cross reactivity with anti-dextran antibodies (see Lawrence Declaration, ¶¶7-8).

For at least the above reasons, the state of the art at the time of filing supports that that the claimed method could be practiced by one skilled in the art without undue experimentation.

Level of Predictability in the Art—a substantial body of research had been performed on iron carbohydrate complexes at the time of filing. Thus is provided an increased level of predictability in the art.

The Office asserts that one of ordinary skill in the art would expect anti-dextran antibodies to cross-react with polyisomaltose because Cisar predicts anti-dextran antibodies recognize both terminal and non-terminal α(1-6) chains of dextran. But as discussed above, the Office has failed to establish that any such binding results in an immune reaction and, as such, the Office has failed to show "cross-reactivity". Furthermore, assertions of the Office are rebutted by Jahn et al., which evidences that the iron isomaltoside Monofer® (i.e., one example of an iron polyisomaltose) is substantially non-immunogenic and has substantially no cross reactivity with anti-dextran antibodies (see Lawrence Declaration, ¶¶7-8).

For at least the above reasons, the level of predictability in the art at the time of filing supports that that the claimed method could be practiced by one skilled in the art without undue experimentation.

Guidance of the specification and claims—The specification and claims provide further guidance with respect to enabling the claims. One of ordinary skill in the art is provided with the sufficient disclosure to perform the steps for 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 iron polyisomaltose has a substantially non-immunogenic carbohydrate component and substantially no cross-reactivity with anti-dextran antibodies.

Furthermore, the specification provides guidance as to testing an iron carbohydrate complex (e.g., an iron polyisomaltose) for immunogencity and/or cross-reactivity to anti-dextran antibodies (see ¶0061 of the Application as filed, citing Bailie et al. (2005) Nephrol Dial Transplant, 20(7), 1443-1449, and Spinowitz et al. (2005) Kidney Intl 68, 1801-1807; ¶0071). Under MPEP §2164.04, unless there is a reason to doubt the objective truth of statements contained in the specification disclosure, the subject matter relied on for enabling support must be taken as being in compliance with the enablement requirement.

Under MPEP §2164.03, the amount of guidance needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. As discussed above, the state of the art understanding of the lack of substantial immunogenicity or substantial cross-reactivity to anti-dextran antibodies for an iron polyisomaltose further reduces the amount of guidance needed to enable the claims.

Thus the amount of direction and guidance provided by the specification and claims supports that the claimed method could be practiced by one skilled in the art without undue experimentation.

Working Examples—The working examples utilize straightforward methodology and experiments for the treatment of 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 a representative iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron; wherein the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component and substantially no cross reactivity with anti-dextran antibodies.

Example 4 describes safety assessment studies in which single dosage unit administration of up to 1,000 mg in 73 patients resulted in few adverse events and no serious adverse events (see page 23, ¶0107). Example 5 describes ten different studies with a total of 2429 subjects where, in 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 events**. Furthermore, in Example 5, the only drug-related treatment-emergent adverse events reported by at least 2% of subjects in the calculated dose/first-dose 1,000 mg studies were headache (3.9%) and blood phosphate decreased (3.3%) (page 29, ¶0126). And the overall incidence of treatment-emergent adverse events was similar among subjects treated with either the 200 mg or 1000 mg doses (page 29, ¶0127).

One of ordinary skill in the art can adapt the methodology and protocols described in such Examples so as to evaluate other iron carbohydrate complexes, such as an iron polyisomaltose.

Thus the working examples support that the claimed method could be practiced by one skilled in the art without undue experimentation.

Proof of Principle Data—Further experiments, reported after filing of the present application, performed consistent with approaches outlined in the present application, demonstrate proof of concept for an iron polyisomaltose (i.e., the iron isomaltoside Monofer®) having a substantially non-immunogenic carbohydrate component and/or having substantially no cross reactivity with anti-dextran antibodies. Additional evidence that the disclosure enables the claimed invention (e.g., "a declaration after the filing date which demonstrates that the claimed invention works") must be must be weighed with all other evidence showing enablement of the claimed invention (MPEP §2164.05).

According to the Lawrence Declaration, Jahn et al. provides evidence that the iron isomaltoside Monofer® (i.e., one example of an iron polyisomaltose) is substantially non-immunogenic (¶7).

According to the Lawrence Declaration, Jahn et al. provides evidence that the iron isomaltoside Monofer® (i.e., one example of an iron polyisomaltose) has substantially no cross reactivity with anti-dextran antibodies, i.e., Monofer® does not effect a substantial immune response and there is substantially no dextran-induced anaphalytic reactions.

As such, the provided proof of principle evidence is pertinent to enablement of the claims and must be considered by the Office (see MPEP §2164.05).

In conclusion—Given the high level of skill in the art, the direction and guidance provided by the specification, the experimentation required for enablement regarding an iron carboxymaltose complex having substantially non-immunogenic carbohydrate component and substantially no cross-reactivity with anti-dextran antibodies is typical of the field and does not rise to the level of undue experimentation. For at least the above

reasons, the specification in view of the art at the time of filing enables the subject matter of claims 1 and 3.

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 Patent No. 3,100,202 ("Muller").

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 gluconate complex, an iron sorbitol complex, and an iron hydrogenated dextran complex, and the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component.

The Office is presently examining claim 1 with respect to the elected species of an iron polyisomaltose.

Species Restriction Establishes Nonobviousness of Iron Polyisomaltose Complex

The Office has acknowledged that the elected species of iron polyisomaltose complex is patently distinct and nonobvious over other species of the genus of iron carbohydrate complex. For a species election requirement to be proper, the species must be patentably distinct (MPEP 806.04; 37 CFR 1.146). By the Office's required species election among the various iron carbohydrate complexes (*see* Restriction Requirement of March 23, 2012), the Office acknowledges that each species, such as elected species of iron polyisomaltose complex, is independent, distinct, and nonobvious over other species of the genus of iron carbohydrate complex.

A showing of *prima facie* obviousness requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art, or motivate one skilled in the art to select the claimed species from the disclosed prior art genus. MPEP § 2144.08(II)(4). The Office has failed to show why one of ordinary skill would select the claimed compounds and the Office's species restriction requirement evidences they would not.

As such, the species restriction requirement rebuts the Office's assertion it would be obvious to substitute an iron polyisomaltose (of Muller) in protocols disclosed in Hamstra featuring an iron dextran.

Cited References Fail to Disclose All Claim Elements

Neither Hamstra nor Muller teach or suggest all features of the claims.

The Office acknowledges Hamstra does not teach the iron carbohydrate complex is an iron polyisomaltose complex of claim 1, nor an iron polyisomaltose single unit dosage of at least about 0.6 grams of elemental iron. The Office asserts that Hamstra discloses intravenous injection of iron dextran 1,000 mg or >1,000 mg of elemental iron per injection. But Hamstra does not disclose such dosage for any other iron carbohydrate.

To overcome the inadequacies of Hamstra, the Office also cites Muller. 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.

Insufficient Reason to Modify Hamstra or Muller to Reach All Claim Features

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 requirements of an iron polyisomaltose as 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).

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, p. 64, col. 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, p. S26, col. 2) and various iron carbohydrate complexes differentially exert acute toxicity and a proinflammatory effect (see Zager, p. S29, col. 1). Thus, disclosure related to the dosage of iron dextran cannot be extrapolated to other iron carbohydrate complexes, such as iron polyisomaltose not having an immunogenic

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. For example, Geisser at al. 1992 Arnzneimittelforschung 42, 1439-1452 (cited in the Application at ¶0007) discloses that doses of iron carbohydrate complexes higher than 200 mg of iron are generally unsuitable and that the conventional therapy prescribes repeated applications of lower doses over several days.

Furthermore, in the Notice of Allowance dated April 5, 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, col. 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.

Third, as discussed above, the Office's acknowledgement that species of iron carbohydrate complexes are patentably distinct is further evidence that one of skill in the art would not have seen a benefit to modifying an iron dextran of Hamstra so as to reach an iron polyisomaltose as claimed (see MPEP 806.04; 37 CFR 1.146).

Conclusion

As shown above, the Office has failed to show Hamstra and/or Muller, either alone or in any known combination, provide for all features of claim 1. Further, the Office has to provide sufficient reason to modify Hamstra and/or Muller so as to reach all features of claim 1. For at least these reasons, claim 1 is not obvious over Hamstra and/or Muller. The above argument applies equally to claim 1, and claims dependent thereon, such as claims 2-20.

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 in view of Muller and further in view of Lawrence et al., US Patent No. 5,624,668 ("Lawrence").

Standards of obviousness are as discussed above.

Claim 17, dependent on claim 1, recites:

> 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.

As described above neither Hamstra nor Muller disclose all features of claim 1, upon which claim 17 depends, and the Office provides insufficient reason to modify such references to reach all features of claim 17.

To overcome the inadequacies of Hamstra and Muller, the Office cites Lawrence. 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 col. 10., ln. 27-31; col. 12, ln. 33-36). And Lawrence fails to disclose iron carbohydrate complexes recited in claim 1.

As shown above, the Office has failed to show Hamstra, Muller, and/or Lawrence, either alone or in any known combination, provide for all features of claim 17. Further, the Office has to provide sufficient reason to modify Hamstra, Muller, and/or Lawrence so as to reach all features of claim 17. For at least these reasons, claim 17 is not prima facie obvious over Hamstra in view of Muller and Lawrence.

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 three month extension of time and submit herewith the requisite extension fee paid by credit card vie 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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **12/787,283**	Examiner: **LAU, Jonathan S**
Applicant: **HELENEK, Mary Jane**	Group Art Unit: **1623**
Filed: **May 25, 2010**	Confirmation No.: **4251**
Title: **30015730-0053**	Customer No.: **26263**
Docket No.: **Methods and Compositions for Administration of Iron**	

FILED ELECTRONICALLY VIA EFS-WEB

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

DECLARATION UNDER 37 C.F.R. § 1.132

I, Richard P. Lawrence, declare and state as follows:

1. I am Director of Research and Development for Luitpold Pharmaceuticals, Inc.

2. I have a B.S. Degree/Fairleigh Dickinson University, with a focus in Chemistry.

I am a named inventor in the following US patents:

7,754,702 Methods and Compositions for Adminsitration of Iron

7,169,359 Bioequivalence test for iron-containing formulations

6,911,342 Bioequivalence test for iron-containing formulations

5,624,668 Iron Dextran Formulations

I have authored the peer-reviewed manuscript:

Lawrence, "Development and Comparison of Iron Dextran Products," *PDA Journal of Pharmaceutical Science & Technology*, Vol. 52, No. 5, September-October 1998, pp. 190-197.

The following provides a brief overview of my experience:

Training:

BS: Chemistry/Mathematics, Fairleigh Dickinson University, Madison, New Jersey, June 1979

Positions:

Luitpold Pharmaceuticals, Inc. (Shirley, New York)

04/03 – Present	Director, Research & Development
09/02 – 04/03	Director, Quality Assurance
05/02 – 09/02	Director, Quality Control
03/83 – 05/02	Manager, Product Development

Gibco Invenex (Milburn, New Jersey)

10/79 – 03/83	Research Chemist

3. I am a named inventor of the subject matter claimed in present U.S. Patent Application 12/787,283 (the "'283 application"), entitled "Methods and Compositions for Administration of Iron", filed on May 25, 2010.

4. Based on my experience, an iron polyisomaltose is 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. 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. In contrast, a dextran is a branched glucan with straight chains having α1-6 glycosidic linkages and

branches beginning from α1-3 linkages. Physiochemical properties of the iron isomaltoside Monofer® are described in Jahn et al. 2011 Eur J Pharma and Biopharma 78, 480-49 (Jahn et al.).

5. Jahn et al. evidences that the iron isomaltoside Monofer® (i.e., one example of an iron polyisomaltose) avoids dextran-induced anaphylactic reactions (see page 487, col. 2, ¶1; page 489, col. 2, ¶2) and reduces immunogenicity compared to dextran (see page 489, col. 1, ¶4; page 489, col. 2, ¶6). Jahn et al. evidences that even in the 1960s it was known that isomaltose oligomers prevent or block anaphylaxis and that later research in the 1970s and 1980s showed that isomaltose oligomers acted as haptens against circulating anti-dextran antibodies (page 489, col. 1, ln. 53-58, ¶5). Per Jahn et al. and consistent with the understanding in the art at the time of filing, a hapten can bind an antibody without inducing anaphylaxis or an immune response (see page 489, col. 2, ¶1). According to Jahn et al., the ability to administer high doses (e.g., up to 1,600 mg elemental iron) of the the iron isomaltoside Monofer® (i.e., one example of an iron polyisomaltose) arises from reduced immunogenic potential and absence of dextran-induced anaphalytic reactions (see page 481, col. 1, ¶3; page 487, col. 2, ¶1; page 489, col. 2, ¶3, ¶6).

7. Claim 1 of the '283 application recites, inter alia, "wherein the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component". It is my opinion that Jahn et al. provides evidence that the iron isomaltoside Monofer® (i.e., one example of an iron polyisomaltose) is substantially non-immunogenic.

8. Claim 3 of the '283 application recites "wherein the iron carbohydrate complex has substantially no cross reactivity with anti-dextran antibodies". Based on my experience, cross-reactivity at the time of filing was understood as a reaction between an antibody and an antigen (that differs from an immunogen) resulting in an immune response. In other words, mere binding of an antibody and an antigen was not understood as "cross-reactivity" in the absence of an immune response. It is my opinion that Jahn et al. provides evidence that the iron isomaltoside Monofer® (i.e., one example of an iron polyisomaltose) has substantially no cross reactivity with anti-dextran

antibodies, i.e., Monofer® does not effect a substantial immune response and there is substantially no dextran-induced anaphalytic reactions.

9. I hereby declare that the statements made of my own knowledge are true and that all statements made on information made on belief are believed to be true. I acknowledge that willful false statements and alike are punishable by fine or imprisonment or both (18 U.S.C. § 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Date: December 5, 2012

Richard P. Lawrence

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Research paper

A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer®), a new intravenous iron preparation and its clinical implications

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ABSTRACT

The treatment of iron deficiency anemia with polynuclear iron formulations is an established therapy in patients with chronic kidney disease but also in other disease areas like gastroenterology, cardiology, oncology, pre/post operatively and obstetrics' and gynecology. Parenteral iron formulations represent colloidal systems in the lower nanometer size range which have traditionally been shown to consist of an iron core surrounded by a carbohydrate shell. In this publication, we for the first time describe the novel matrix structure of iron isomaltoside 1000 which differs from the traditional picture of an iron core surrounded by a carbohydrate. Despite some structural similarities between the different iron formulations, the products differ significantly in their physicochemical properties such as particle size, zeta potential, free and labile iron content, and release of iron in serum. This study compares the physiochemical properties of iron isomaltoside 1000 (Monofer®) with the currently available intravenous iron preparations and relates them to their biopharmaceutical properties and their approved clinical applications. The investigated products encompass low molecular weight iron dextran (CosmoFer®), sodium ferric gluconate (Ferrlecit®), iron sucrose (Venofer®), iron carboxymaltose (Ferinject®/Injectafer®), and ferumoxytol (Feraheme®) which are compared to iron isomaltoside 1000 (Monofer®). It is shown that significant and clinically relevant differences exist between sodium ferric gluconate and iron sucrose as labile iron formulations and iron dextran, iron carboxymaltose, ferumoxytol, and iron isomaltoside 1000 as stable polynuclear formulations. The differences exist in terms of their immunogenic potential, safety, and convenience of use, the latter being expressed by the opportunity for high single-dose administration and short infusion times. Monofer is a new parenteral iron product with a very low immunogenic potential and a very low content of labile and free iron. This enables Monofer, as the only IV iron formulation, to be administered as a rapid high dose infusion in doses exceeding 1000 mg without the application of a test dose. This offers considerable dose flexibility, including the possibility of providing full iron repletion in a single infusion (one-dose iron repletion).

1. Introduction

Parenteral iron therapy is today widely used for the treatment of iron deficiency anemia. Patients with chronic kidney disease (CKD) also frequently need treatment with parenteral iron preparations in addition to erythropoietin stimulating agents [1]. For renal failure patients on dialysis, the average iron requirements due to blood loss are equivalent to 1–3 g of elemental iron per year [2]. This can easily be accomplished by frequent low dose IV iron administrations, during the regular dialysis sessions.

From initial, generalized use in nephrology parenteral iron therapy has spread in recent years to other disease areas; gastroenterology [3], cardiology [4,5], oncology [6], pre/post operatively [7], obstetrics', and gynecology [8]. However, care providers in these segments have less frequent patient contact, resulting in an increased demand for convenient administration of large IV iron doses in one clinical session.

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Historically, the first parenteral iron preparations were toxic, being administered as an iron oxyhydroxide complex. This problem was circumvented with the introduction of compounds containing iron in a core surrounded by a carbohydrate shell [9]. The currently marketed parenteral iron preparations are considered equally efficacious but vary in molecular size, pharmacokinetics, and adverse reaction profiles. The intravenous iron agents currently available include high molecular weight iron dextran (Dexferrum®), low molecular weight iron dextran (Cosmofer®, Infed®), sodium ferric gluconate (Ferrlecit®), iron sucrose (Venofer®), iron carboxymaltose (Ferinject®/Injectafer®), and ferumoxytol (Feraheme®). High molecular weight iron dextran has been linked to an increased risk of anaphylaxis and anaphylactoid reactions, and it is not available in Europe [10–13]. Although this problem is very much reduced with low molecular weight iron dextran [10–13], there is still a test dose requirement and the infusion of larger doses is hampered by a 4–6 h infusion time. Sodium ferric gluconate and iron sucrose can only be used in moderate iron doses due to the relative weakness of the iron complex [14]. Two new parenteral iron compounds, iron carboxymaltose, and ferumoxytol were recently introduced in the EU and the US markets, respectively. The FDA failed to approve iron carboxymaltose for distribution in the USA due to unexplained hypophosphatemia, an increased number of adverse cardiac events and an imbalance in death rates in the treatment arm compared to the control arm in different RCTs [15].

Although more stable than sodium ferric gluconate and iron sucrose, the administration of iron carboxymaltose and ferumoxytol is still limited to a maximum total dose of 1000 mg and 510 mg, respectively.

The newest IV iron agent Iron isomaltoside 1000 (Monofer®) (e.g., iron oligo isomaltoside (1000) as generic name) is developed and manufactured by Pharmacosmos in Denmark and was introduced in Europe in 2010. The carbohydrate isomaltoside 1000 is a pure linear chemical structure of repeating α1-6 linked glucose units, with an average size of 5.2 glucose units and an average molecular weight of 1000 Da, respectively. It is a nonbranched, nonanaphylactic carbohydrate [16,17], structurally different from branched polysaccharides used in iron dextran (Cosmofer).

The production method and the short nonionic isomaltoside 1000 allows for the construction of a special matrix-like structure with interchanging iron molecules and linear isomaltoside 1000 oligomers. The resulting matrix contains about 10 iron molecules per one isomaltoside pentamer in a strongly bound structure that enables a controlled and slow release of bioavailable iron to iron-binding proteins with little risk of free iron toxicity [18,19]. This allows iron isomaltoside 1000 to be administered safely as a rapid high dose intravenous infusion or bolus injection offering considerable dose flexibility, including the possibility of providing full iron repletion in a single infusion, the so-called one-dose iron repletion.

This article introduces and compares physicochemical properties of iron isomaltoside 1000 (Monofer®) with currently marketed iron formulations. In addition, this comparative study of polynuclear iron formulations currently used in the treatment of anemic disorders includes perspectives on the relevance of these properties with respect to safety, efficacy, and convenience of administration.

2. Materials and methods

2.1. Materials

Sodium ferric gluconate (Ferrlecit®, 12.5 mg Fe/mL in 3.2 mL ampoules; Sanofi-Aventis, Frankfurt, Germany), iron sucrose (Venofer®, 20 mg Fe/mL in 5 mL ampoules; Vifor, München, Germany), low molecular weight iron dextran (CosmoFer®, 50 mg Fe/mL in 2 mL ampoules; Teva, Mörfelden-Walldorf, Germany), iron isomaltoside 1000 (Monofer®, 100 mg Fe/mL in vials; Pharmacosmos, Holbaek, Denmark), iron carboxymaltose (Ferinject®, 50 mg Fe/mL in 2 mL vials; Vifor, München, Germany), and ferumoxytol (Feraheme®, 30 mg Fe/mL, in 17 mL vials; AMAG Pharmaceuticals, Lexington, MA, USA) were obtained from a pharmacy or directly from the manufacturer. The Ferrozine® reaction kit was purchased from Roche Diagnostics GmbH, Mannheim. All iron formulations were used immediately after opening the vial or kept at 4 °C under nitrogen. Solutions were made from double-distilled water.

2.2. Gel permeation chromatography (GPC)

The apparent average molecular weight was analyzed by gel permeation chromatography. Prior to sample analysis, the columns were calibrated using dextran standards. The dextran standards used for GPC calibration were the commercial available Pharmacosmos standards and consisted of Dextran 25, 50, 80, 150, 270, and 410, respectively. The average molecular weights M_w and the peak average molecular weights M_P were 23.000, 21.400; 48.600, 43.500; 80.900, 66.700; 147.600, 123.600; 273.000, 196.300; 409.800, 276.500 for Dextran 25, 50, 80, 150, 270, and 410, respectively. The standards have been evaluated against the Ph.EUR and USP dextran standards.

The detector used in the GPC measurements is a VE 3580 RI detector (Viscotec). Data are collected and calculations are made using the Omnisec 4.1 software from Viscotec.

The hydrodynamic diameter d_h was calculated from the hydrodynamic volume $V_h = M_p \cdot |\eta|$, where the intrinsic viscosity $|\eta|$ is given by the Mark Houwink equation [20]

$$|\eta| = k\overline{M}_v^a$$

where $\overline{M}_v^a$ is the viscosity average molecular weight.

2.3. Dynamic light scattering (DLS) and zeta potential

The size distribution and zeta potential of the whole particle, which can include an iron hydroxide core plus a carbohydrate shell, was determined by DLS. The diluted samples (0.4 mg Fe/mL double-distilled and sterile filtered water) were measured using a Zetasizer Nano S (Malvern Instruments Ltd.; Worcestershire, UK) including a He–Ne Laser with a wavelength of $\lambda = 633$ nm, which illuminated the samples and detects the scattering information at an angle of 173° (Noninvasive Back-scatter technology). Zeta potential measurements were performed at different pH values by addition of 0.1 N HCl or NaOH, respectively. The data were analyzed with the firmware, Zetasizer Software DTSv612 yielding volume distribution data.

2.4. Transmission electron microscopy (TEM)

The dimension of the iron complex nanoparticle core was determined with an EM420 transmission electron microscope (FEI/Philips, Oregon, USA) at 120 kV. All preparations (1 mg Fe/mL, double-distilled water) were deposited onto a hydrophilized copper grid (300 mesh, Ø 3 mm) and were allowed to dry. The median of the geometrical diameter $d_g = \sqrt{(d_s^2 + d_l^2)/2}$ was determined ($n = 50$, d_s = shortest dimension, d_l = longest dimension).

2.5. X-ray diffraction (XRD)

X-ray measurements of dried out solutions (30 °C) were performed with a XRD 3000 TT (Seifert, Ahrensburg, Germany) using Cu radiation ($\lambda = 1{,}54178$ Å, 40 kV, 30 mA) in Bragg Brentano configuration (automatic divergence slit, angular rate 0,18°/min).

The particles mean diameter d was determined from the Scherrer equation: $d = \frac{\lambda}{\beta \cdot \cos\theta}$, where β is the full width at half maximum of the peak at 36° 2θ or 63° 2θ.

2.6. Mössbauer spectroscopy

Mössbauer spectra of iron isomaltoside 1000 were recorded using a conventional spectrometer in the constant-acceleration mode. Isomer shifts are given relative to α-Fe at room temperature. The spectra were measured in a closed cycle cryostat (Cryo Industries of America, USA) at 150 K, equipped with permanent magnets. The magnetically split spectra were analyzed by least-square fits using Lorentzian line.

2.7. Dialysable iron in buffer

The amount of free iron was estimated using the dialysis technique following pH adjustment of each iron dispersion to 7.5. A dispersion volume containing 150 mg of iron (7.5 mL for LMW iron dextran, iron isomaltoside 1000, iron carboxymaltose and ferumoxytol, respectively; 15.0 mL for sodium ferric gluconate, and 11.25 mL for iron sucrose) was added resulting in concentrations of 20.0 mg Fe/mL for all iron products except for sodium ferric gluconate (10.0 mg Fe/mL) and iron sucrose (13.3 mg Fe/mL). Dilutions were made with water and 0.9% sodium chloride solution, respectively. The volumes were added inside the dialysis tubing (12,000–14,000 MWCO, Medicell, London, United Kingdom) and dialyzed for 24 h at 20 °C against 100 mL of water or sodium chloride solution, respectively. The total volume including the dialysis tube was 107.5 mL. Dialysis of each iron agent was performed in duplicate. Iron in the surrounding solution was quantified using ICP-MS (inductively coupled plasma mass spectrometry). The ICP-MS instrument was a Thermo iCap 6000 ICP-OES (Thermo Scientific, Danmark).

Iron is measured at 238,201 nm. The measurement is made axial. Two-point (left–right) baseline correction and external linear calibration curve are used.

The experiments were carried out at room temperature (20–24 °C). In order to evaluate the effect of pH on the level of dialysable, free iron above experiments were conducted also for the high dose IV iron formulations low molecular weight iron dextran, iron isomaltose, iron carboxymaltose, and ferumoxytol without pH adjustment.

2.8. Acid soluble FeOOH

The acidic hydrolysis of the FeOOH in $[FeOOH]_mL_n$ was followed by quantifying the decreasing FeOOH concentration with UV-spectroscopy. The spectrometer used was a Lambda 20 (Perkin Elmer). Readings at 287.3 nm were made from a scan using data interval 1.0 nm, scan speed 249 nm/min, a slit with of 2.0 nm and a smooth with of 2.0 nm.

The absorbance of iron agents (10 mg Fe/l, 10 mm path length) in 0.9% NaCl/0.2375 M HCl was measured at 287.3 nm from t = 0 min to t = 48 h, unless otherwise specified. Initial absorbance after dilution of the iron preparation at $t \approx 0$ min was set to 1 according to 100% undissolved FeOOH and all other measurements were normalized for this. Ln(normalized data) was plotted against time and fitted with a second degree polynomial ($R^2 > 0.990$). Half-life $t_{0.5}$ was calculated from $f_{\text{polynomial}}(t_{0.5}) = \ln(0,5)$.

2.9. Ferrozine®-detectable labile iron

The dissolution of iron in serum was determined by the Ferrozine®-method [21–24]. Ferrozine® does not only detect the free iron but also the weakly bound iron in the complex and the transferrin bound iron in serum, this determination allows one to quantify the in vitro labile iron pool of the investigated intravenous iron formulations. By this method, iron is detected in the ferrous as well as the ferric state as the ferric iron is reduced by ascorbate to ferrous iron. Briefly, human serum was incubated with the iron preparation corresponding to theoretical doses of 200 mg and 500 mg iron, leading to a serum concentration of 66.7 μg/mL and 166.7 μg/mL for a person with a body mass of 70 kg, respectively. These serum concentrations are consequences of a blood volume of 0.07 L per kg and a serum fraction of 60% of the blood volume, yielding a total serum volume of approx. 3 L [25]. The experiment was performed at room temperature (22 °C) in 1.5 mL Eppendorf-tubes. Incubations were done for 10 and 45 min, respectively. Thereafter, a 100 μL sample was analyzed by addition of 700 μL reagent 1 containing thiourea (115 mM) and citric acid (200 mM), followed by addition of 350 μL of reagent 2 containing sodium ascorbate (150 mM) and Ferrozine® (6 mM). Absorption of the complex was measured at 562 nm over approximately 60 min using a PERKIN ELMER Lambda 20 (Perkin Elmer Inc., Waltham, MA, USA) UV–Vis spectrometer. The obtained absorbance versus time curve was fitted to a second degree polynomial for each incubation period and the intercept with the ordinate was calculated to receive the comparable theoretical amount of Ferrozine®-detectable iron. The regression coefficient for the polynomial function was always better than 0.995. The labile iron pool was calculated by linear regression analysis of the obtained intercepts from curves at 10 min incubation and 45 min incubation.

2.10. Elucidation of molecular structure of iron isomaltoside 1000

Proton and carbon NMR spectra were obtained on a Bruker 800 MHz NMR instrument as ca. 5% solutions in D_2O at 300 K. Signals were referenced to external dioxane.

The iron isomaltoside 1000 formulation (10.3 mg) was dissolved in D_2O (600 μL). The sample was transferred to a 5 mm NMR-tube and the ^{13}C NMR spectrum was recorded at 20 °C on a Bruker Avance 800 instrument at 201.12 MHz for carbon (799.96 MHz for proton), integrated and compared with the spectrum of the oligosaccharide alone (7.3 mg) in D_2O (600 μL) [26]. Both samples were measured again and the signals integrated after addition of 2.24 mg of methyl β-maltoside as internal reference.

Molecular modeling: First the isomaltodisaccharide was constructed and an MD calculation using the modeling program, MOE (Molecular Operating Environment, Version 2009.10, Chemical Computing Group Inc., Montreal, Canada), at 450 K, stepsize 0,1 fs clearly showed a significant preference for the gt conformation of C-5–C-6 bonds independent of the starting point. The O-1–C-6 of the glycosidic bond had a weak preference for a trans-arrangement and the orientation of the C-1–O-1 bond satisfied the exoanomeric effect.

The isomaltoside pentamer (composed of 5 α1-6 linked glucose molecules) with glucitol at the reducing end was built from disaccharides in their preferred conformation and energy minimized. The molecule was soaked in water (eight layers) and molecular dynamics was performed at the above conditions corresponding to a period of 2 ns. The additive effect of the oligosaccharide repeat to stabilize the preferred conformation when compared to the disaccharide was significant. The resulting structure was re-soaked and was subjected to energy minimization in water.

3. Results

3.1. Overall particle size

3.1.1. Gel permeation chromatography

The distributions calculated from the GPC chromatograms of the iron preparations show homogenous distributions with the

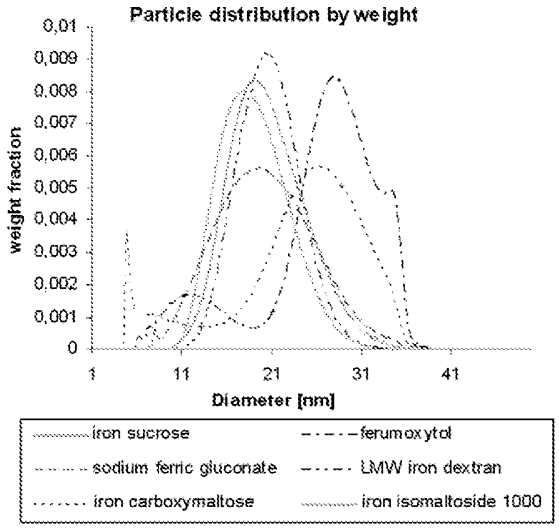

Fig. 1. Weight distribution vs. particle diameter as determined by gel permeation chromatography.

Table 1
Shell /Particle dimensions as determined by gel permeation chromatography (GPC) and dynamic light scattering (DLS).

Iron complex	MW (kDa)	Calculated shell-Ø (nm)[c]	Shell-Ø (nm)	
	GPC		DLS	
Sodium ferric gluconate	164.1	20.3	8.6[a]	0.244[b]
Iron sucrose	140.1	19.1	8.3[a]	0.192[b]
LMW iron dextran	165.0	20.7	12.2[a]	0.149[b]
Iron isomaltoside 1000	150.0	20.5	9.9[a]	0.182[b]
Iron carboxymaltose	233.1	23.8	23.1[a]	0.07[b]
Ferumoxytol	275.7	26.3	23.6[a]	0.143[b]

[a] Median-Ø.
[b] Polydispersity index.
[c] The most frequently found particle diameter in the distribution.

exception of ferumoxytol and iron carboxymaltose which show additional smaller and larger diameter peaks (Fig. 1). The hydrodynamic diameters d_h rise in the order iron sucrose < sodium ferric gluconate < iron isomaltoside 1000 < LMW iron dextran < iron carboxymaltose < ferumoxytol (Table 1). Ferumoxytol was eluted near the exclusion volume, indicating that both its diameter and molecular weight might be underestimated.

3.1.2. Dynamic light scattering (DLS)

The hydrodynamic diameter determined with DLS also measures the carbohydrate shell of the IV iron agents and therefore is larger than iron oxide core diameters determined by TEM or XRD. In Fig. 2 narrow volume distributions of the whole particle diameters are shown. The medians of the hydrodynamic diameters rise from 8.3 to 23.6 nm in the order iron sucrose < sodium ferric gluconate < iron isomaltoside 1000 < LMW iron dextran ≪ ferumoxytol < iron carboxymaltose (Table 1). The zeta potentials of the iron preparations are shown in Table 2. Without pH adjustment, all iron preparations are negatively charged with the exception of iron carboxymaltose. The order of particle charges starting with the most negative iron preparation is ferumoxytol (−43.2 mV) < iron gluconate ≈ iron sucrose < iron isomaltoside 1000 < iron dextran < iron carboxymaltose (+3.7 mV). Acidification of the samples increased the zeta potential of iron carboxymaltose and decreased the negative zeta potential of all other compounds. At a pH value close to the physiological pH, all formulations showed a negative zeta potential, though that for iron carboxymaltose was much smaller.

3.2. Size and structure of core

3.2.1. Transmission electron microscopy (TEM)

TEM images of IV iron agents are shown in Fig. 3. Dark, electron dense, beadlike structures present the cores of the iron oxide complexes, surrounded by a less electron dense matrix, which may be attributed to a carbohydrate fraction. The medians of the geometrical diameter of the core rise from 4.1 to 6.2 nm in the order sodium ferric gluconate < iron sucrose < LMW iron dextran < iron isomaltoside 1000 ≈ ferumoxytol (Table 3). In case of iron carboxymaltose cores tend to cluster and single cores are not definable. The median geometrical core diameter of these clusters is 11.7 ± 4.4 nm.

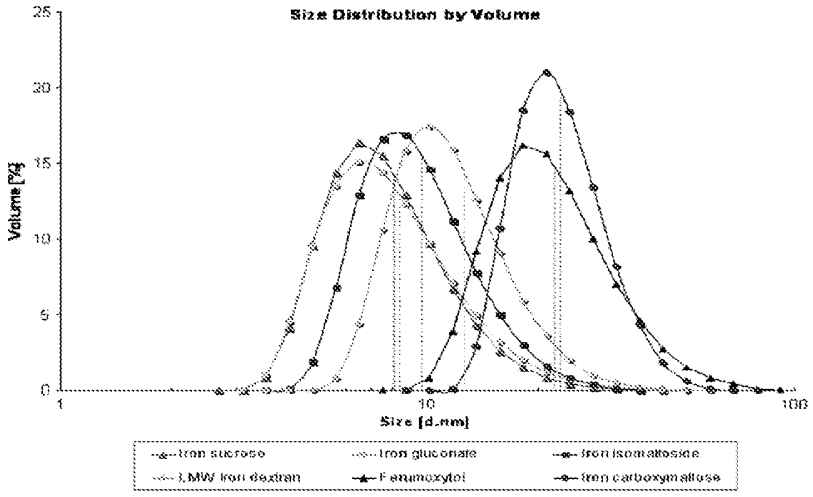

Fig. 2. Volume distribution of the hydrodynamic diameter of intravenous iron preparations as determined by dynamic light scattering (DLS). Conditions: 0.4 mg Fe/ml. Vertical lines assign the median diameter.

Table 2
Zeta potentials ζ of IV iron polynuclear complexes at different pH values.

Iron gluconate		Iron sucrose		LMW iron dextran		Ferumoxytol		Iron isomalto-side 1000		Iron carboxymaltose	
pH	ζ (mV)	pH	ζ (mV)	pH	ζ (mV)	pH	ζ (mV)	pH	ζ (mV)	pH	ζ (mV)
4.35	−16.50	4.49	−14.25	3.02	−3.56	3.39	−11.95	3.3	−3.98	3.26	9.46
7.4	−29.70	7.43	−26.20	6.4[a]	−15.30	6.6[a]	−43.20	6.3[a]	−22.00	5.36[a]	3.68
8.36[a]	−29.10	11.03[a]	−28.15	7.31	−17.25	7.36	−30.55	7.35	−21.05	7.26	−8.52
10.5	−29.60			11.8	−15.75	10.4	−34.40	9.03	−28.95	9.54	−16.35
								11.5	−26.40		

[a] pH in bidistilled sterile-filtrated water, without any pH adjustment.

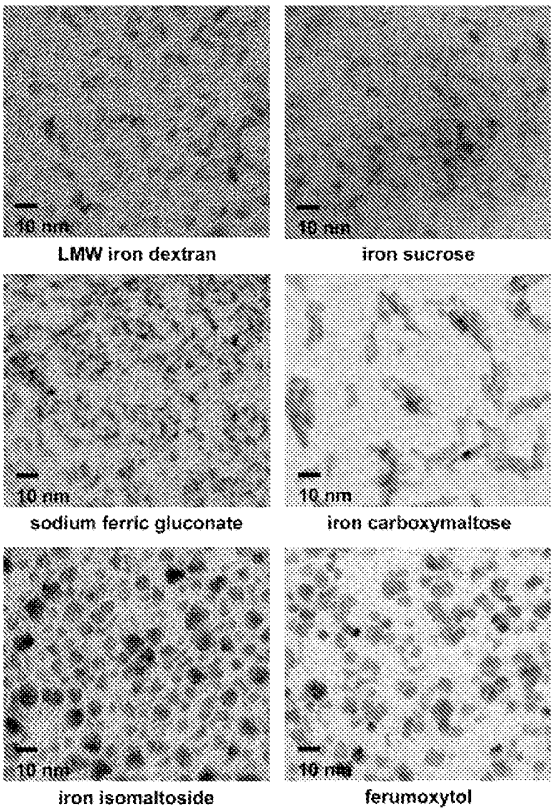

Fig. 3. Transmission electron microscopy images of intravenous iron preparations. Conditions: 1 mg Fe/ml.

3.2.2. X-ray diffraction (XRD)

The particles mean diameters d of the cores were determined using the Scherrer equation and are presented in Table 3. The mean diameters of single core complexes are in the range of 3.3–6.4 nm and appear in accordance with diameters measured by TEM.

In Fig. 4, X-ray diffractograms of IV iron agents (upper part of figure) are compared with diffraction data of standard iron oxides from the ICDD (lower part of figure, International Centre for Diffraction Data). Peaks belonging to the carbohydrate fraction are marked with arrows. With the exception of ferumoxytol the IV iron agents show broad regions of high intensities at in part similar angle values of diffraction with similar intensities.

The patterns of iron sucrose and sodium ferric gluconate show a structure similar to 2-line ferrihydrite as there are just two major iron oxide peaks at 36° 2θ and 62° 2θ. Two others at 14° 2θ and 22° 2θ belong to amorphous sucrose [27]. Small reflections at 40° 2θ and 56° 2θ could be a hint that also other structures are mixed in like akaganeite.

The X-ray results of iron carboxymaltose indicate the akaganeite structure with same intensities at same angles except for a minor peak instead of a major peak at 12° 2θ. LMW iron dextran and iron isomaltoside 1000 show a pattern which is similar to akaganeite as well, but conformity is not as good (minor peaks instead of major peaks at 12° 2θ and 35° 2θ, in part missing minor peaks).

The diffractogram of ferumoxytol, which is used as IV iron agent and contrast agent in magnetic resonance imaging as well, is close to pattern of magnetite and maghemite. Sharp peaks in the diffractogram belong to crystalline mannitol in the formulation.

3.3. Ferrous iron content

3.3.1. Mössbauer spectroscopy

The mössbauer spectrum of iron isomaltoside 1000 shows a doublet with an isomer shift δ = 0.44 mm/s and a quadrupole splitting EQ = 0.78 mm/s (Fig. 5). Both parameters are characteristic for iron in the ferric state. There is no indication of iron in the ferrous state as characteristic isomer shifts and splittings are absent.

3.4. Dialysable iron content

3.4.1. Dialysis

The results of the determination of the dialyzable "free" iron content are shown in Table 3. It appears that iron isomaltoside 1000, iron carboxymaltose, and ferumoxytol yield very low free iron contents smaller than 0.002% of the total iron content. This was independent of the liquid used for the dilution and dialysis (water versus sodium chloride solution). Iron dextran yielded free iron contents of 0.1% and 0.2% in water and sodium chloride solution, respectively. The highest free iron content was observed for sodium ferric gluconate yielding more than 1% in sodium chloride dilutions. However, the free iron content in the iron sucrose preparation (0.067% in NaCl and 0.057% in water) was lower than expected. The experiment without pH adjustment showed that only iron carboxymaltose was affected by pH. As depicted in Fig. 6 the content of free iron in iron carboxymaltose increases from below the detection limit (<0.002%) at pH 7.5–0.262% when the experiment is conducted in nonbuffered 0.9% NaCl.

3.5. Labile iron

3.5.1. Acid soluble iron

In acidic solution, FeOOH is dissociated: $FeOOH + 3HCl \rightarrow Fe^{3+} + 3Cl^- + 2H_2O$. In this study, iron formulations $[FeOOH]_mL_n$ with different carbohydrate ligands L were decomposed similarly: $[FeOOH]_mL_n + 3mHCl \rightarrow mFe^{3+} + 3mCl^- + 2mH_2O + nL$. As the molar extinction coefficient of the complex at 287.3 nm ($\varepsilon^{287.3nm}_{[FeOOH]_mL_n} \approx 3000\ M^{-1}\ cm^{-1}$) is substantially higher than the extinction coefficient of Fe^{3+} ($\varepsilon^{287.3nm}_{[FeOOH]mLn} \approx 580\ M^{-1}\ cm^{-1}$) or carbohydrate (negligible), the decreasing FeOOH concentration is approximately proportional to the measured absorbance.

Table 3
Core dimensions as determined by transmission electron microscopy (TEM) and X-ray diffraction (XRD), acidic hydrolysis stability and dialysable iron with and without pH adjustment.

Iron complex	Core-Ø (nm)		$t_{0.5}$ (h)	Dialysable iron[e] (%)		
	TEM	XRD	Acidic hydrolysis	WFI[f]	NaCl[f]	NaCl[g]
Sodium ferric gluconate	4.1[a] ± 1.7	3.4	4.0 ± 0.1	0.789 ± 0.048	1.338[d]	
Iron sucrose	5.0[a] ± 0.8	3.3	4.9 ± 0.1	0.057[d]	0.067[d]	
LMW iron dextran	5.6[a] ± 1.2	4.4	21.0 ± 1.2	0.100 ± 0.0096	0.207 ± 0.0071	0.172[h] ± 0.0048
Iron isomaltoside 1000	6.3[a] ± 1.2	4.2	25.2 ± 1.2	<0.002[c]	<0.002[c]	0.014[h] ± 0.0029
Iron carboxymaltose	11.7[a,b] ± 44	4.3	25.6 ± 1.6	<0.002[c]	<0.002[c]	0.2621[h] ± 0
Ferumoxytol	6.2[a] ± 1.4	6.4	62.4 ± 0.4	<0.002[c]	<0.002[c]	0.005[h] ± 0.0047

[a] Median-Ø.
[b] Median-Ø of an agglomeration of several cores. Single cores are not definable.
[c] Detection limit.
[d] Only one sample.
[e] Calculated from ICP-MS measurements.
[f] Adjustment to pH 7.5.
[g] Without pH adjustment.
[h] Product approved for high dose administration.

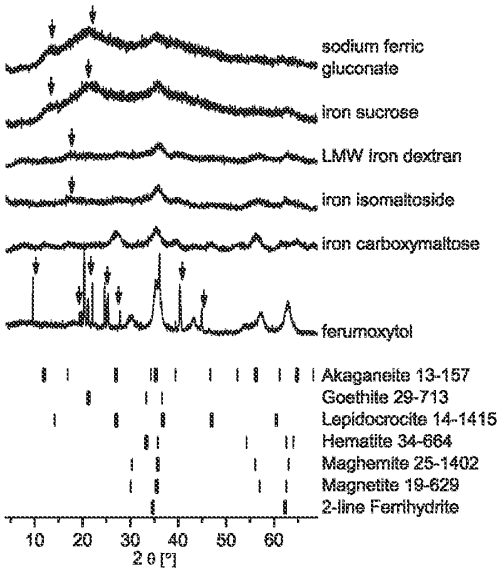

Fig. 4. X-ray spectra of intravenous iron preparations. At the bottom, the spectra are compared with diffraction data of standard iron oxides from the ICDD (International Centre for Diffraction Data). Thick reflexion lines of standard iron oxides: Intensity 70–100%. Thin reflexion lines of standard iron oxides: 30–69% intensity. Peaks belonging to carbohydrate fraction are assigned by arrows.

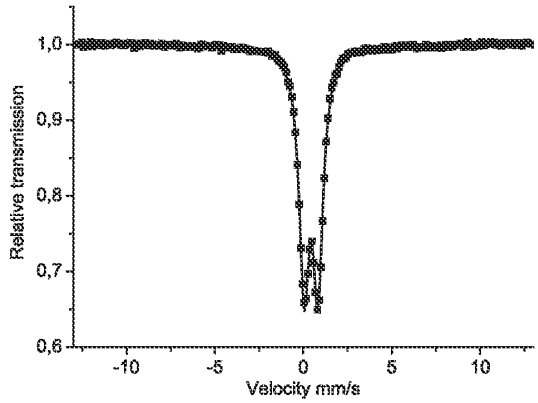

Fig. 5. Mössbauer spectrum of MonoFer as powder measured at 150 K. Measuring points are fitted with a line of Lorentz shape. Isomer shift $\delta = 0.44$ mm/s, quadrupole splitting $E_Q = 0.78$ mm/s, line widths $\Gamma = 0.69$ mm/s.

The rate of hydrolysis is a measure of the relative stability of the FeOOH entity. In Fig. 7, it can be seen that the fraction of FeOOH remaining decreases with time, and in Table 3, the half-times of FeOOH decomposition of the various iron preparations are compared. The complex stability is increasing in the order of iron gluconate < iron sucrose ≪ iron dextran < iron carboxymaltose ≈ iron isomaltoside 1000 ≪ ferumoxytol. There is some indication that the rate of degradation relates to the surface area of the iron complex formulation and decreasing with increasing particle size (Fig. 8).

3.5.2. Ferrozine®-detectable labile iron in human serum

The results of the determination on detectable labile iron with the Ferrozine®-method are shown in Fig. 9. The amount of the labile iron, measured by this test was nearly equivalent to the administered dose of 200 mg and 500 mg, respectively. The products which show the highest fraction of labile, Ferrozine®-detectable iron are, by far, iron gluconate and iron sucrose (3.2 ± 0.4% for iron gluconate, 3.5 ± 0.2% for iron sucrose at a 200 mg dose, respectively). For the different compounds, the fraction of labile

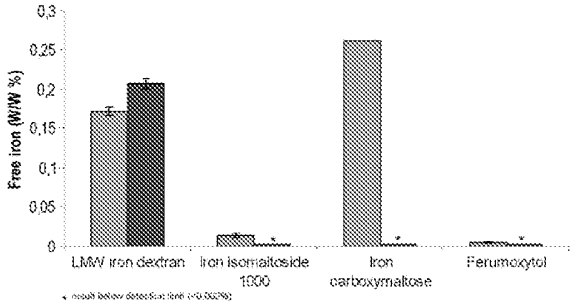

Fig. 6. Comparative free iron content in high dose IV iron products. The detection limit was 0.002%. Red bars indicate free iron content following adjustment of the diluted preparation to pH 7; blue bars indicate results obtained without pH adjustment. Star indicates concentrations below detection limit. SD's are listed in Table 3.

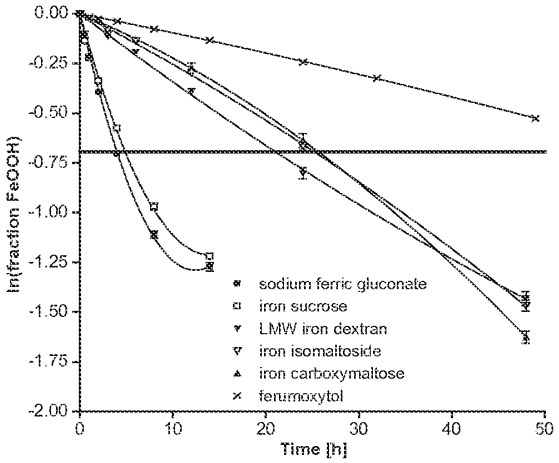

Fig. 7. Acid soluble iron. Concentration: 10 μg Fe/ml, 0.2375 M HCl. At $t = 0$ min, the fraction of FeOOH is 1 according to 100% not hydrolyzed FeOOH. Each point represents the average of three measurements; error bars are sometimes smaller than symbols. Data were fitted with a second degree polynomial ($R^2 > 0.990$). The solid line labels the half-time. SD's are listed in Table 3. For further details refer to methods.

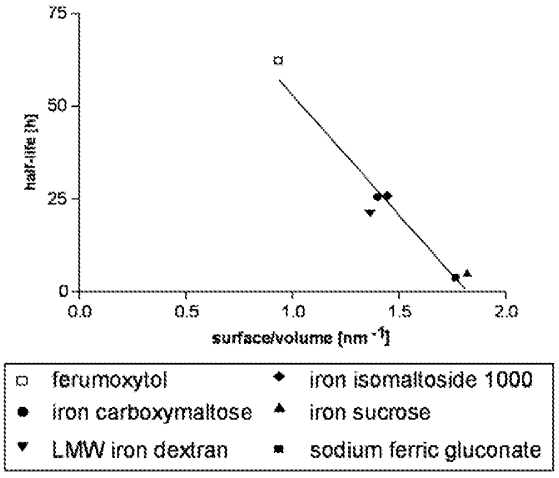

Fig. 8. Half-time of FeOOH hydrolysis against FeOOH core surface.

iron is decreasing in the order of iron sucrose ≈ iron gluconate ≫ iron dextran > iron isomaltoside 1000 ≈ ferumoxytol > iron carboxymaltose.

3.6. Molecular structure of iron isomaltoside 1000

Proton NMR spectra obtained at 800 MHz of 6-O-D-glucityl oligoisomaltoside (isomaltoside 1000) indicate a pure sample of higher oligomeric isomaltoside 1000s with an average polymerization of about 5.2, i.e., less than 1.5% reducing sugar is left (data not shown). The proton NMR data particularly the coupling constant between hydrogen H-5 and H-6 and H-6′ for the internal residues being 3.0 and 5.0 Hz, respectively, indicate the population of the rotational isomers of the hydroxymethyl group is approximately 60/40 for the gt/gg isomers [28]. ^{13}C NMR spectra obtained at

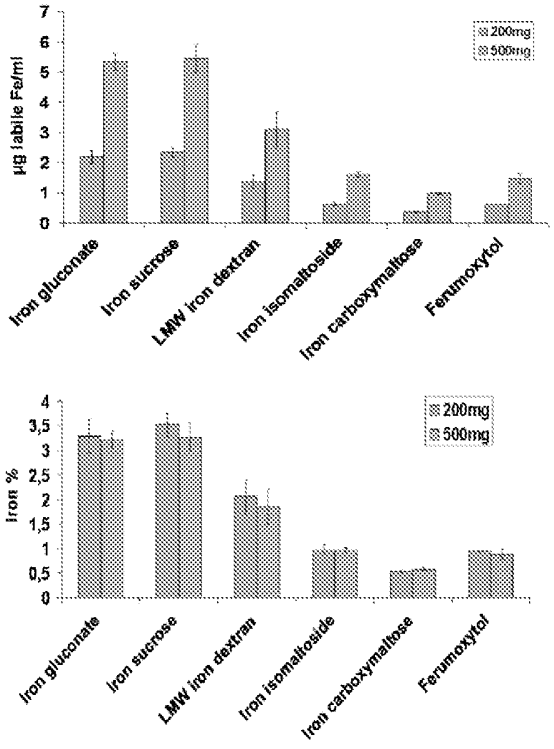

Fig. 9. Comparative labile iron pools of parenteral iron products. Upper diagram: Concentration of the Ferrozine®-detectable labile iron pool in μg/ml. The bars represent the average of at least four measurements. Lower diagram: Ferrozine®-detectable labile iron in percentage of the total used dose. For each measurement, the iron complex was incubated in human serum for 10 and 45 min, respectively. Thereafter, the Ferrozine® reaction was performed and in each case an intercept of a second degree polynomial regression function of the absorption versus time curve with the ordinate was calculated. These intercepts were extrapolated to an incubation time of $t = 0$ by linear regression, yielding the labile iron pool in serum for each intravenous iron product.

200 MHz of isomaltoside 1000 confirmed the above-mentioned conclusions as shown in Fig. 10a. Data of ^{13}C NMR measurements for the iron isomaltoside 1000 complex as prepared described in patent [26] showed line broadening of signals as seen in Fig. 10b. The spectrum demonstrates a significant line broadening of the carbon signals carbon C-1, C-5, and C-6 and a smaller line broadening of C-3 and C-2 all from the "internal" glucose residues, suggesting that the complexation of the iron in the isomaltoside 1000 matrix preferentially takes place in the cavity shown in Fig. 11. While carbon signals in presence of iron were only subjected to some line broadening no signals could be obtained in proton spectra of the complex. The suppression of signal intensity in integrated signals of individual carbon atoms was a measure of complex formation between their attached oxygen atoms and the iron atoms.

The following relative intensities as compared to the free oligosaccharide were measured for central sugar residues in the oligosaccharide-iron complex: C-1: 48% (98 ppm); C-2: 60% (71.6 ppm); C-3: 48% (73.7 ppm); C-4: 67% (69.7 ppm); C-5: 53% (70.4 ppm); C-6: 52% (65.7 ppm). This indicates that iron complex formation occurs primarily via O-3, O-5, and O-6 of these sugar residues.

Molecular dynamics modeling followed by energy minimization of 6-O-D-glucityl isomaltopentaoside isomaltoside 1000 using the MOE program resulted in the minimum energy conformation which, with all the rotational isomers around the 6-position in

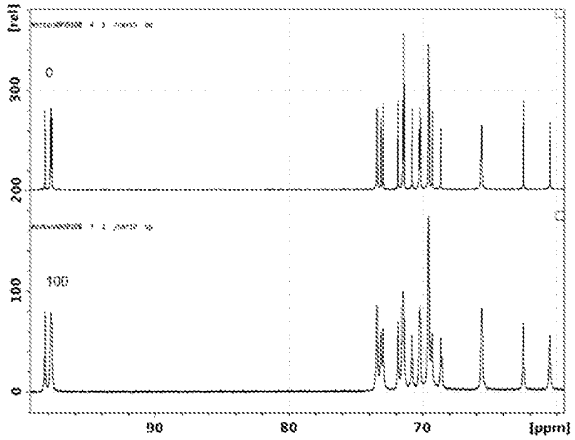

Fig. 10. (a/b) 200 MHz carbon-13 NMR spectra of isomaltoside (upper) and isomaltoside/iron complex (lower) prepared according to Ref. [26].

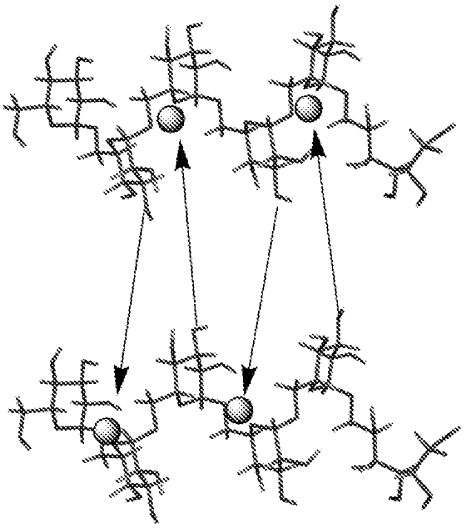

Fig. 11. Schematic representation of possible complexation site based on carbon-13 NMR line broadening studies.

the "gt" conformation, show that the structure repeats itself every second glucose residue leaving O-5 and O-6 from each residue and O-3 from residues in a neighboring chain positioned to interact and chelate with iron atoms. This allows chains to stack through iron oxygen interactions. Every second residue is to the same face of the molecule available for further complexation with iron (Fig. 12).

4. Discussion

4.1. Structure

Iron isomaltoside 1000 contains isomaltoside 1000, a pure linear chemical structure of repeating α1-6 linked glucopyranose residues. It is an unbranched, nonanaphylactic carbohydrate with an average size of 5.2 glucose units and an average molecular weight of 1000 Da, respectively, structurally different from the branched dextran polysaccharides present in iron dextran. Low molecular weight dextran has a molecular weight around 5000 and on average one α-1-3 branch point per 32 glucose residues. A computer model using the same approach as described in the experimental part of one of such structures is shown in Fig. 13 and is clearly very different from the isomaltoside 1000 shown in Fig. 12. Isomaltoside 1000 consists predominantly of 3–5 glucose units and is prepared from oligomers used for prevention of dextran-induced anaphylactic reaction. Hence, this preparation does not contain dextran, and therefore, there is no requirement for a test dose. Analysis by XRD does not show sharp diffraction peaks for any of the iron preparations, indicating structures with little crystallinity, which is the consequence of small crystal size and structural disorder. The iron oxyhydroxide in iron isomaltoside 1000 seems to consist of a "mixed layer" similar to Akaganeite.

The core of iron sucrose has a structure close to 2-line Ferrihydrite, possibly mixed with layers of Akaganeite. Earlier investigations already have identified the iron oxyhydroxide core of iron sucrose as 2-line Ferrihydrite (X-ray diffraction, SEAD) [29,30] and Akaganeite (X-ray diffraction, Mössbauer) [31], respectively.

The iron carboxymaltose pattern is in accordance with Akaganeite. The consideration that the distance between latticed planes at small diffraction angles is close to 1 nm indicates that a 5 nm core is just a few lattice planes wide and that the formation of a long-range order, which is characteristic for crystals, is hardly possible.

In the case of sodium ferric gluconate, earlier investigations already have identified the iron oxyhydroxide core as Akaganeite (X-ray diffraction, Mössbauer) [31]. LMWID and Ferumoxytol structures resemble akaganeite (LMWID) and magnetite and maghemite (Ferumoxytol), respectively, an observation which has not been reported before.

The visual appearance of the iron formulations as viewed by TEM varied considerably as shown in Fig. 3, both in terms of size and shape. Some preparations are well defined in terms of spherically shaped particles (iron isomaltoside 1000) whereas others display irregularly shaped particles, varying in size. Results of the instrumental size analysis of the parenteral iron preparations demonstrated that these results are also partly dependent on the method of determination. In this work, four different methods for size analysis were applied, two of them measuring the hydrodynamic diameter (GPC, DLS) and the other two the diameter of the iron core (XRD and TEM). The latter methods yielded generally smaller particle sizes, except for iron isomaltoside, where more or less identical diameters were obtained by DLS and TEM, which supports the formation of a matrix-type structure and thus confirms structural dissimilarities between iron isomaltoside and the other iron complexes. Discrepancies between DLS and GPC might be due to dilution effects, since higher concentrations of iron preparations tend to form clusters which may result in higher diameters of the respective iron preparation. Another explanation for the diverging results based on DLS vs. GPC can be given by the zeta potential of the investigated preparations. The highest differences were observed for iron gluconate, iron sucrose, LMW iron dextran, and iron isomaltoside 1000 (Table 1). This may be due to their negative charge at small particle size, which may interact with the spherical silica particles containing polar diol groups of the column material yielding shorter retention times and thus higher hydrodynamic radii for GPC. Ferumoxytol, which is also negatively charged, has a much higher diameter, thus the charge per unit surface area is lower leading to a lower interaction with the column material. It is noteworthy that, except for iron carboxymaltose, the zeta potentials of all iron formulations indicated that they carried a negative charge in the pH-range 3–11 (Table 2). Iron carboxymaltose underwent a change in sign from positive zeta potential at acidic and neutral pH-conditions to negative potential at alkaline pH. Interestingly, an FDA Advisory Committee meeting on safety of iron

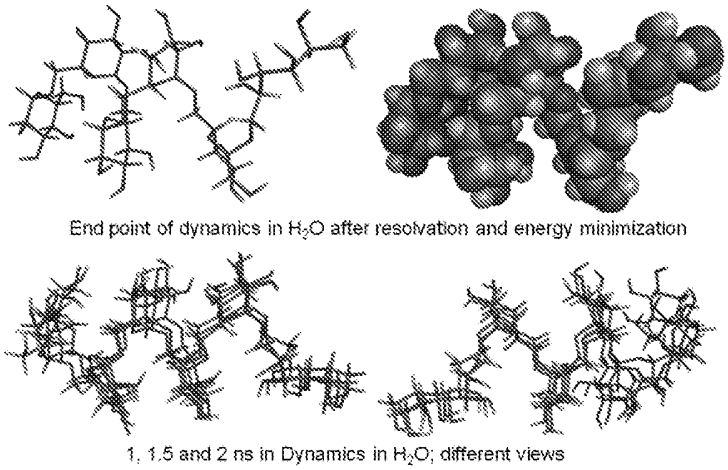

Fig. 12. End point of MD simulation.

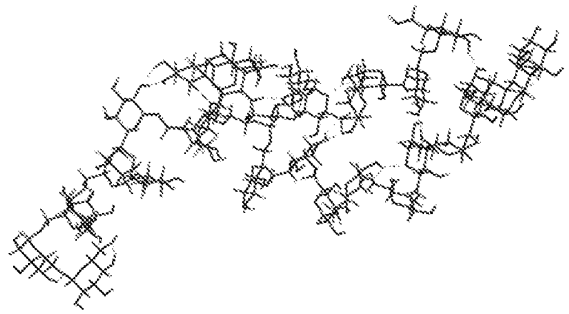

Fig. 13. computer model of low molecular weight dextran , 5000 Daltons, and one branch point. main chain 23 residues, side chain 9 residues.

carboxymaltose pointed out the existence of an imbalance in the occurrence of clinically important hypophosphatemia following high dose intravenous iron carboxymaltose, whereas this effect was not observed in a control group receiving oral iron and is not documented for other intravenous iron products [15]. Maybe the difference in Zeta potentials and thereby the positive charge on iron carboxymaltose can be a lead in explaining the mechanism behind iron carboxymaltose induced hypophosphatemia. If iron carboxymaltose carries a positive charge when it is in the circulation, negatively charged phosphate could potentially be trapped by electrostatic interaction with iron carboxymaltose.

It is also noteworthy to mention that with the exception of iron carboxymaltose and ferumoxytol all parenteral iron preparations followed a monomodal size distribution. As determined by GPC, both iron carboxymaltose and ferumoxytol showed an additional peak at smaller particle sizes and ferumoxytol in addition contained a shoulder indicating some fraction of the particle size having distinct higher molecular weight than the average number given (Fig. 1).

Detailed investigations presented in this manuscript using ^{13}C NMR and molecular modeling studies strongly suggest a spheroidal matrix structure for iron isomaltoside 1000 in which iron atoms are bound and dispersed [approx 10 iron atoms per oligosaccharide molecule]. This seems to be a much more likely description of the true iron isomaltoside 1000 molecular assembly than that of an iron core surrounded by a carbohydrate shell. Comparison of TEM images and DLS curves shows that these give more or less identical diameters for iron isomaltoside whereas for the other iron complexes DLS diameters strongly overestimate the diameters given by TEM. This also supports the results that a real matrix is formed and shows that iron isomaltoside is quite different from the other products since all the other TEM/DLS comparisons seem to suggest a core shell structure. A possible explanation for this unique molecular assembly could be given by the short, linear, and nonionic isomaltoside 1000 structure combined with proprietary Pharmacosmos production technology. This enables the production of a matrix structure composed of interchanging layers of linear isomaltoside 1000 with iron atoms placed in cavities between, and within, the oligosaccharide molecules (Figs. 11 and 12).

Integration of the ^{13}C NMR spectra of iron isomaltoside 1000 and the parent oligosaccharide against an internal reference indicate that more than 90% of the iron sample signals are visible.

Future studies should investigate the underlying mechanism for the existence of these structural differences in the iron carbohydrate complex.

4.2. Free iron

Free iron was determined following dialysis of the diluted iron preparations In general, the free iron fractions were observed to be low, although for sodium ferric gluconate a free iron content of 1.33% was found. This coincides with the known low stability of this iron complex [32]. Surprisingly, the free iron content of the other low stability complex iron sucrose was less than 0.1%, a value which is not reflected by the lability of the complex. Generally, iron sucrose is considered as a semi-robust moderately strong complex, whereas iron gluconate is labile and weak. Other investigators have found similar results for iron sucrose [25]. The underlying reason for this observation is currently unknown, an interaction of the complex with the dialysis membrane may not be ruled out For iron isomaltoside 1000, iron carboxymaltose and ferumoxytol free iron content was below the detection limit of the method (<0.002%) when the experiment was done in a pH 7.4 buffered 0.9% NaCl solution. Interestingly, the content of free iron in iron carboxymaltose jumps from <0.002% to 0.262% when the experiment is conducted in standard saline, which does not contain a buffer. This indicated that the dialyzable iron in iron carboxymaltose is sensitive to pH. It may be worth noting that dilutions of IV iron formulations for drip infusion are prepared in nonbuffered

physiological saline solutions. On the other hand, for a 1000 mg iron dose, this will represent the release of a maximum of 2.62 mg free iron over 24 h, only 40% of the capacity of transferring to bound iron, such that the probability of increasing free iron in blood seems low.

4.3. Labile iron

Labile iron is not identical to free iron in the iron products, since it can be considered as weakly bound iron within the nanoparticle which is readily mobilized by chemical reactions or in the presence of iron complex forming agents, such as proteins in blood plasma. In acidic solutions, labile bound iron may be mobilized in the presence of H_3O^+ ions from the oxyhydroxide structure. Iron sucrose and sodium ferric gluconate released their iron content at the highest rate, followed by a group consisting of iron dextran, iron carboxymaltose, and iron isomaltoside 1000, whereas ferumoxytol was most resistant toward iron mobilization at acidic pH (Fig. 7). One explanation for these observed differences may be a reasonable inverse correlation between the size of the iron complex/oxyhydroxide particle size as determined by TEM and the release rate, which was lowest for ferrumoxytol (highest half-time) and highest for iron sucrose (lowest half-time) (Figs. 7 and 8). As depicted in Fig. 9, the amount of labile iron determined by diluting the iron formulations with human serum (Ferrozine®-method) show similar results to those obtained in the experiments on release of iron under acidic conditions and results from our investigations on labile and free iron. The percentage of labile iron released as shown in this study is independent on the iron dose employed and covers free as well as labile bound iron to iron-binding proteins such as transferrin and other serum proteins.

Overall, these results demonstrate that labile iron content in all parenteral iron products designed for rapid and high dose administration [iron isomaltoside 1000, iron carboxymaltose and ferumoxytol] is less than 1% of the administered iron dose. Therefore, these parenteral iron products can be considered as optimized dosage forms with respect to burst release of iron from the carbohydrate iron complex.

4.4. Immunogenic properties of the carbohydrate

Similar to the risk of free iron reactions, anaphylactic or anaphylactoid reactions have traditionally been a concern when using IV iron compounds [9]. On the one hand, it has been assumed that antibody-mediated anaphylactic reactions caused by circulating dextran antibodies occur more frequently with iron dextran products. On the other hand, iron induced anaphylactoid reactions can occur with all IV iron preparations, but they are generally not thought to be mediated through an immune response [9]. Today there is only a test dose requirement for Dexferrum (high Mw iron dextran), CosmoFer (low Mw iron dextran), and Venofer (iron sucrose)—and for Venofer this only applies within Europe. All the newly introduced high dose IV preparations (Monofer [iron isomaltoside 1000], Ferinject®/Injectafer® [iron carboxymaltose], Feraheme [ferumoxytol]) are based on carbohydrates with a reduced immunogenic potential and no test doses are required.

In the case of Monofer, the carrier carbohydrate isomaltoside 1000 is based on a chemical modification of oligomers known to prevent dextran-induced anaphylactic reactions. The ability of isomaltose oligomers (5 glucose units) to prevent or block anaphylaxis to dextrans was first reported by Coulson and Stevens [33] in the 1960s, but intensive research by Richter et al. [34–36] in the 1970s and 1980s revealed its unique role as a specific monovalent hapten against circulating anti-dextran antibodies. Studies by Richter et al. documented that even in animals maximally sensitized against dextran isomaltose oligomers of 1430 Da or lower were nonanaphylactogenic and desensitizing [16].

The term hapten is defined as a substance capable of binding to specific antibodies without inducing anaphylaxis or induction of antibody formation. Thus, by binding to the receptor sites on circulating anti-dextran IgG, isomaltose oligomers block and prevent these sites from participation in the formation of large immune complexes exhibiting multiple (polyvalent) IgG-specific epitopes, thereby avoiding classical anaphylactic reactions.

In later multinational clinical trials involving over 5 million patients, it was shown that a pre-injection of isomaltose oligomers was able to reduce the risk of anaphylaxis to polyvalent clinical dextran from ca. 1 in 3000 to less than 1 in 200,000 patients [33,35,37–39]. Therefore, isomaltose oligomers are well-documented inhibitor haptens of dextran anaphylaxis with a convincing clinical record that establishes their non-anaphylactic nature, thus providing the rationale for eliminating test dosing when administering Monofer.

4.5. Clinical consequences

The efficacy of IV iron is directly related to the amount of iron administered, but differences in core size and carbohydrate chemistry determine pharmacological and biologic differences between the different iron formulations. These include clearance after injection, iron release in vitro, early evidence of iron bioactivity in vivo, and maximum tolerated dose and rate of infusion, as well as effects on oxidative markers, propensity for inducing hypophosphatemia (Ferinject®/Injectafer®), and propensity to cause transient proteinuria (Venofer®) or hepatic damage (Ferrlecit®) following administration [40–45]. Thus, efficacy, safety, and convenience of dosage should be taken into account when selecting an IV iron compound.

The efficacy of all IV iron preparations for treating anemia has been consistently proved in a variety of clinical settings with a very low rate of severe ADEs, e.g. [5], although iron dextran complexes may cause well-known dextran-induced anaphylactic reactions, which are significantly more frequent with high molecular weight iron dextran (HMWID) than with low molecular weight iron dextran (LMWID) [13]. The risks of total ADEs (OR 3.2, 95%CI 2.7–3.8) and life-threatening ADEs (OR 3.4, 95%CI 2.0–5.9) were significantly increased among recipients of HMWID compared with LMWID. Nevertheless, it is worth noting that there were no significant differences in mortality rates between LMWID and iron gluconate (OR 0.3, 95%CI 0.1–1.3) or iron sucrose (OR 0.2, 95%CI 0.1–1.0), although life-threatening ADEs were significantly more frequent among recipients of LMWID [13]. In addition, excluding HMWID, the rates of life-threatening ADEs associated with IV iron (1.4 per million doses), including iron-related deaths (0.3 per million doses) [13], are much lower than that of ABT-related (allogenic blood transfusion) severe side effects (10 per million units) and ABT-related deaths (4 per million units) [46].

Therefore, with the exception of HMWID (increased rates of severe ADEs and deaths), the acute safety differences among IV iron products are small and clinically irrelevant when given at the recommended doses, though whenever possible a product based on a carbohydrate with reduced immunogenic activity should be preferred (comparator trials are needed to be certain). In this regard, the new IV iron formulations (Monofer®, Ferinject®/Injectafer® and Feraheme®) are all based on carbohydrates with reduced immunogenic properties thereby avoiding the need for a test dose (reduction of treatment time). At least Monofer® and Ferinject® are based on a carbohydrate with documented reduced immunogenic activity. Feraheme® was also supposed to be based on a carbohydrate with documented reduced immunogenic activity but recently published case reports have shown that dextran sensitive patients can react to Feraheme® as well [47].

Table 4
Summary of clinical properties of IV iron formulations.

Product	CosmoFer®[a] (low Mw iron dextran)	Ferrlecit®[b] (iron gluconate)	Venofer®[a] (iron sucrose)	Ferinject®[a] (iron carboxymaltose)	Feraheme®[c] (ferumoxytol)	Monofer®[a] (iron isomaltoside 1000)
Carbohydrate	Dextran (branched polysaccharides)	Gluconate (monosaccharides)	Sucrose (disaccharides)	Carboxymaltose (branched polysaccharides)	Carboxymethyl dextran (branched polysaccharides)	Isomaltoside 1000 (unbranched linear oligosaccharides)
Maximum single dose	20 mg/kg	125 mg	200 mg	15 mg/kg single dose limit: 1000 mg	510 mg	20 mg/kg
Maximum single-dose administration in a 80 kg man	1600 mg	125 mg	200 mg	1000 mg	510 mg	1600 mg
Maximum single-dose administration in a 60 kg woman	1200 mg	125 mg	200 mg	900 mg	510 mg	1200 mg
One dose iron repletion (TDI)	Yes	No	No	No	No	Yes
Infusion within 1 h	No	NA	NA	Yes	Yes	Yes
Test dose required	Yes	NA	Yes/No*	No	No but must wait 60 min after injection	No
Iron concentration (mg/ml)	50	12.5	20	50	30	100
Vial volume (ml)	2 and 10	5	5	2 and 10	17	1, 5 and 10

[a] eMC, Summary of Product Characteristics (SPC) electronic Medicines Compendium.
[b] Bridgewater, NJ; Sanofi Aventis, Inc., US Ferriedt Prescribing information 2010.
[c] AMAG Pharmaceuticals, Feraheme Prescribing information.
* Test dose in Eroupe (yes) but not in US (no).

All IV preparations may cause anaphylactoid reactions caused by labile iron which are characterized by nausea, hypotension, tachycardia, chest pain, dyspnoea (lung edema), and bilateral edema of the hands and feet, and should not be misread as anaphylaxis [40]. Hence, formulation stability and free or labile iron content determine the maximal dose and maximal speed of infusion. Accordingly, large doses of iron isomaltoside 1000 (20 mg/kg), iron carboxymaltose (15 mg/kg, max 1000 mg), LMWID (20 mg/kg), and ferumoxytol (510 mg) can be administered in a single session, as they are all strong and robust formulations, with very low content of free or labile iron (Table 4). However, Ferinject® may cause unexplained hypophosphatemia, and its free iron content looks very sensitive to pH (Table 3, Fig. 6) and dilution (according to the Ferinject® SPC), whereas the administration of large doses of InFed/CosmoFer is hampered by an extended infusion time (4–6 h). In contrast, a much lower single dose is allowed for ferric gluconate (125 mg) or iron sucrose (200 mg), as they are more labile and weak formulations. Thus, correction of iron deficiency with these IV compounds is a time- and resource-consuming option (8–12 sessions to administer 1500 mg iron). A summary of the clinically relevant product characteristics is given in Table 4.

5. Conclusions

The analyzed polynuclear iron formulations are all characterized by a nanosized structure resembling Lepidocrocite, Akaganeite, Ferrihydrite, Magnetite or Maghemite, or mixture of these depending on the product. The homogenicity of the products varied a lot with iron isomaltoside 1000 displaying very well defined spherically shaped particles. With the exception of iron carboxymaltose and ferumoxytol, all parenteral iron preparations followed a monomodal size distribution.

^{13}C NMR and molecular modeling studies indicate that iron isomaltoside 1000 is a iron carbohydrate matrix structure contrary to the classical iron core–carbohydrate shell description. The high dose IV iron products are all characterized by a low content of labile and free iron. The content of free iron measured in physiological saline was the lowest in ferumoxytol and iron isomaltoside 1000 followed by low Mw iron dextran and iron carboxymaltoside which had the highest content of free iron.

In conclusion, iron isomaltoside 1000 (Monofer®) is a new IV iron source that is based on iron (III) and chemically modified isomalto-oligosaccharides. In contrast to the polysaccharides in iron dextrans, the carbohydrate isomaltoside 1000 is linear and unbranched with a low immunological activity. Hence, a test dose is not necessary. Compared to the existing IV iron preparations iron isomaltoside 1000 contains strongly bound iron in an iron carbohydrate matrix, with a very low content of labile and free iron. This enables Monofer, as the only IV iron formulation, to be administered as a rapid high dose infusion in doses over 1000 mg. This allows flexible dosing including high and rapid iron repletion, offering convenient one visit iron therapy for a wide range of patients.

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Electronic Patent Application Fee Transmittal	
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First Named Inventor/Applicant Name:	Mary Jane Helenek
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Patent-Appeals-and-Interference:				
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 1

Complete if Known	
Application Number	12/787,283
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First Named Inventor	Mary Jane Helenek
Art Unit	1623
Examiner Name	Jonathan S. Lau
Attorney Docket Number	30015730-0053

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]
	1.	European Official Communication dated 04 June 2012 in related Application No. EP 07716309.5 filed 08 January 2007, 4 pages.	

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Art Unit:	1623		
Title:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON		

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-SB08B 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; 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).

The references herein were cited in corresponding European Application No. EP 077163093.5. All references cited in the listed European Official Communication are already of record.

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 $180.00, 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 SNR Denton US LLP Deposit Account No. 19-3140.

Respectfully Submitted,

October 2, 2012
Date

/Kathleen E. Chaffee/
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/787,283	05/25/2010	Mary Jane Helenek	30015730-0053	4251

26263 7590 06/06/2012

SNR DENTON US LLP
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EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
06/06/2012	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	12/787,283	HELENEK ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *19 April 2012*.

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) *7 and 13-16* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-6,8-12 and 17-20* is/are rejected.

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

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

Application Papers

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

11)☒ The drawing(s) filed on *25 May 2010, 6 Jul 2010* 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).

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

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *17 Jun 2010, 20 Jan 2012*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a domestic application, filed 25 May 2010; and claims benefit as a CON of 11/620,986, filed 8 Jan 2007, issued as PAT 7,754,702, which claims benefit of provisional application 60/757,119, filed 6 Jan 2006.

Claims 1-20 are pending in the current application. Claims 7 and 13-16, drawn to non-elected species, are withdrawn. Claims 1-6, 8-12 and 17-20 are examined on the merits herein.

Election/Restrictions

Applicant's election of species of iron deficiency anemia associated with chronic blood loss or acute blood loss, iron polyisomaltose, and intravenous infusion, in the reply filed on 19 Apr 2012 is acknowledged.

Claims 7 and 13-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election of species was made in the reply filed on 19 Apr 2012. Upon finding of an allowable generic or linking claim, species will be rejoined.

Claim Rejections - 35 USC § 112

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

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for iron polyisomaltose complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies (instant claims 2 and 3). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

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

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

Nature of the invention: A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism comprising administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron wherein the iron carbohydrate complex is selected from the group consisting of an iron carboxymaltose complex, iron mannitol complex, iron polyisomaltose complex, iron polymaltose complex, iron gluconate complex, iron sorbitol complex and iron hydrogenated dextran complex

having substantially non-immunogenic carbohydrate complex (instant claim 2) and substantially no cross reactivity with anti-dextran antibodies (instant claim 3).

The state of the prior art: Cisar et al. (Journal of Experimental Medicine, 1975, 142, p435-459, provided by Applicant in IDS mailed 17 Jun 2010) discloses that while dextrans are branched polymers, anti-dextran antibodies recognize both terminal and non-terminal α(1-6) chains of dextran binding to a trisaccharide to hexasaccharide sized site (page 436, paragraphs 2-3). Cisar et al. discloses an antibody that binds to dextran binding with synthetic dextran that reacts as a completely linear molecule (paragraph spanning bottom of page 436 and top of page 437), or polyisomaltose. Therefore one of skill in the art would expect anti-dextran antibodies to cross react with polyisomaltose, which is a linear α(1-6) chain of dextran.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: One of skill in the art would expect anti-dextran antibodies to cross react with polyisomaltose, which is a linear α(1-6) chain of dextran. The prior art predicts anti-dextran antibodies recognize both terminal and non-terminal α(1-6) chains of dextran.

The Breadth of the claims: The scope of the claims encompasses iron polyisomaltose complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies (instant claims 2 and 3).

The amount of direction or guidance presented: The specification speaks generally about certain characteristics of iron carbohydrate complexes that make them

amenable to administration at doses high than contemplated by current administration protocols, such as a non-immunogenic carbohydrate component and no cross reactivity with anti-dextran antibodies at page 17, paragraph 60. The specification provides that it is within the skill in the art to test for said characteristics. The specification discloses the preferred embodiment of iron carboxy-maltose complex at page 18, paragraph 62. However the specification does not provide specific guidance as to what structural features other than those necessarily present in the disclosed embodiment give rise to said characteristics.

The presence or absence of working examples: No working example is provided of an iron polyisomaltose complex having substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies.

The quantity of experimentation necessary: In order to practice the invention with the full range of all possible methods of administration beyond those known in the art, (such as those causing significant adverse reaction or cross reactivity with anti-dextran antibodies) one skilled in the art would undertake a novel and extensive research program into what specific structural features are recognized by each anti-dextran antibody and how to remove such structural recognition from iron polyisomaltose complex. Because this research would have to be exhaustive, and because it would involve such a wide and unpredictable scope of patient populations having anti-dextran antibodies, it would constitute an undue and unpredictable experimental burden.

> *Genentech*, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in

> return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims, Applicants fail to provide information sufficient to practice the claimed invention for the full scope of the claim wherein iron polyisomaltose complex has a substantially non-immunogenic carbohydrate complex and substantially no cross reactivity with anti-dextran antibodies.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-6, 8-12 and 18-20 are rejected under 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 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. discloses as above.

Hamstra et al. in view of Muller et al. does not specifically disclose 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.

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 1623

/SHAOJIA ANNA JIANG/
Supervisory Patent Examiner
Art Unit 1623

Notice of References Cited	Application/Control No. 12/787,283	Applicant(s)/Patent Under Reexamination HELENEK ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-3,100,202	08-1963	ARTHUR MULLER et al.	536/113
	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	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.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12787283	HELENEK ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

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

CLAIM		DATE								
Final	Original	03/21/2012	06/01/2012							
	1	÷	✓							
	2	÷	✓							
	3	÷	✓							
	4	÷	✓							
	5	÷	✓							
	6	÷	✓							
	7	÷	N							
	8	÷	✓							
	9	÷	✓							
	10	÷	✓							
	11	÷	✓							
	12	÷	✓							
	13	÷	N							
	14	÷	N							
	15	÷	N							
	16	÷	N							
	17	÷	✓							
	18	÷	✓							
	19	÷	✓							
	20	÷	✓							

Did you mean: iron OR ferric OR ferrous isomaltose OR ***poly isomaltose*** anemia bleeding OR blood

[CITATION] Parenteral treatment of **iron** deficiency
WG Figueroa - Iron Metabolism: An International Symposium, ..., 1964 - Springer
Cited by 3 - Related articles - All 2 versions

PROCESS FOR PREPARING AN **IRON** HYDROXIDE
A Miller - US Patent 3,100,202, 1963 - Google Patents
... employed have been to react dextran with divalent **iron** salt to form **ferrous** hydroxide dextran **...** which are subsequently con- 10 verted by oxidation into the corresponding **ferric** hy- droxide **...** with the process of this invention, we produce a parenterally injectible **iron** hydroxide poly **...**
Cited by 4 - Related articles - All 2 versions

Composition for increasing the hematocrit of a normal mammal
JFA Vance... - EP Patent 0,266,439, 1992 - freepatentsonline.com
... the **ferrous iron**. Parenteral preparations of **iron** such as solutions of **iron** dextran, **iron** sorbitex, green **ferric** ammonium citrate, **ferrous** gluconate, **iron** adenylate and **iron polyisomaltose** may also be used. The preferred route **...**
Cited by 9 - Related articles - Cached

[CITATION] **Blood** and Antianemic Agents
D Pecoraro - Clinical pharmacology in pregnancy: fundamentals ..., 1984 - Thieme-Stratton
Related articles

[HTML] Polyglucose dialysis solution influences serum **iron** parameters [HTML] from advancesinpd.com
AE Grzegorzewska... - ADVANCES IN ..., 2000 - advancesinpd.com
... CD, Fox JE, Mallick NP, Gokal R. Circulating maltose and **isomaltose** in chronic **...** Effect of Caloreen supplementation on some haematological values and urinary **iron** excretion during **...** The **Anemia** Work Group of the National Kidney Foundation, Dialysis Outcomes Quality Initiative **...**
Cited by 2 - Related articles - Cached - BL Direct - All 2 versions

Method for increasing the hematocrit of a normal mammal
JFA Vance, RI Abels, FD Anderson... - US Patent ..., 1996 - Google Patents
... containing amino acids) may be added to the **iron** formulation to increase absorption of the **ferrous iron**. **...** preparations of **iron** such as solutions of **iron** dextran, **iron** sorbitex, green **ferric** ammonium citrate, fer- rous gluconate, **iron** adenylate and **iron polyisomaltose** may also **...**
Cited by 19 - Related articles - All 2 versions

PROCESS FOR PREPARING A FEISIC HYDROX
A Mueller - US Patent 3,076,798, 1963 - Google Patents
... of **ferric** compound corresponding to 10 grams of elemental **iron** or an amount of **ferrous** compound corresponding to 20 grams of elemental **iron**. 70 The alkaline **ferric** hydroxide-polymaltose solution, be- fore being isolated and purified, can be neutralized with **...**
Cited by 7 - Related articles - All 2 versions

[PDF] On potential carcinogenicity of the **iron** macromolecular complexes [PDF] from pnlee.co.uk
FJC Roe - Potential carcinogenic hazards from drugs: evaluation ..., 1967 - pnlee.co.uk
... These findings of HUEPER and the observations of HAD- DOW, DUKES and MITCHLEY (1961) that simple **iron** salts, such as **ferric** citrate, **ferric** salicylate, **ferrous** sulphate, **ferrous** lactate or **ferrous** gluconate, do not in- duce injection-site sarcomas, suggest that **...**
Cited by 7 - Related articles - View as HTML - All 3 versions

Methods and compositions for administration of **iron** for the treatment of restless leg syndrome
MJ Helenek, PA Lange, FB Oldham... - US Patent ..., 2005 - Google Patents
... Also in the **anemia** of chronic disease the only effective way to deliver 65 **...** injection preparations for **ferric** gluconate (also known as sodium **ferric** gluconate complex in **...** complexes, and **iron** polysaccharide complexes, such as: **iron** sucrose, **iron polyisomaltose** (**iron** dextran), **iron ...**
Cited by 2 - Related articles - All 4 versions

Copper deficiency complicating severe chronic intestinal malabsorption
A Cordano... - Pediatrics, 1956 - Am Acad Pediatrics
... After a few weeks, the hemogram gradually reverted to mixed **anemia** and neutro- penia. Reticulocytes were found to be 3.0, 1.6, **...** Red **blood** cell indices 10 days after transfusion were within normal limits. **...** Serum **iron** was found to be 73 tg/100 ml. **...**
Cited by 70 - Related articles - All 5 versions

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BIB DATA SHEET

CONFIRMATION NO. 4251

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/787,283	05/25/2010	435	1623	30015730-0053

APPLICANTS

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

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

This application is a CON of 11/620,986 01/08/2007 PAT 7,754,702
which claims benefit of 60/757,119 01/06/2006

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
06/04/2010

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

ADDRESS

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

TITLE

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

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PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	12787283
	Filing Date	2010-05-25
	First Named Inventor	Mary Jane Helenek
	Art Unit	1623
	Examiner Name	Johnathan S. Lau
	Attorney Docket Number	30015730-0053

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12787283
	Filing Date	2010-05-25
	First Named Inventor	Mary Jane Helenek
	Art Unit	1623
	Examiner Name	Johnathan S. Lau
	Attorney Docket Number	30015730-0053

/J.L./	1	Australian Office Action dated 15 September 2011 in related Application No. AU2007205167 filed 08 January 2007, 3 pages.	☐
/J.L./	2	Chinese Office Action dated 30 April 2010 in related Application No. CN200780002006 filed 08 January 2007, English translation, 7 pages.	☐
/J.L./	3	European Official Communication dated 05 October 2011 in related Application No. EP077163093.5 filed 08 January 2007, 6 pages.	☐
/J.L./	4	International Search Report and Written Opinion dated 12 September 2007 in related PCT Application No. PCT/US07/00176 filed 08 January 2007, 6 pages.	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Mary Jane Helenek
	Art Unit	1623
	Examiner Name	Johnathan S. Lau
	Attorney Docket Number	30015730-0053

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☐ A certification statement is not submitted herewith.

SIGNATURE

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

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	12787283
Filing Date	2010-05-25
First Named Inventor	Mary Jane HELENEK
Art Unit	1618
Examiner Name	TBA
Attorney Docket Number	30015730-0053

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/J.L./	1	5624668		1997-04-29	Lawrence et al.	
/J.L./	2	6599498		2003-07-29	Groman et al.	
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/J.L./	1	20040180849		2004-09-16	Helenek et al.	

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/J.L./	1	1997011711	WO		1997-04-03	Luitpold Pharm., Inc.		☐

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	Examiner Name	TBA
	Attorney Docket Number	30015730-0053

/J.L./	2	2004037865	WO		2004-05-06	Vifor Int. AG		☐
/J.L./	3	2007023154	WO		2007-03-01	Vifor Int. AG		☐

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/J.L./	1	ANDERSSON, "Clinical investigations on a new intramuscular haematinic", British Medical Journal, 1961, 275-279	☐
/J.L./	2	BAILIE et al., "Hypersensitivity reactions and deaths associated with intravenous iron preparations", Nephrol Dial Transplant, 2005, 20:1443-1449	☐
/J.L./	3	BESHARA et al., "Pharmacokinetics and red cell utilization of 52Fe/59Fe-labelled iron polymaltose in anaemic patients using positron emission tomography", Br J of Haematol, 2003, 120:853-859	☐
/J.L./	4	CISAR et al., "Binding properties of immunoglobulin combining sites specific for terminal or nonterminal antigenic determinants in dextran", J Exp Med, 1975, 142:435-459	☐
/J.L./	5	ESCHBACH et al., "NKF-K/DOQI clinical practice guidelines for anemia of chronic kidney disease: update 2000", Am J Kidney Dis, 2001, 37(1 Supp 1):S182-238	☐
/J.L./	6	European Search Report issued October 21, 2009, in the related application EP 07716309.5	☐
/J.L./	7	FIELDING, "Intravenous iron-dextrin in iron-deficiency anaemia", British Medical Journal, 1961, 279-283	☐

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	Attorney Docket Number	30015730-0053

/J.L./	8	FISHBANE, "Safety in iron management", Am J Kidney Dis, 2003, 41(6 Suppl 5):S18-S26	☐
	9	GEISSER et al., "Structure/histotoxicity relationship of parenteral iron preparations", Drug Research, 1992, 42 (12):1439-1452	☐
	10	HAINES et al., "Delayed adverse reactions to total-dose intravenous iron polymaltose", Internal Medicine Journal, 2009, 39:252-255	☐
	11	KUDASHEVA et al., "Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanoparticles in parenteral formulations", Journal of Inorganic Biochemistry, 2004, 98:1757-1769	☐
	12	LANDRY et al., "Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients", Am J Nephrol, 2005, 25:400-410	☐
	13	MACDOUGALL, "Intravenous administration of iron in epoetin-treated haemodialysis patients—which drugs, which regimen?", Nephrol Dial Transplant, 2000, 15:1743-1745	☐
	14	NEWNHAM et al., "Safety of iron polymaltose given as a total dose iron infusion", Internal Medicine Journal, 2006, 36 (10):672-674	☐
	15	NISSENSON et al., "Controversies in iron management", Kidney International, 2003, 64(Supplement 87):S64-S71	☐
	16	SIPE et al., "Brain iron metabolism and neurodegenerative disorders", Dev Neurosci, 2002, 24(2-3):188-196	☐
	17	SOFIC et al., "Increased iron (III) and total iron content in post mortem substantia nigra of parkinsonian brain", J. Neural Transm, 1988, 74:199-205	☐
/J.L./	18	SPINOWITZ et al., "The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients", Kidney International, 2005, 68:1801-1807	☐

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	Attorney Docket Number	30015730-0053

/J.L./	19	VAN WYCK et al., "Making sense: a scientific approach to intravenous iron therapy", J Am Soc Nephrol, 2004, 15 (Suppl 2):S91-S92	☐
/J.L./	20	VAN WYCK, "Labile iron: manifestations and clinical implications", J Am Soc Nephrol, 2004, 15(Suppl 2):S107-S111	☐

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The effect of iv **iron** alone or in combination with low-**dose** erythropoietin in the rapid correction of **anemia** of chronic renal failure in the predialysis period.
DS Silverberg, M Blum, Z Agbaria, V Deutsch... - Clinical ..., 2001 - ukpmc.ac.uk
BACKGROUND: It is now more and more evident that **anemia** of predialysis chronic renal failure (CRF) should be actively treated, since long-standing **anemia** may cause irremediable damage to the heart. The most common form of treatment of this **anemia** is ...
Cited by 84 - Related articles - Cached - BL Direct - All 3 versions

The use of subcutaneous erythropoietin and intravenous **iron** for the treatment of the **anemia** of severe, resistant congestive heart failure improves cardiac and renal ... [HTML] from onlinejacc.org
DS Silverberg, D Wexler, M Blum, G Keren... - Journal of the American ..., 2000 - Elsevier
... Correction of the **anemia**. ... Gallen, Switzerland), a ferric sucrose product, was given in a **dose** of 200 mg IV in 150 ml saline over 60 min every week until the serum ferritin reached 400 μg/liter or the percent Fe saturation (%Fe Sat: serum **iron**/total **iron** binding capacity × 100 ...
Cited by 598 - Related articles - BL Direct - All 12 versions

... **dose** daily **iron** supplementation improves **iron** status and appetite but not **anemia**, whereas quarterly anthelminthic treatment improves growth, appetite and **anemia** ... [PDF] from idpas.org
RJ Stoltzfus, HM Chway, A Montresor... - The Journal of ..., 2004 - Am Soc Nutrition
Iron deficiency and helminth infections are two common conditions of children in developing countries. The consequences of helminth infection in young children are not well described, and the efficacy of low **dose iron** supplementation is not well documented in malaria- ...
Cited by 120 - Related articles - BL Direct - All 7 versions

[BOOK] Guidelines for the use of **iron** supplements to prevent and treat **iron** deficiency **anemia** [PDF] from who.int
RJ Stoltzfus, ML Dreyfuss... - 1998 - who.int
... Because the efficiency of absorption of **iron** increases as **iron** deficiency **anemia** becomes more severe, this **dose** should provide adequate supplemental **iron** to women who do not have clinically severe **anemia** if it is given for an adequate duration. ...
Cited by 365 - Related articles - View as HTML - Library Search - All 30 versions

Lead-induced **anemia**: **dose**-response relationships and evidence for a threshold. [PDF] from nih.gov
J Schwartz, PJ Landrigan... - ... journal of public ..., 1990 - ajph.aphapublications.org
... Discussion The results of this study show a strongly negative, non-linear **dose**-response relationship ... of lead on hematocrit, the data from this study suggest that lead-induced **anemia** is a ... **Iron** deficiency may have accounted for some of the observed effect of lead on hematocrit ...
Cited by 82 - Related articles - All 13 versions

Intravenous **iron** optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related **anemia**: a multicenter, open-label, ... [HTML] from ascopubs.org
M Auerbach, H Ballard, JR Trout... - Journal of Clinical ..., 2004 - jco.ascopubs.org
... efficacy of oral **iron** was similar to that of no-**iron**. 14,15 In the CKD population, IV

iron therapy has been shown to decrease the rHuEPO **dose** needed to ameliorate **anemia**, which increases the cost-effectiveness of the drug. 14. ...
Cited by 293 - Related articles - BL Direct - All 7 versions

Intravenous infusion of total **dose iron** is superior to oral **iron** in treatment of **anemia** in peritoneal dialysis patients: a single center comparative study [PDF] from asnjournals.org
N Ahsan - Journal of the American Society of Nephrology, 1998 - Am Soc Nephrol
In the treatment of **anemia** of chronic renal failure, the most common cause of recombinant human erythropoietin (rhEPO) resistance is **iron** deficiency. In peritoneal dialysis (PD) patients, oral **iron** therapy is an accepted and convenient method of **iron** supplementation. ...
Cited by 75 - Related articles - BL Direct - All 6 versions

Clinical use of the total **dose** intravenous infusion of **iron** dextran.
M Auerbach, D Witt, W Toler... - The Journal of ..., 1988 - ncbi.nlm.nih.gov
... Department of Medicine, Franklin Square Hospital Center, Baltimore, MD 21237. Eighty-seven patients with **anemia** and absent bone marrow hemosiderin were given treatment with total **dose** intravenous infusions of **iron** dextran. ...
Cited by 89 - Related articles - All 2 versions

Intravenous **iron** dextran in clinical medicine [PDF] from ama-assn.org
RD Hamstra, MH Block... - JAMA: the journal of the ..., 1980 - Am Med Assoc
... Twenty-three patients, however, received their entire **dose** (1.0 to 2.5 g) in one injection. ... The total amount of **iron** injected varied from 2.5mg to 29 g (Table 3). Patients usually received 1.5 to 3.0 g to correct **anemia**, including 1.0 g to replenish tissue stores of **iron**. ...
Cited by 294 - Related articles - All 4 versions

Total **dose** intravenous infusion of **iron** dextran for **iron**-deficiency **anemia** in children with inflammatory bowel disease
P Mamula, DA Piccoli, SN Peck... - Journal of pediatric ..., 2002 - journals.lww.com
Background: **Iron**-deficiency **anemia** is a frequent complication in children with inflammatory bowel disease (IBD). Parenteral **iron** therapy is rarely prescribed because of concern about potential side effects. The aim of this study was to retrospectively evaluate the safety and ...
Cited by 57 - Related articles - BL Direct - All 6 versions

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	Examiner	Art Unit
	JONATHAN S LAU	1623

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST - inventor name search (Mary Helenek, Marc Tokars, Richard Lawrence)	6/1/2012	JSL
EAST - see attached notes	6/1/2012	JSL
Google Scholar - see attached notes	6/1/2012	JSL

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **12/787,283**	Examiner: **Johnathan S. Lau**
Applicant: **Mary Jane Helenek**	Group Art Unit: **1623**
Filed: **May 25, 2010**	Confirmation No.: **4251**
Docket No.: **30015730-0053**	Customer No.: **26263**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	

April 19, 2012

FILED VIA EFS-WEB

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

RESPONSE TO ELECTION REQUIREMENTS

Sir:

In response to the Election Requirements of March 23, 2012, Applicants request the Office consider the following remarks.

REMARKS

Upon entry of this amendment, claims 1-20 are pending. No claims have been amended. No claims have been added. No claims have been withdrawn. No claims have been canceled.

Election of Species

The Office requires a series of species elections as follows:

(i) species of disease, disorder or condition;

(ii) species of iron carbohydrate complex; and

(iii) species of route of administration.

The Office acknowledges that all claims are generic to (i) and (iii) and at least claims 1-12 and 17-20 are generic to (ii).

In response to the Office's restriction of species of disease, disorder or condition, Applicants elect to prosecute: **iron deficiency anemia associated with chronic blood loss or acute blood loss**, as recited in claim 6. At least claims 1-6 and 8-20 read on the elected species. By the Office's required species election, the Office acknowledges that each specie of disease, disorder or condition is independent, distinct, and a nonobvious variant over other species (MPEP 806.04; 37 CFR 1.146).

In response to the Office's restriction of species of iron carbohydrate complex, Applicants elect to prosecute: **iron polyisomaltose**, as recited in claim 1. At least claims 1-12 and 17-20 read on the elected species. By the Office's required species election, the Office acknowledges that each specie of iron carbohydrate complex is independent, distinct, and a nonobvious variant over other species (MPEP 806.04; 37 CFR 1.146).

In response to the Office's restriction of species of route of administration, Applicants elect to prosecute **intravenous infusion**, as recited in claim 19. All claims read on the elected species. By the Office's required species election, the Office

acknowledges that each specie of route of administration is independent, distinct, and a nonobvious variant over other species (MPEP 806.04; 37 CFR 1.146).

To the extent necessary to do so, it appears that claims 1-6 and 17-19 are generic to all of the elected species, and thus are designated for examination in connection therewith.

In electing the above species, Applicants reserve the right to request REJOINDER, under MPEP § 821.04, and examination of non-elected species upon allowance of any claims generic to the non-elected species.

CONCLUSION

Applicants believe that the claims as presented represent allowable subject matter. If the Examiner desires, Applicants welcome a telephone interview to expedite prosecution. As always, the Examiner is free to call the undersigned at the number below. Applicants believe there are no additional fees due at this time. However, the Commissioner is hereby authorized to charge any applicable fees to Deposit Account No. 19-3140.

Respectfully submitted,

By: /David R. Metzger/ (Reg. 32,919)

SNR Denton US LLP
P.O. Box 061080
Wacker Drive Station, Willis Tower
Chicago, IL 60606-1080
Telephone: 312-876-8000
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ATTORNEYS FOR APPLICANT

Electronic Acknowledgement Receipt	
EFS ID:	12587394
Application Number:	12787283
International Application Number:	
Confirmation Number:	4251
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/787,283	05/25/2010	Mary Jane Helenek	30015730-0053	4251

26263 7590 03/23/2012

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

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

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No.	Applicant(s)	
	12/787,283	HELENEK ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *25 May 2010*.

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) _____ is/are rejected.

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

9)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

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).

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

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

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

DETAILED ACTION

This Office Action details three Election of Species requirements.

Election of Species

This application contains claims directed to the following patentably distinct First species of disease, disorder or condition treated, Second species of iron carbohydrate complex, and Third species of route of administration. The species are independent or distinct because a different disease, disorder or condition defines a different patient population, symptoms and causes, the species of methods administer a different complex having different chemical components by different routes. In addition, these species are not obvious variants of each other based on the current record.

Examples of First species of disease, disorder or condition treated are:

1a) iron deficiency anemia associated with blood chronic or acute blood loss disclosed in claim 6,

1b) iron deficiency anemia associated with idiopathic pulmonary siderosis disclosed in claim 6,

1c) anemia of the chronic disease rheumatoid arthritis disclosed in claim 6, and

1d) restless leg syndrome disclosed in claim 7.

Examples of Second species of iron carbohydrate complex are:

2a) iron hydrogenated dextran complex disclosed in claim 1,

2b) iron carboxymaltose complex having the formula disclosed in (i) in claim 14,

2c) iron carboxymaltose complex having the formula disclosed in (ii) in claim 14, and

2d) iron polyglucose sorbitol carboxymethyl ether complex disclosed in claims 15 and 16.

Examples of Third species of route of administration are:

3a) intravenous infusion disclosed in claim 19,

3b) intramuscular injection disclosed in claim 19, and

3c) bolus injection that is not intramuscular implicitly disclosed in claim 19.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, all claims are generic or subgeneric to the first and third species, and claims 1-12, 14 and 17-20 are generic or subgeneric to the second species.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply:

(c) the species require a different field of search (for example, employing different search queries for treating a specific patient population or by specific methods of administration).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or a grouping of patentably indistinct species

to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Due to the complexity of the species election requirements, no telephone communication was made. See MPEP 812.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

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

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

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

Jonathan Lau
Patent Examiner
Art Unit 1623

/SHAOJIA ANNA JIANG/
Supervisory Patent Examiner
Art Unit 1623

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12787283	HELENEK ET AL.
	Examiner	**Art Unit**
	JONATHAN S LAU	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

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

CLAIM		DATE								
Final	Original	03/21/2012								
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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	12787283
	Filing Date	2010-05-25
	First Named Inventor	Mary Jane Helenek
	Art Unit	1623
	Examiner Name	Johnathan S. Lau
	Attorney Docket Number	30015730-0053

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					
If you wish to add additional U.S. Patent citation information please click the Add button.						Add

U.S.PATENT APPLICATION PUBLICATIONS						Remove
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					
If you wish to add additional U.S. Published Application citation information please click the Add button.						Add

FOREIGN PATENT DOCUMENTS							Remove	
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐
If you wish to add additional Foreign Patent Document citation information please click the Add button							Add	

NON-PATENT LITERATURE DOCUMENTS			Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12787283
	Filing Date	2010-05-25
	First Named Inventor	Mary Jane Helenek
	Art Unit	1623
	Examiner Name	Johnathan S. Lau
	Attorney Docket Number	30015730-0053

	1	Australian Office Action dated 15 September 2011 in related Application No. AU2007205167 filed 08 January 2007, 3 pages.	☐
	2	Chinese Office Action dated 30 April 2010 in related Application No. CN200780002006 filed 08 January 2007, English translation, 7 pages.	☐
	3	European Official Communication dated 05 October 2011 in related Application No. EP077163093.5 filed 08 January 2007, 6 pages.	☐
	4	International Search Report and Written Opinion dated 12 September 2007 in related PCT Application No. PCT/US07/00176 filed 08 January 2007, 6 pages.	☐

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	12787283
	Filing Date	2010-05-25
	First Named Inventor	Mary Jane Helenek
	Art Unit	1623
	Examiner Name	Johnathan S. Lau
	Attorney Docket Number	30015730-0053

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☐ A certification statement is not submitted herewith.

SIGNATURE

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

Signature		Date (YYYY-MM-DD)	
Name/Print		Registration Number	

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/00176

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/715 (2007.01)
USPC - 514/53
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)
USPC - 514/53

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC 514/53 and 514/184 - see keywords below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest(PGPUB, USPT, EPAB, JPAB), Google Scholar
Search Terms Used: maltodextrin, iron carboxymaltose, dextrose, iron

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0180849 A1 (HELENEK et al.) 16 September 2004 (16.09.2004), para [0008]-[0010], [0012]-[0015], [0017], [0020]-[0022], [0051], [0052], [0096], and [0097].	1-3, 5, and 20

☐ Further documents are listed in the continuation of Box C. ☐

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

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 2007 (12.07.2007)	12 SEP 2007
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/00176

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

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

3. ☒ Claims Nos.: 4 and 6-19
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

PATENT COOPERATION TREATY

237

From the
INTERNATIONAL SEARCHING AUTHORITY

To: G Harley Blosser
Sonnenschein Nath & Rosenthal LLP
PO Box 061080
Wacker Drive Station Sears Tower
Chicago IL 60606-1080

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	12 SEP 2007
Applicant's or agent's file reference 30015730-0042	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 07/00176	08 January 2007 (08.01.2007)	06 January 2006 (06.01.2006)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/715 (2007.01)
USPC - 514/53

Applicant Luitpold Pharmaceuticals Inc

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	12 July 2007 (12.07.2007)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/00176

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/00176

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 4 and 6-19

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 4 and 6-19 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 4 and 6-19 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 4 and 6-19

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/00176

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	20	YES
	Claims	1-3 and 5	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-3, 5, and 20	NO
Industrial applicability (IA)	Claims	1-3, 5, and 20	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-3 and 5 lack novelty under PCT Article 33(2) as being anticipated by US 2004/0180849 A1 to Helenek et al., (hereinafter 'Helenek').

As per claim 1, Helenek teaches a method of treating a disorder characterized by iron deficiency or dysfunctional iron metabolism, comprising administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about .6 grams of elemental iron, wherein the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component and substantially no cross reactivity with anti-dextran antibodies (para [0017] and [0051]).

As per claim 2, Helenek teaches a method wherein the disorder is an anemia of a chronic disease (para [0008]-[0010]).

As per claim 3, Helenek teaches the method wherein the disorder is restless leg syndrome (para [0012]-[0015]).

As per claim 5, Helenek teaches a method wherein the dosage unit of elemental iron is administered in about 5 minutes or less (para [0097]).

Claim 20 lacks an inventive step under PCT Article 33(3) as being obvious over Helenek. Helenek teaches a method of treating a disorder characterized by iron deficiency comprising: intravenously administering to a subject in need thereof an iron carboxymaltose complex in a single dosage unit of at least about 1000 mg of elemental iron in about 200 ml to about 300 ml of diluent in 5 minutes or less; and wherein the mean size of a particle of the iron carboxymaltose complex is no greater than about 30nm (35nm); wherein the complex is about 100,000 daltons (para [0051], [0052], [0096]). Furthermore, Helenek teaches an iron complex obtained from iron (III) oxidation state, complexed with an organic compound (para [0020]-[0022]). Helenek does not teach a specific dextrose equivalent or a specific chemical formula of the iron complex. It would have been obvious to one of ordinary skill in the art to measure the dextrose equivalent and create the specific iron complex without undue experimentation according to the disclosed method.

Claims 1-3, 5, and 20 have industrial applicability as defined by PCT Article 33(4) because the claimed invention can be made or used in industry.

Electronic Acknowledgement Receipt

EFS ID:	11882100
Application Number:	12787283
International Application Number:	
Confirmation Number:	4251
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	David Richard Metzger/Kathleen Chaffee
Filer Authorized By:	David Richard Metzger
Attorney Docket Number:	30015730-0053
Receipt Date:	20-JAN-2012
Filing Date:	25-MAY-2010
Time Stamp:	11:53:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_Transmittal_30015730-0053.pdf	92098 3b7b6cf01c565e45e675496cc3667c1f4808b72b	no	2
Warnings:					
Information:					

2	Information Disclosure Statement (IDS) Form (SB08)	0053US_SB08A_updated_IDS.pdf	769995 58b408ad147dd448ee78d730a5ccdc2f43608288	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Non Patent Literature	0047AU_OA_.pdf	537330 cf6f0515f09abf6d1733988f8df211751b74c5d9	no	3
Warnings:					
Information:					
4	Non Patent Literature	0050CN_OA.pdf	228820 c0821fa3c2fb4d46492a13626449b1ed82c3cf8e	no	7
Warnings:					
Information:					
5	Non Patent Literature	0051EP_2ndOA.pdf	673049 f531d93fbd846b57d1390c54fdab961f7eab4936	no	6
Warnings:					
Information:					
6	Non Patent Literature	0042WO_ISRandWO_12Sep2007.pdf	343993 d19a5c56e4b06cd1196d0318e7da2c7da15c2979	no	6
Warnings:					
Information:					
			Total Files Size (in bytes):	2645285	

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

Applicant(s):	Mary Jane Helenek et al.	Confirmation No:	4251
Serial No:	12/787,283	Customer No:	26263
Filed:	25 May 2010	Docket No:	30015730-0053
Examiner:	Johnathan S. Lau		
Art Unit:	1623		
Title:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON		

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(b)

Sir:

In accordance with the provisions of 37 C.F.R. § 1.56, Applicants request citation and examination of the references identified on the attached PTO-SB08A, 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. The listed items are office actions and search reports issued in foreign counterpart applications. The citations in these office actions and search reports are already of record.

Under 37 C.F.R. § 1.97(b), the information disclosure statement submitted herewith is being filed ***before*** the mailing of a first Office action on the merits.

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

It is believed that no fees are due with the filing of this Information Disclosure Statement. However, the Commissioner is hereby authorized to charge any fees that may be required or credit any overpayments to SNR Denton US LLP Deposit Account No. 19-3140.

Respectfully Submitted,

Janaury 20, 2012
Date

/David R. Metzger/
David R. Metzger, Reg. No. 32,919
Attorney for Applicant(s)

SNR Denton US LLP
P.O. Box 061080
Wacker Drive Station, Willis Tower
Chicago, IL 60606-1080
Phone: 312.876.8000
Fax: 312.876.7934

23184342\V-2

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/787,283	05/25/2010	Mary Jane Helenek	30015730-0053

CONFIRMATION NO. 4251

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

PUBLICATION NOTICE

Title:METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

Publication No.US-2010-0266644-A1
Publication Date:10/21/2010

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/787,283	05/25/2010	1618	527	30015730-0053	20	1

CONFIRMATION NO. 4251

UPDATED FILING RECEIPT

26263
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, WILLIS TOWER
CHICAGO, IL 60606-1080

OC000000042536517

Date Mailed: 07/14/2010

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**

Applicant(s)

Mary Jane Helenek, Brookville, NY;
Marc L. Tokars, Douglassville, PA;
Richard P. Lawrence, Southold, 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 11/620,986 01/08/2007 PAT 7,754,702
which claims benefit of 60/757,119 01/06/2006

Foreign Applications

If Required, Foreign Filing License Granted: 06/04/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/787,283**

Projected Publication Date: 10/21/2010

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****

Title

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

Preliminary Class

424

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

Attorney Docket No. 30015730-0053 **Patent**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: **12/787,283**	Examiner: **TBA**
Applicant: **Mary Jane HELENEK et al.**	Group Art Unit: **1618**
Filed: **May 25, 2010**	Confirmation No.: **4251**
Docket No.: **30015730-0053**	Customer No.: **26263**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	

July 6, 2010

FILED ELECTRONICALLY VIA EFS-WEB

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

RESPONSE TO NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

Dear Sir:

In response to the Notice to File Missing Parts dated June 7, 2010, Applicants submit an executed Declaration and Power of Attorney and our payment of the $65 surcharge to cover this fee.

Applicants also submit herewith a replacement drawing for Figure 1. Support for the replacement figure can be found at least on Figure 1 of the parent application, USSN 11/620,986.

The Commissioner is hereby authorized to credit overpayments or to charge any deficiency in connection with this filing to Deposit Account No. 19-3140.

Respectfully submitted,

By: /Karen I. Deak/
Karen Imgrund Deak
Registration No. 65,638
Patent Agent
SONNENSCHEIN NATH & ROSENTHAL LLP
(314) 259-5833

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare:

That my residence, post office address and citizenship are as stated below next to my name.

That I verily believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

the specification of which (check one)

☐ Is attached hereto.
☒ Was filed on: 25 May 2010 As
☒ Application Serial No.: 12/787,283
and was amended on: _____

That I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

That I acknowledge the duty to disclose information known to be material to patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

That I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate on this invention having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s) Priority Claimed

Prior United States Provisional Application(s)

That I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

60/757,119	06 January 2006
(Application Number)	(Filing Date)
_____	_____
(Application Number)	(Filing Date)

Prior United States Application(s)

That I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

11/620,986	08 January 2007	Allowed
(Application Serial No.)	(Filing Date)	(Status)-(Patented, pending, abandoned)

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 issuing thereon.

I hereby appoint G. Harley Blosser (Reg. 33,650), and agents of Sonnenschein Nath & Rosenthal associated with **Customer Number 26263**, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith and request that all correspondence and telephone calls in respect to application be directed to **G. Harley Blosser at SONNENSCHEIN, NATH & ROSENTHAL LLP, 8000 Sears Tower, 233 S. Wacker Drive, Chicago, Illinois 60606-6404, Phone: 314-259-5806, Fax: 312-876-7934:**

Address for Correspondence:	**G. Harley Blosser** Sonnenschein Nath & Rosenthal LLP P.O. Box 061080, Wacker Drive Station SEARS TOWER, 233 S. Wacker Drive Chicago, Illinois 60606-6404
Full name of first inventor:	Mary Jane Helenek
Inventor's signature:	Mary Jane Helenek
Date:	6.28.10
Citizenship:	US
Address:	13 Evans Drive Brookville, New York 11545
Full name of second inventor:	Marc L. Tokars
Inventor's signature:	
Date:	June 24, 2010
Citizenship:	US
Address:	202 Farmingdale Drive Douglassville, Pennsylvania 19618

Full name of third inventor: Richard P. Lawrence

Inventor's signature: [signature]

Date: 6/28/2010

Citizenship: US

Address: ~~94 Young Avenue~~ 425 Sleepy Hollow Lane
~~Calverton, New York 11933~~ Southold, NY 11971

6/28/2010 6/28/2010

REPLACEMENT SHEET

FIGURE 1

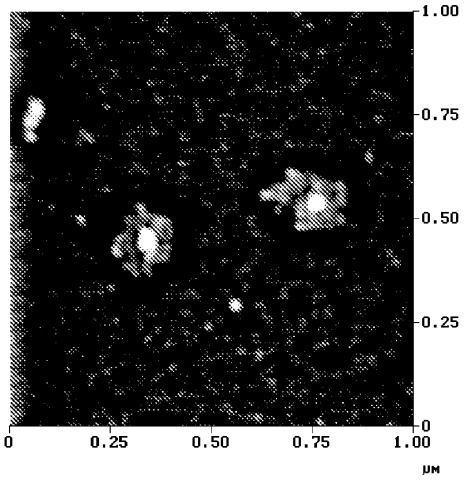

FIG. 1A

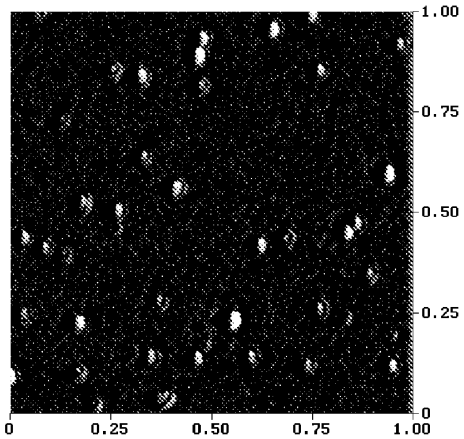

FIG. 1B

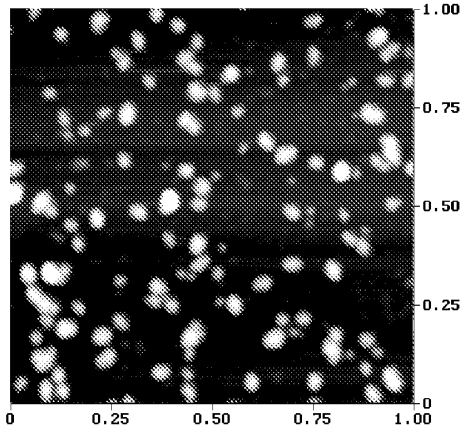

FIG. 1C

Electronic Patent Application Fee Transmittal

Application Number:	12787283
Filing Date:	25-May-2010
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Filer:	Karen Imgrund Deak
Attorney Docket Number:	30015730-0053

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	2051	1	65	65
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**65**

Electronic Acknowledgement Receipt	
EFS ID:	7956924
Application Number:	12787283
International Application Number:	
Confirmation Number:	4251
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	Karen Imgrund Deak
Filer Authorized By:	
Attorney Docket Number:	30015730-0053
Receipt Date:	06-JUL-2010
Filing Date:	25-MAY-2010
Time Stamp:	14:50:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$65
RAM confirmation Number	1060
Deposit Account	
Authorized User	

File Listing:

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

1	Miscellaneous Incoming Letter	30015730_0053_RNMP_transmittal_July2010.pdf	452864 f8406a5272d0db694b4d84d1dc99260fd837db10	no	1
Warnings:					
Information:					
2	Oath or Declaration filed	30015730_0053_Executed_Dec_POA_July2010.pdf	52011 baee4513ee72a30bcafefdf73553e4fd4eb32824	no	3
Warnings:					
Information:					
3	Drawings-other than black and white line drawings	30017530_0053_Replacement_Figs_july2010.pdf	861172 05e3ace58036878dcc27f119bff17c534502ecb0	no	1
Warnings:					
Information:					
4	Fee Worksheet (PTO-875)	fee-info.pdf	29812 b0a228359f96aa55f0917b562be22aa4731b4c45	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1395859		

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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.

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 12787283 Document Date: 7/6/10

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Form Revision Date: May 1, 2009

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	12787283
Filing Date	2010-05-25
First Named Inventor	Mary Jane HELENEK
Art Unit	1618
Examiner Name	TBA
Attorney Docket Number	30015730-0053

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5624668		1997-04-29	Lawrence et al.	
	2	6599498		2003-07-29	Groman et al.	
	3	6960571		2005-11-01	Helenek et al.	

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20040180849		2004-09-16	Helenek et al.	

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

FOREIGN PATENT DOCUMENTS Remove

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12787283
	Filing Date	2010-05-25
	First Named Inventor	Mary Jane HELENEK
	Art Unit	1618
	Examiner Name	TBA
	Attorney Docket Number	30015730-0053

	2	2004037865	WO		2004-05-06	Vifor Int. AG		☐
	3	2007023154	WO		2007-03-01	Vifor Int. AG		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	ANDERSSON, "Clinical investigations on a new intramuscular haematinic", British Medical Journal, 1961, 275-279	☐
	2	BAILIE et al., "Hypersensitivity reactions and deaths associated with intravenous iron preparations", Nephrol Dial Transplant, 2005, 20:1443-1449	☐
	3	BESHARA et al., "Pharmacokinetics and red cell utilization of 52Fe/59Fe-labelled iron polymaltose in anaemic patients using positron emission tomography", Br J of Haematol, 2003, 120:853-859	☐
	4	CISAR et al., "Binding properties of immunoglobulin combining sites specific for terminal or nonterminal antigenic determinants in dextran", J Exp Med, 1975, 142:435-459	☐
	5	ESCHBACH et al., "NKF-K/DOQI clinical practice guidelines for anemia of chronic kidney disease: update 2000", Am J Kidney Dis, 2001, 37(1 Supp 1):S182-238	☐
	6	European Search Report issued October 21, 2009, in the related application EP 07716309.5	☐
	7	FIELDING, "Intravenous iron-dextrin in iron-deficiency anaemia", British Medical Journal, 1961, 279-283	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12787283
	Filing Date	2010-05-25
	First Named Inventor	Mary Jane HELENEK
	Art Unit	1618
	Examiner Name	TBA
	Attorney Docket Number	30015730-0053

	8	FISHBANE, "Safety in iron management", Am J Kidney Dis, 2003, 41(6 Suppl 5):S18-S26	☐
	9	GEISSER et al., "Structure/histotoxicity relationship of parenteral iron preparations", Drug Research, 1992, 42 (12):1439-1452	☐
	10	HAINES et al., "Delayed adverse reactions to total-dose intravenous iron polymaltose", Internal Medicine Journal, 2009, 39:252-255	☐
	11	KUDASHEVA et al., "Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanoparticles in parenteral formulations", Journal of Inorganic Biochemistry, 2004, 98:1757-1769	☐
	12	LANDRY et al., "Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients", Am J Nephrol, 2005, 25:400-410	☐
	13	MACDOUGALL, "Intravenous administration of iron in epoetin-treated haemodialysis patients—which drugs, which regimen?", Nephrol Dial Transplant, 2000, 15:1743-1745	☐
	14	NEWNHAM et al., "Safety of iron polymaltose given as a total dose iron infusion", Internal Medicine Journal, 2006, 36 (10):672-674	☐
	15	NISSENSON et al., "Controversies in iron management", Kidney International, 2003, 64(Supplement 87):S64-S71	☐
	16	SIPE et al., "Brain iron metabolism and neurodegenerative disorders", Dev Neurosci, 2002, 24(2-3):188-196	☐
	17	SOFIC et al., "Increased iron (III) and total iron content in post mortem substantia nigra of parkinsonian brain", J. Neural Transm, 1988, 74:199-205	☐
	18	SPINOWITZ et al., "The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients", Kidney International, 2005, 68:1801-1807	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12787283
	Filing Date	2010-05-25
	First Named Inventor	Mary Jane HELENEK
	Art Unit	1618
	Examiner Name	TBA
	Attorney Docket Number	30015730-0053

	19	VAN WYCK et al., "Making sense: a scientific approach to intravenous iron therapy", J Am Soc Nephrol, 2004, 15 (Suppl 2):S91-S92	☐
	20	VAN WYCK, "Labile iron: manifestations and clinical implications", J Am Soc Nephrol, 2004, 15(Suppl 2):S107-S111	☐

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12787283
	Filing Date	2010-05-25
	First Named Inventor	Mary Jane HELENEK
	Art Unit	1618
	Examiner Name	TBA
	Attorney Docket Number	30015730-0053

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☐ None

SIGNATURE

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

Signature		Date (YYYY-MM-DD)	
Name/Print		Registration Number	

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

Electronic Acknowledgement Receipt

EFS ID:	7832710
Application Number:	12787283
International Application Number:	
Confirmation Number:	4251
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary Jane Helenek
Customer Number:	26263
Filer:	Karen Imgrund Deak
Filer Authorized By:	
Attorney Docket Number:	30015730-0053
Receipt Date:	17-JUN-2010
Filing Date:	25-MAY-2010
Time Stamp:	11:06:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	30015730_0053_transmittal_June2010.pdf	464204 a3da9650e87d6f74dbe629a00b7a4c04a7a409b2	no	2

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Filed (SB/08)	30015730_0053_SB08_June2010.pdf	1114339 0536713b5d7bc7db6478033ab51f37f7c1b21b4f	no	6
Warnings:					
Information:					
			Total Files Size (in bytes):	1578543	

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.: **12/787,283**	Examiner: **TBA**
Applicant: **Mary Jane HELENEK et al.**	Group Art Unit: **1618**
Filed: **May 25, 2010**	Confirmation No.: **4251**
Title: **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**	Customer No.: **26263**
Docket No.: **30015730-0053**	

June 17, 2010

FILED ELECTRONICALLY VIA EFS-WEB

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

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT

UNDER 37 C.F.R. §1.97(b)

Sir:

In accordance with the provisions of 37 C.F.R. § 1.56, Applicants request consideration 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(b), the information disclosure statement submitted herewith is being filed: (1) within three months of the filing date of a national application other than a continued prosecution application under § 1.53(d); (2) within three months of the date of entry of the national stage as set forth in § 1.491 in an international application; (3) before the mailing of a first Office action on the merits; or (4) before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

All of the references cited in the attached PTO-SB08A form were cited by either the Applicant or the Patent and Trademark Office during prosecution of the related application serial number 11/620,986. Therefore, pursuant to 37 C.F.R. § 1.98(d), Applicant is not providing copies of these references herewith.

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

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

Respectfully submitted,

SONNENSCHEIN NATH & ROSENTHAL LLP

By: /Karen I. Deak/
Karen Imgrund Deak
Patent Agent
Reg. No. 65,638
Telephone No. 314 259-5833

23184342\V-2

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/787,283	05/25/2010	Mary Jane Helenek	30015730-0053

CONFIRMATION NO. 4251

26263
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, WILLIS TOWER
CHICAGO, IL 60606-1080

FORMALITIES LETTER

OC000000041952939

Date Mailed: 06/07/2010

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - More than one figure is present and each figure is not labeled "Fig." with a consecutive Arabic numeral (1, 2, etc.) or an Arabic numeral and capital letter in the English alphabet (A, B, etc.)(see 37 CFR 1.84(u)(1)). See Figure(s) 1C. A brief description of the several views of the drawings (see 37 CFR 1.74) should be added or amended to correspond to the corrected numbering of the figures. See also 37 CFR 1.77(b)(7).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**65** for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**65** for a small entity
- $**65** Surcharge.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

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/mhaile/

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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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
12/787,283	05/25/2010	1618	462	30015730-0053	20	1

CONFIRMATION NO. 4251

26263
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, WILLIS TOWER
CHICAGO, IL 60606-1080

FILING RECEIPT

OC000000041952938

Date Mailed: 06/07/2010

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**

Applicant(s)

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

Assignment For Published Patent Application

LUITPOLD PHARMACEUTICALS, INC., Shirley, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 11/620,986 01/08/2007
which claims benefit of 60/757,119 01/06/2006

Foreign Applications

If Required, Foreign Filing License Granted: 06/04/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/787,283**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****

Title

METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

Preliminary Class

424

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0053
	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.
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Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0053
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

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Customer Number	26263		
Email Address	patents@sonnenschein.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON		
Attorney Docket Number	30015730-0053	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	2	**Suggested Figure for Publication (if any)**	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0053
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

Customer Number	26263

Domestic Benefit/National Stage Information:

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Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	11620986	2007-01-08
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
11620986	non provisional of	60757119	2006-01-06

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Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
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Assignee 1 Remove

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

Organization Name	Luitpold Pharmaceuticals, Inc.		
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Phone Number		Fax Number	
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	30015730-0053
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON	

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.					
Signature	/G. Harley Blosser/			Date (YYYY-MM-DD)	2010-05-25
First Name	G. Harley	Last Name	Blosser	Registration Number	33650

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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.

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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. 11/620,986, filed on January 8, 2007, which in turn claims priority from U.S. Provisional Application Serial No. 60/757,119, filed on January 6, 2006, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention generally relates to treatment of iron-related conditions with iron carbohydrate complexes.

BACKGROUND

[0003] Parenteral iron therapy is known to be effective in a variety of diseases and conditions including, but not limited to, severe iron deficiency, iron deficiency anemia, problems of intestinal iron absorption, intestinal iron intolerance, cases where regular intake of an oral iron preparation is not guaranteed, iron deficiency where there is no response to oral therapy (*e.g.*, dialysis patients), and situations where iron stores are scarcely or not at all formed but would be important for further therapy (*e.g.*, in combination with erythropoietin). Geisser et al., Arzneimittelforschung (1992) 42(12), 1439-1452. There exist various commercially available parenteral iron formulations. But many currently available parenteral iron drugs, while purportedly effective at repleting iron stores, have health risks and dosage limitations associated with their use.

[0004] Currently available parenteral iron formulations approved for use in the U.S. include iron dextran (*e.g.*, InFed, Dexferrum), sodium ferric gluconate complex in sucrose (Ferrlecit), and iron sucrose (Venofer). Although serious and life-threatening reactions occur most frequently with iron dextran, they are also known to occur with other parenteral iron products. In addition,

non-life threatening reactions such as arthralgia, back pain, hypotension, fever, myalgia, pruritus, vertigo, and vomiting also occur. These reactions, while not life-threatening, often preclude further dosing and therefore iron repletion.

[0005] Iron dextran, the first parenteral iron product available in the United States (US), has been associated with an incidence of anaphylactoid-type reactions (*i.e.*, dyspnea, wheezing, chest pain, hypotension, urticaria, angioedema). *See generally* Fishbane, Am J Kidney Dis (2003) 41(5Suppl), 18-26; Landry et al. (2005) Am J Nephrol 25, 400-410, 407. This high incidence of anaphylactoid reactions is believed to be caused by the formation of antibodies to the dextran moiety. Other parenteral iron products (*e.g.*, iron sucrose and iron gluconate) do not contain the dextran moiety, and the incidence of anaphylaxis with these products is markedly lower. Fishbane, Am J Kidney Dis (2003) 41(5Suppl), 18-26; Geisser et al., Arzneimittelforschung (1992) 42(12), 1439-52. However, the physical characteristics of, for example, iron gluconate and iron sucrose lead to dosage and administration rate limitations. Negative characteristics include high pH, high osmolarity, low dosage limits (*e.g.*, maximum 500 mg iron once per week, not exceeding 7 mg iron/kg body weight), and the long duration of administration (*e.g.*, 100 mg iron over at least 5 minutes as an injection; 500 mg iron over at least 3.5 hours as a drip infusion). Furthermore, injectable high molecular mass substances produce more allergic reactions than the corresponding low molecular mass substances. Geisser et al. (1992) *Arzneimittelforschung* 42: 1439-1452.

[0006] Ferumoxytol is a newer parenteral iron formulation but limited information is available as to its efficacy and administration. *See e.g.*, Landry et al. (2005) Am J Nephrol 25, 400-410, 408; and Spinowitz et al. (2005) Kidney Intl 68, 1801-1807; U.S. Patent No. 6,599,498.

[0007] Various pharmacokinetic studies suggest that doses of iron complexes higher than 200 mg of iron are generally unsuitable and that the conventional therapy model prescribes repeated applications of lower doses over several days. *See* Geisser et al., (1992) *Arzneimittelforschung* 42: 1439-1452. For example, to achieve iron repletion under current therapy models, a

total dose of 1 g typically requires 5 to 10 sessions over an extended period of time. These delivery modes incur significant expense for supplies such as tubing and infusate, costly nursing time, multiple administrations, and patient inconvenience.

SUMMARY OF THE INVENTION

[0008] Among the various aspects of the present invention is the provision of a method of treatment of iron-associated diseases, disorders, or conditions with iron formulations. Briefly, therefore, the present invention is directed to use of iron carbohydrate complexes that can be administered parenterally at relatively high single unit dosages, thereby providing a safe and efficient means for delivery of a total dose of iron in fewer sessions over the course of therapeutic treatment.

[0009] The present teachings include methods of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism through the administration of at least 0.6 grams of elemental iron via a single unit dosage of an iron carbohydrate complex to a subject that is in need of such therapy.

[0010] In various embodiments, the method treats anemia. In some embodiments, the anemia is an iron deficiency anemia, such as that associated with chronic blood loss; acute blood loss; pregnancy; childbirth; childhood development; psychomotor and cognitive development in children; breath holding spells; heavy uterine bleeding; menstruation; chronic recurrent hemoptysis; idiopathic pulmonary siderosis; chronic internal bleeding; gastrointestinal bleeding; parasitic infections; chronic kidney disease; dialysis; surgery or acute trauma; and chronic ingestion of alcohol, chronic ingestion of salicylates, chronic ingestion of steroids; chronic ingestion of non-steroidial anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents. In some aspects, the anemia is anemia of chronic disease, such as rheumatoid arthritis; cancer; Hodgkins leukemia; non-Hodgkins leukemia; cancer chemotherapy; inflammatory bowel disease; ulcerative colitis thyroiditis; hepatitis; systemic lupus erythematosus; polymyalgia rheumatica; scleroderma;

mixed connective tissue disease; Sojgren's syndrome; congestive heart failure / cardiomyopathy; or idiopathic geriatric anemia. In some embodiments, the anemia is due to impaired iron absorption or poor nutrition, such as anemia associated with Crohn's Disease; gastric surgery; ingestion of drug products that inhibit iron absorption; and chronic use of calcium. In various embodiments, the method treats restless leg syndrome; blood donation; Parkinson's disease; hair loss; or attention deficit disorder.

[0011] In various embodiments, the single dosage unit of elemental iron is between at least about 0.6 grams and 2.5 grams. In some embodiments, the single dosage unit of elemental iron is at least about 0.7 grams; at least about 0.8 grams; at least about 0.9 grams; at least about 1.0 grams; at least about 1.1 grams; at least about 1.2 grams; at least about 1.3 grams; at least about 1.4 grams; at least about 1.5 grams; at least about 1.6 grams; at least about 1.7 grams; at least about 1.8 grams; at least about 1.9 grams; at least about 2.0 grams; at least about 2.1 grams; at least about 2.2 grams; at least about 2.3 grams; at least about 2.4 grams; or at least about 2.5 grams.

[0012] In various embodiments, the single dosage unit of elemental iron is administered in about 15 minutes or less. In some embodiments, the single dosage unit of elemental iron is administered in about 10 minutes or less, about 5 minutes or less, or about 2 minutes or less.

[0013] In various embodiments, the subject does not experience a significant adverse reaction to the single dosage unit administration.

[0014] In various embodiments, the iron carbohydrate complex has a pH between about 5.0 to about 7.0; physiological osmolarity; an iron core size no greater than about 9 nm; a mean diameter particle size no greater than about 35 nm; a blood half-life of between about 10 hours to about 20 hours; a substantially non-immunogenic carbohydrate component; and substantially no cross reactivity with anti-dextran antibodies.

[0015] In various embodiments, the iron carbohydrate complex contains about 24% to about 32% elemental iron; contains about 25% to about

50% carbohydrate; has a molecular weight of about 90,000 daltons to about 800,000 daltons, or some combination thereof.

In various embodiments, the iron carbohydrate complex is an iron monosaccharide complex, an iron disaccharide complex, or an iron polysaccharide complex. In some embodiments, the iron carbohydrate complex is iron carboxymaltose complex, iron mannitol complex, iron polyisomaltose complex, iron polymaltose complex, iron gluconate complex, iron sorbitol complex, or an iron hydrogenated dextran complex. In some embodiments, the iron carbohydrate complex is an iron polyglucose sorbitol carboxymethyl ether complex. In some preferred embodiments, the iron carboxymaltose complex contains about 24% to about 32% elemental iron, about 25% to about 50% carbohydrate, and is about 100,000 daltons to about 350,000 daltons. In some preferred embodiments, the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between 5 and 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between 5 and 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between 2 and 20. In some preferred embodiments, the iron carboxymaltose complex has a chemical formula of $[FeO_x(OH)_y(H_2O)_z]_n[\{(C_6H_{10}O_5)_m(C_6H_{12}O_7)\}_l]_k$, where n is about 103, m is about 8, l is about 11, and k is about 4; contains about 28% elemental iron; and has a molecular weight of about 150,000 Da. In some preferred embodiments, the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

[0016] In various embodiments, the iron carbohydrate complex comprises an iron core with a mean iron core size of no greater than about 9 nm. In some embodiments, the mean iron core size is at least about 1 nm but no greater than about 9 nm; at least about 3 nm but no greater than about 7 nm; or at least about 4 nm but not greater than about 5 nm.

[0017] In various embodiments, the mean size of a particle of the iron carbohydrate complex is no greater than about 35 nm. In some embodiments, the particle mean size is no greater than about 30 nm. In some embodiments, the particle mean size is no greater than about 25 nm. In some embodiments, the particle mean size is no greater than about 20 nm; no greater than about 15 nm; no greater than about 10 nm; or at least about 6 nm but no greater than about 7 nm.

[0018] In various embodiments, the iron carbohydrate complex is administered parenterally, for example intravenously or intramuscularly. In some embodiments, the iron carbohydrate complex is intravenously infused. In certain embodiments, the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, for example, about 250 ml of diluent or about 215 ml of diluent. In some embodiments, the iron carbohydrate complex is intravenously injected as a bolus. In certain embodiments, the iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, for example, about 250 ml of diluent or about 215 ml of diluent. In some embodiments, the iron carbohydrate complex is intramuscularly infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, for example, about 250 ml of diluent or about 215 ml of diluent. In some embodiments, the iron carbohydrate complex is intramuscularly infused at a concentration of about 500 mg elemental iron in less than about 10 ml diluent.

[0019] In various embodiments, the method also includes a second administration of the iron carbohydrate complex upon recurrence of at least one symptom of the treated disease, disorder, or condition.

[0020] In various embodiments, the method also includes a second administration of the iron carbohydrate complex after 1 day to 12 months after the first administration.

[0021] In a preferred embodiment, the method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron

metabolism comprises intravenously administering to a subject in need thereof an iron carboxymaltose complex in a single dosage unit of at least about 1000 mg of elemental iron in about 200 ml to about 300 ml of diluent in about 5 minutes or less; wherein the iron carboxymaltose complex comprises an iron core with a mean iron core size of at least about 1 nm but no greater than about 9 nm; mean size of a particle of the iron carboxymaltose complex is no greater than about 35 nm; and the iron carboxymaltose complex is administered intravenously infused or intravenously injected at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent. In some these embodiments, the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. In some these embodiments, the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between about 5 and about 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between about 5 and about 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between about 2 and about 20.

[0022] Other objects and features will be in part apparent and in part pointed out hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Those of skill in the art will understand that the drawings, described below, are for illustrative purposes only. The drawings are not intended to limit the scope of the present teachings in any way.

[0024] FIG 1 is a series of electron micrographs that depict the particle size of three iron carbohydrate complexes. FIG 1A is an electron micrograph depicting the particle size of Dexferrum (an iron dextran). FIG 1B is an electron micrograph depicting the particle size of Venofer (an iron sucrose). FIG 1C is an electron micrograph depicting the particle size of polynuclear iron (III)-hydroxide

4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate ("VIT-45", an iron carboxymaltose complex).

[0025] FIG 2 is a schematic representation of an exemplary iron carboxymaltose complex.

DETAILED DESCRIPTION OF THE INVENTION

[0026] The present invention makes use of iron carbohydrate complexes that can be administered parenterally at relatively high single unit dosages for the therapeutic treatment of a variety of iron-associated diseases, disorders, or conditions. Generally, states indicative of a need for therapy with high single unit dosages of iron carbohydrate complexes include, but are not limited to iron deficiency anemia, anemia of chronic disease, and states characterized by dysfunctional iron metabolism. Efficacious treatment of these, and other, diseases and conditions with parenteral iron formulations (supplied at lower single unit dosages than those described herein) is generally known in the art. *See e.g.*, Van Wyck et al. (2004) J Am Soc Nephrol 15, S91-S92. The present invention is directed to use of iron carbohydrate complexes that can be administered parenterally at relatively high single unit dosages, thereby providing a safe and efficient means for delivery of a total dose of iron in fewer sessions over the course of therapeutic treatment.

[0027] Iron deficiency anemia is associated with, for example, chronic blood loss; acute blood loss; pregnancy; childbirth; childhood development; psychomotor and cognitive development in children; breath holding spells; heavy uterine bleeding; menstruation; chronic recurrent hemoptysis; idiopathic pulmonary siderosis; chronic internal bleeding; gastrointestinal bleeding; parasitic infections; chronic kidney disease; dialysis; surgery or acute trauma; and chronic ingestion of alcohol, chronic ingestion of salicylates, chronic ingestion of steroids; chronic ingestion of non-steroidial anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents.

[0028] Anemia of chronic disease is associated with, for example, rheumatoid arthritis; cancer; Hodgkins leukemia; non-Hodgkins leukemia; cancer chemotherapy; inflammatory bowel disease; ulcerative colitis thyroiditis;

hepatitis; systemic lupus erythematosus; polymyalgia rheumatica; scleroderma; mixed connective tissue disease; Sojgren's syndrome; congestive heart failure / cardiomyopathy; and idiopathic geriatric anemia.

[0029] Anemia is also associated with, for example, Crohn's Disease; gastric surgery; ingestion of drug products that inhibit iron absorption; and chronic use of calcium.

[0030] States characterized by dysfunctional iron metabolism and treatable with the single unit dosages of iron carbohydrate complexes described herein include, but are not limited to, restless leg syndrome; blood donation; Parkinson's disease; hair loss; and attention deficit disorder.

[0031] Again, each of the above listed states, diseases, disorders, and conditions, as well as others, can benefit from the treatment methodologies described herein. Generally, treating a state, disease, disorder, or condition includes preventing or delaying the appearance of clinical symptoms in a mammal that may be afflicted with or predisposed to the state, disease, disorder, or condition but does not yet experience or display clinical or subclinical symptoms thereof. Treating can also include inhibiting the state, disease, disorder, or condition, *e.g.*, arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof. Furthermore, treating can include relieving the disease, *e.g.*, causing regression of the state, disease, disorder, or condition or at least one of its clinical or subclinical symptoms.

[0032] The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician. Measures of efficacy of iron replacement therapy are generally based on measurement of iron-related parameters in blood. The aim of treatment is usually to return both Hb and iron stores to normal levels. Thus, efficacy of iron replacement therapy can be interpreted in terms of the ability to normalise Hb levels and iron stores. The effectiveness of treatment with one or more single unit doses of iron carbohydrate complex, as described herein, can be demonstrated, for example, by improvements in ferritin and transferrin saturation, and in raising hemoglobin levels in anemic patients. Iron stores can be assessed by interpreting serum

ferritin levels. TfS is frequently used, in addition, to diagnose absolute or functional iron deficiencies. In patients with iron deficiency, serum transferrin is elevated and will decrease following successful iron treatment.

[0033] Administration

[0034] Methods of treatment of various diseases, disorders, or conditions with iron complex compositions comprise the administration of the complex in single unit dosages of at least 0.6 grams of elemental iron to about at least 2.5 grams of elemental iron. Administration of single unit dosages can be, for example, over pre-determined time intervals or in response to the appearance and/or reappearance of symptoms. For example, the iron carbohydrate complex can be re-administered upon recurrence of at least one symptom of the disease or disorder. As another example, the iron carbohydrate complex can be re-administered at some time period after the initial administration (*e.g.*, after 4 days to 12 months).

[0035] Any route of delivery of the single unit dose of iron carbohydrate complex is acceptable so long as iron from the iron complex is released such that symptoms are treated. The single unit dose of iron carbohydrate complex can be administered parenterally, for example intravenously or intramuscularly. Intravenous administration can be delivered as a bolus or preferably as an infusion. For example, the single unit dose of iron carbohydrate complex can be intravenously infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, preferably about 215 ml of diluent or about 250 ml of diluent. The iron carbohydrate complex can be intravenously injected as a bolus. For example, the iron carbohydrate complex can be intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, preferably about 215 ml of diluent or about 250 ml of diluent. The iron carbohydrate complex can be intramuscularly infused at a concentration of, for example, about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, preferably, about 250 ml of diluent or about 215 ml of diluent. If applied as an infusion, the iron carbohydrate complex can be diluted with sterile saline (*e.g.*, polynuclear iron

(III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate ("VIT-45") 0.9% m/V NaCl or 500 mg iron in up to 250 mL NaCl). The iron carbohydrate complex can be intravenously injected as a bolus without dilution. As an example, the iron carbohydrate complex can be intramuscularly injected at a concentration of about 500 mg elemental iron in less than about 10 ml diluent, preferably about 5 ml.

[0036] Generally, total iron dosage will depend on the iron deficit of the patient. One skilled in the art can tailor the total iron dose required for a subject while avoiding iron overload, as overdosing with respect to the total required amount of iron has to be avoided, as is the case for all iron preparations.

[0037] The total iron dosage can be delivered as a single unit dosage or a series of single unit dosages. An appropriate single unit dosage level will generally be at least 0.6 grams of elemental iron, particularly at least 0.7 grams; at least 0.8 grams; at least 0.9 grams; at least 1.0 grams; at least 1.1 grams; at least 1.2 grams; at least 1.3 grams; at least 1.4 grams; at least 1.5 grams; at least 1.6 grams; at least 1.7 grams; at least 1.8 grams; at least 1.9 grams; at least 2.0 grams; at least 2.1 grams; at least 2.2 grams; at least 2.3 grams; at least 2.4 grams; or at least 2.5 grams. For example, a single unit dosage is at least 1.0 grams of elemental iron. As another example, a single unit dosage is at least 1.5 grams of elemental iron. As a further example, a single unit dosage is at least 2.0 grams of elemental iron. In yet another example, a single unit dosage is at least 2.5 grams of elemental iron.

[0038] An appropriate single unit dosage level can also be determined on the basis of patient weight. For example, an appropriate single unit dosage level will generally be at least 9 mg of elemental iron per kg body weight, particularly at least 10.5 mg/kg, at least 12 mg/kg, at least 13.5 mg/kg, at least 15 mg/kg, at least 16.5 mg/kg, at least 18 mg/kg, at least 19.5 mg/kg, at least 21 mg/kg, at least 22.5 mg/kg, at least 24 mg/kg, at least 25.5 mg/kg, at least 27 mg/kg, at least 28.5 mg/kg, at least 30 mg/kg, at least 31.5 mg/kg, at least 33 mg/kg, at least 34.5 mg/kg, at least 36 mg/kg, or at least 37.5 mg/kg.

[0039] Preferably, a single unit dosage can be administered in 15 minutes or less. For example, the single unit dosage can be administered in 14 minutes or less, 13 minutes or less, 12 minutes or less, 11 minutes or less, 10 minutes or less, 9 minutes or less, 8 minutes or less, 7 minutes or less, 6 minutes or less, 5 minutes or less, 4 minutes or less, 3 minutes or less, or 2 minutes or less.

[0040] Administration of iron can occur as a one-time delivery of a single unit dose or over a course of treatment involving delivery of multiple single unit doses. Multiple single unit doses can be administered, for example, over pre-determined time intervals or in response to the appearance and reappearance of symptoms. The frequency of dosing depends on the disease or disorder being treated, the response of each individual patient, and the administered amount of elemental iron. An appropriate regime of dosing adequate to allow the body to absorb the iron from the bloodstream can be, for example, a course of therapy once every day to once every eighteen months.

[0041] Such consecutive single unit dosing can be designed to deliver a relatively high total dosage of iron over a relatively low period of time. For example, a single unit dose (*e.g.*, 1000 mg) can be administered every 24 hours. As illustration, a total dose of 2000, 2500, 3000, 3500, 4000, 4500, or 5000 mg of elemental iron can be delivered via consecutive daily single unit doses of about 600 mg to about 1000 mg of elemental iron. Given that a single unit dose of 1000 mg can be intravenously introduced into a patient in a concentrated form over, for example, two minutes, such administrative protocol provides a practitioner and patient with an effective, efficient, and safe means to deliver elemental iron.

[0042] As another example, a single unit dose can be administered every 3-4 days. As a further example, a single unit dose can be administered once per week. Alternatively, the single unit doses of iron complex may be administered *ad hoc*, that is, as symptoms reappear, as long as safety precautions are regarded as practiced by medical professionals.

[0043] It will be understood, however, that the specific dose and frequency of administration for any particular patient may be varied and depends upon a variety of factors, including the activity of the employed iron complex, the metabolic stability and length of action of that complex, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity and nature of the particular condition, and the host undergoing therapy.

[0044] The following provides but a few examples of treatment protocols for various diseases or disorders.

[0045] Iron carbohydrate complex can be given as a single unit dose for the treatment of Restless Leg Syndrome. For example, 1000 mg of elemental iron from an iron carboxymaltose (*e.g.*, polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate) can be intravenously injected as a single dose (*e.g.*, 1.5-5 mg iron/ml in normal saline) to a subject suffering from Restless Leg Syndrome. A single intravenous treatment can provide relief of symptoms for an extended period of time, approximately two to twelve months, although relief may be granted for shorter or longer periods. *See* U.S. Patent Pub. No. 2004/0180849, incorporated herein by reference. If desired, post-infusion changes in central nervous system iron status can be monitored using measurements of cerebral spinal fluid (CSF) ferritin (and other iron-related proteins) and of brain iron stores using MRI. Post-infusion changes in Restless Leg Syndrome are assessed using standard subjective (*e.g.*, patient diary, rating scale) and objective (*e.g.*, P50, SIT, Leg Activity Meters) measures of clinical status. If desired, to better evaluate RLS symptom amelioration, CSF and serum iron values, MRI measures of brain iron and full clinical evaluations with sleep and immobilization tests are obtained prior to treatment, approximately two weeks after treatment, and again twelve months later or when symptoms return. Clinical ratings, Leg Activity Meter recordings and serum ferritin are obtained monthly after treatment. CSF ferritin changes can also be used to assess symptom dissipation.

[0046] Iron carbohydrate complex can be given as a single unit dose for the treatment of iron deficiency anemia secondary to heavy uterine bleeding. For example, a single unit dose of 1,000 mg of elemental iron from an iron carboxymaltose in about 250 cc normal saline can be intravenously injected into a subject suffering from iron deficiency anemia secondary to heavy uterine bleeding over 15 minutes every week until a calculated iron deficit dose has been administered. The iron deficit dose can be calculated as follows:

If baseline TSAT < 20% or Baseline Ferritin < 50 ng/ml: Dose = Baseline weight (kg) x (15-Baseline Hgb [g/dL]) x 2.4 + 500 mg

OR

If baseline TSAT >20% and Baseline Ferritin > 50 ng/mL: Dose = Baseline weight (kg) x (15-Baseline Hgb [g/dL]) x 2.4

(NOTE: Baseline Hgb equals the average of the last two central lab Hgb's)

[0047] Iron carbohydrate complex can be given as a single unit dose for the treatment of iron deficiency anemia. A subject diagnosed as suffering from iron deficiency anemia can be, for example, intravenously injected with a dose of 1,000 mg of iron as VIT- 45 (or 15 mg/kg for weight < 66 kg) in 250 cc of normal saline over 15 minutes. Subjects with iron deficiency anemia secondary to dialysis or non-dialysis dependent-Chronic Kidney Disease (CKD) as per K/DOQI guidelines will generally have Hgb < 12 g/dL; TSAT < 25%; and Ferritin < 300 ng/mL. Subjects with iron deficiency anemia secondary to Inflammatory Bowel Disease will generally have Hgb < 12 g/dL; TSAT < 25%; and Ferritin < 300 ng/mL. Subjects with iron deficiency anemia secondary to other conditions will generally have Hgb < 12 g/dL; TSAT < 25%; and Ferritin < 100 ng/mL.

[0048] Subject in need thereof

[0049] Single unit dosages of intravenous iron described herein can be administered to a subject where there is a clinical need to deliver iron rapidly or in higher doses and/or in subjects with functional iron deficiency such as those on erythropoietin therapy. A determination of the need for treatment with parenteral iron is within the abilities of one skilled in the art. For example, need

can be assessed by monitoring a patient's iron status. The diagnosis of iron deficiency can be based on appropriate laboratory tests, for example, haemoglobin (Hb), serum ferritin, serum iron, transferrin saturation (TfS), and hypochromic red cells.

[0050] A determination of the need for treatment with high dosages of parenteral iron can be also be determined through diagnosis of a patient as suffering from a disease, disorder, or condition that is associated with iron deficiency or dysfunctional iron metabolism. For example, many chronic renal failure patients receiving erythropoietin will require intravenous iron to maintain target iron levels. As another example, most hemodialysis patients will require repeated intravenous iron administration, due to dialysis-associated blood loss and resulting negative iron balance.

[0051] Monitoring frequency can depend upon the disease, disorder, or condition the patient is afflicted with or at risk for. For example, in a patient initiating erythropoietin therapy, iron indices are monitored monthly. As another example, in patients who have achieved target range Hb or are receiving intravenous iron therapy, TSAT and ferritin levels can be monitored every 3 months.

[0052] A patient's iron status can be indicative of an absolute or a functional iron deficiency, both of which can be treated with the compositions and methods described herein. An absolute iron deficiency occurs when an insufficient amount of iron is available to meet the body's requirements. The insufficiency may be due to inadequate iron intake, reduced bioavailability of dietary iron, increased utilization of iron, or chronic blood loss. Prolonged iron deficiency can lead to iron deficiency anemia—a microcytic, hypochromic anemia in which there are inadequate iron stores. Absolute iron deficiency is generally indicated where TSAT <20% and Ferritin <100 ng/mL.

[0053] Functional iron deficiency can occur where there is a failure to release iron rapidly enough to keep pace with the demands of the bone marrow for erythropoiesis, despite adequate total body iron stores. In these cases, ferritin levels may be normal or high, but the supply of iron to the erythron is

limited, as shown by a low transferrin saturation and an increased number of microcytic, hypochromic erythrocytes. Functional iron deficiency can be characterized by the following characteristics: Inadequate hemoglobin response to erythropoietin; Serum ferritin may be normal or high; Transferrin saturation (TSAT) usually <20%; and/or reduced mean corpuscular volume (MCV) or mean corpuscular hemoglobin concentration (MCHC) in severe cases. Functional iron deficiency (*i.e.*, iron stores are thought to be adequate but unavailable for iron delivery) is generally indicated where TSAT <20% and Ferritin >100 ng/mL.

[0054] Assessing the need for intravenous iron therapy as described herein can be according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative. *See* NKF-K/DOQI, Clinical Practice Guidelines for Anemia of Chronic Kidney Disease (2000); Am J Kidney Dis (2001) 37(supp 1), S182-S238. The DOQI provides optimal clinical practices for the treatment of anemia in chronic renal failure. The DOQI guidelines specify intravenous iron treatment of kidney disease based on hemoglobin, transferrin saturation (TSAT), and ferritin levels.

[0055] Assessment of need for intravenous iron therapy can also be according to a patient's target iron level. For example, the target hemoglobin level of a patient can be selected as 11.0 g/dL to 12.0 g/dL (hematocrit approximately 33% to 36%). To achieve target hemoglobin with optimum erythropoietin doses, sufficient iron, supplied via an iron carbohydrate complex, is provided to maintain TSAT ≥20% and ferritin ≥100 ng/mL. In erythropoietin-treated patients, if TSAT levels are below 20%, the likelihood that hemoglobin will rise or erythropoietin doses fall after iron administration is high. Achievement of target hemoglobin levels with optimum erythropoietin doses is associated with providing sufficient iron to maintain TSAT above 20%.

[0056] Iron therapy can be given to maintain target hemoglobin while preventing iron deficiency and also preventing iron overload. Adjusting dosage of iron to maintain target levels of hemoglobin, hematocrit, and laboratory parameters of iron storage is within the normal skill in the art. For example, where a patient is anemic or iron deficient, intravenous iron can be administered

when a patient has a ferritin <800, a TSAT<50, and/or a Hemoglobin <12. Iron overload can be avoided by withholding iron for TSAT >50% and/or ferritin >800 ng/mL.

[0057] Where a patient is not anemic or iron deficient but is in need of iron administration, for example a patient suffering from Restless Leg Syndrome, hemoglobin and TSAT levels are not necessarily relevant, while ferritin >800 can still provides a general cut off point for administration.

[0058] Iron Carbohydrate Complex

[0059] Iron carbohydrate complexes are commercially available, or have well known syntheses. Examples of iron carbohydrate complexes include iron monosaccharide complexes, iron disaccharide complexes, iron oligosaccharide complexes, and iron polysaccharide complexes, such as: iron carboxymaltose, iron sucrose, iron polyisomaltose (iron dextran), iron polymaltose (iron dextrin), iron gluconate, iron sorbitol, iron hydrogenated dextran, which may be further complexed with other compounds, such as sorbitol, citric acid and gluconic acid (for example iron dextrin-sorbitol-citric acid complex and iron sucrose-gluconic acid complex), and mixtures thereof.

[0060] Applicants have discovered that certain characteristics of iron carbohydrate complexes make them amenable to administration at dosages far higher than contemplated by current administration protocols. Preferably, iron carbohydrate complexes for use in the methods described herein are those which have one or more of the following characteristics: a nearly neutral pH (*e.g.*, about 5 to about 7); physiological osmolarity; stable carbohydrate component; an iron core size no greater than about 9 nm; mean diameter particle size no greater than about 35 nm, preferably about 25 nm to about 30 nm; slow and competitive delivery of the complexed iron to endogenous iron binding sites; serum half-life of over about 7 hours; low toxicity; non-immunogenic carbohydrate component; no cross reactivity with anti-dextran antibodies; and/or low risk of anaphylactoid / hypersensitivity reactions.

[0061] It is within the skill of the art to test various characteristics of iron carbohydrate complexes as so determine amenability to use in the methods

described herein. For example, pH and osmolarity are straightforward determinations performed on a sample formulation. Likewise, techniques such as electron micrograph imaging, transmission electron microscopy, and atomic force microscopy provide direct methods to analyze both iron core and particle size. *See e.g.*, Figure 1; Table 1. The stability of the carbohydrate complex can be assessed through physicochemical properties such as kinetic characteristics, thermodynamic characteristics, and degradation kinetics. *See* Geisser et al., Arzneimittelforschung (1992) 42(12), 1439-1452. Useful techniques to assess physical and electronic properties include absorption spectroscopy, X-ray diffraction analysis, transmission electron microscopy, atomic force microscopy, and elemental analysis. *See* Kudasheva et al. (2004) J Inorg Biochem 98, 1757-1769. Pharmacokinetics can be assessed, for example, by iron tracer experiments. Hypersensitivity reactions can be monitored and assessed as described in, for example, Bailie et al. (2005) Nephrol Dial Transplant, 20(7), 1443-1449. Safety, efficacy, and toxicity in human subjects can be assessed, for example, as described in Spinowitz et al. (2005) Kidney Intl 68, 1801-1807.

[0062] A particularly preferred iron carbohydrate complex will have a pH between 5.0-7.0; physiological osmolarity; an iron core size no greater than 9 nm; mean diameter particle size no greater than 30 nm; serum half-life of over 10 hours; a non-immunogenic carbohydrate component; and no cross reactivity with anti-dextran antibodies. One example of a preferred iron carbohydrate complex for use in the methods described herein is an iron carboxy-maltose complex (*e.g.*, polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate, “VIT-45”). Another example of a preferred iron carbohydrate complex for use in the methods described herein is a carboxyalkylated reduced polysaccharide iron oxide complex (*e.g.*, ferumoxytol, described in U.S. Patent No. 6,599,498).

[0063] Preferably, an iron carbohydrate complex, for use in methods disclosed herein, contains about 24% to about 32% elemental iron, more preferably about 28% elemental iron. Preferably, an iron carbohydrate complex, for use in methods disclosed herein, contains about 25% to about 50% carbohydrate (*e.g.*, total glucose). Preferably, an iron carbohydrate complex, for

use in methods disclosed herein, is about 90,000 daltons to about 800,000 daltons, more preferably 100,000 daltons to about 350,000 daltons.

[0064] Iron carboxymaltose complex

[0065] One preferred iron carbohydrate complex for use in the methods described herein is an iron carboxymaltose complex. An example of an iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate ("VIT-45"). VIT-45 is a Type I polynuclear iron (III) hydroxide carbohydrate complex that can be administered as parenteral iron replacement therapy for the treatment of various anemia-related conditions as well as other iron-metabolism related conditions. VIT-45 can be represented by the chemical formula: [FeOx(OH)y(H2O)z]n [{(C6H10O5)m (C6H12O7)}l]k, where n is about 103, m is about 8, l is about 11, and k is about 4). The molecular weight of VIT-45 is about 150,000 Da. An exemplary depiction of VIT-45 is provided in Figure 2.

[0066] The degradation rate and physicochemical characteristics of the iron carbohydrate complex (*e.g.*, VIT-45) make it an efficient means of parenteral iron delivery to the body stores. It is more efficient and less toxic than the lower molecular weight complexes such as iron sorbitol/citrate complex, and does not have the same limitations of high pH and osmolarity that leads to dosage and administration rate limitations in the case of, for example, iron sucrose and iron gluconate.

[0067] The iron carboxymaltose complex (*e.g.*, VIT-45) generally does not contain dextran and does not react with dextran antibodies; therefore, the risk of anaphylactoid /hypersensitivity reactions is very low compared to iron dextran. The iron carboxymaltose complex (*e.g.*, VIT-45) has a nearly neutral pH (5.0 to 7.0) and physiological osmolarity, which makes it possible to administer higher single unit doses over shorter time periods than other iron-carbohydrate complexes. The iron carboxymaltose complex (*e.g.*, VIT-45) can mimic physiologically occurring ferritin. The carbohydrate moiety of iron carboxymaltose complex (*e.g.*, VIT-45) is metabolized by the glycolytic pathway. Like iron dextran, the iron carboxymaltose complex (*e.g.*, VIT-45) is more stable

than iron gluconate and sucrose. The iron carboxymaltose complex (*e.g.*, VIT-45) produces a slow and competitive delivery of the complexed iron to endogenous iron binding sites resulting in an acute toxicity one-fifth that of iron sucrose. These characteristics of the iron carboxymaltose complex (*e.g.*, VIT-45) allow administration of higher single unit doses over shorter periods of time than, for example, iron gluconate or iron sucrose. Higher single unit doses can result in the need for fewer injections to replete iron stores, and consequently is often better suited for outpatient use.

[0068] After intravenous administration, the iron carboxymaltose complex (*e.g.*, VIT-45) is mainly found in the liver, spleen, and bone marrow. Pharmacokinetic studies using positron emission tomography have demonstrated a fast initial elimination of radioactively labeled iron (Fe) $^{52}Fe/^{59}Fe$ VIT-45 from the blood, with rapid transfer to the bone marrow and rapid deposition in the liver and spleen. *See e.g.*, Beshara et al. (2003) Br J Haematol 2003; 120(5): 853-859. Eight hours after administration, 5 to 20% of the injected amount was observed to be still in the blood, compared with 2 to 13% for iron sucrose. The projected calculated terminal half-life ($t_{½}$) was approximately 16 hours, compared to 3 to 4 days for iron dextran and 6 hours for iron sucrose.

[0069] The iron in the iron carboxymaltose complex (*e.g.*, VIT-45) slowly dissociates from the complex and can be efficiently used in the bone marrow for Hgb synthesis. Under VIT-45 administration, red cell utilization, followed for 4 weeks, ranged from 61% to 99%. Despite the relatively higher uptake by the bone marrow, there was no saturation of marrow transport systems. Thus, high red cell utilization of iron carboxymaltose complex occurs in anemic patients. In addition, the reticuloendothelial uptake of this complex reflects the safety of polysaccharide complexes. Non-saturation of transport systems to the bone marrow indicated the presence of a large interstitial transport pool (*e.g.*, transferrin).

[0070] Other studies in patients with iron deficiency anemia revealed increases in exposure roughly proportional with VIT-45 dose (maximal total serum iron concentration was approximately 150 µg/mL and 320 µg/mL following

500 mg and 1000 mg doses, respectively). In these studies, VIT-45 demonstrated a monoexponential elimination pattern with a $t_{1/2}$ in the range 7 to 18 hours, with negligible renal elimination.

[0071] Single-dose toxicity studies have demonstrated safety and tolerance in rodents and dogs of intravenous doses of an iron carboxymaltose complex (VIT-45) up to 60 times more than the equivalent of an intravenous infusion of 1,000 mg iron once weekly in humans. Pre-clinical studies in dogs and rats administered VIT-45 in cumulative doses up to 117 mg iron/kg body weight over 13 weeks showed no observed adverse effect level in dose-related clinical signs of iron accumulation in the liver, spleen, and kidneys. No treatment-related local tissue irritation was observed in intra-arterial, perivenous, or intravenous tolerance studies in the rabbit. In vitro and in vivo mutagenicity tests provided no evidence that VIT-45 is clastogenic, mutagenic, or causes chromosomal damage or bone marrow cell toxicity. There were no specific responses to VIT-45 in a dextran antigenicity test.

[0072] Approximately 1700 subjects have been treated with an iron carboxymaltose complex (VIT-45) in open label clinical trials (*see e.g.*, Example 5). Many of these subjects have received at least one dose of 15mg/kg (up to a maximum dose of 1,000 mg) of VIT-45 over 15 minutes intravenously. Few adverse events and no serious adverse events or withdrawals due to adverse events related to VIT-45 administration have been reported. No clinically relevant adverse changes in safety laboratories have been seen.

[0073] The physicochemical characteristics of the iron carboxymaltose complex (*e.g.*, VIT-45), the pattern of iron deposition, and the results of the above described studies demonstrate that iron carboxymaltose complex can be safely administered at high single unit therapeutic doses as described herein.

[0074] Polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite

[0075] Another preferred iron carbohydrate complex for use in the methods described herein is a polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite (*e.g.*, “ferumoxytol”). Ferumoxytol is known in the

art to be effective for treating anemia (at single unit doses lower than described herein). *See e.g.*, Spinowitz et al. (2005) Kidney Intl 68, 1801-1807. Ferumoxytol is a superparamagnetic iron oxide that is coated with a low molecular weight semi-synthetic carbohydrate, polyglucose sorbitol carboxymethyl ether. Ferumoxytol and its synthesis are described in U.S. Patent No. 6,599,498, incorporated herein by reference. Safety, efficacy, and pharmacokinetics of ferumoxytol are as described, for example, in Landry et al. (2005) Am J Nephrol 25, 400-410, 408; and Spinowitz et al. (2005) Kidney Intl 68, 1801-1807.

[0076] The iron oxide of ferumoxytol is a superparamagnetic form of non-stoichiometric magnetite with a crystal size of 6.2 to 7.3 nm. Average colloidal particle size can be about 30 nm, as determined by light scattering. Molecular weight is approximately 750 kD. The osmolarity of ferumoxytol is isotonic at 297 mOsm/kg and the pH is neutral. The blood half-life of ferumoxytol is approximately 10-14 hours. It has been previously reported that ferumoxytol can be given by direct intravenous push over 1-5 minutes in doses up to 1,800 mg elemental iron per minute, with maximal total dose up to 420 mg per injection. Landry et al. (2005) Am J Nephrol 25, 400-410, 408.

[0077] Core and Particle Size

[0078] Intravenous iron agents are generally spheroidal iron-carbohydrate nanoparticles. At the core of each particle is an iron-oxyhydroxide gel. The core is surrounded by a shell of carbohydrate that stabilizes the iron-oxyhydroxide, slows the release of bioactive iron, and maintains the resulting particles in colloidal suspension. Iron agents generally share the same core chemistry but differ from each other by the size of the core and the identity and the density of the surrounding carbohydrate. *See* Table 1; Figure 1.

Table 1: Core and Particle Size of Iron Carbohydrate Complexes

Iron (III) Control	Size of the Particle (nm) +/- SEM

Release Test

	T_{75} (min)	Iron core	Total Particle
Dexferrum (an iron dextran)	122.5	11.8 ± 4	27 ± 6
VIT -45 (an iron carboxymaltose)	117.8	4.4 ±1.4	6.7 ± 2.5
Venofer (an iron sucrose)	10.2	2.8 ± 1	6.5 ± 4

[0079] Differences in core size and carbohydrate chemistry can determine pharmacological and biological differences, including clearance rate after injection, iron release rate in vitro, early evidence of iron bioactivity in vivo, and maximum tolerated dose and rate of infusion.

[0080] One of the primary determinants of iron bioactivity is the size of the core and the surface area to volume ratio. Generally, the rate of labile iron release in each agent is inversely related to the size of its iron core. Van Wyck (2004) J. Am. Soc. Nephrology 15, S107-S111, S109. Furthermore, in vitro iron donation to transferrin is inversely related to core size. Core size can depend upon the number of iron atoms contained within. For example, the number of iron atoms contained within a 1 nm core is calculated to be 13, while a 10 nm core is calculated to contain 12770 iron atoms. Where agents share the same core chemistry, the rate of iron release per unit surface area is likely similar, differing perhaps by the strength of the carbohydrate ligand-core iron bound. But for the same total amount of core iron, surface area available for iron release increases dramatically as core radius decreases. That is to say, for equal amounts of iron, the smaller the core, the greater the surface area available for iron release. Of course, the explanation for this non-linear trend is the fact that volume is radius cubed. In short, a collection of many small spheres exposes a greater total surface area than does a collection of an equal mass of fewer, larger spheres.

[0081] A smaller iron core size of an iron complex administered for the treatment of various diseases, disorders, or conditions allows wider distribution through tissues, a greater rate of labile iron release, and increased in vitro iron donation to transferrin. Furthermore, the iron complex is more evenly distributed and metabolizes faster due to the smaller core size. But if the core size is too small, the iron complex can move into cells unable to metabolize iron. In one embodiment, an iron complex with a mean iron core size of no greater than about 9 nm is administered. In various embodiments, mean iron core size is less than about 9 nm but greater than about 1 nm, about 2 nm, about 3 nm, about 4 nm, about 5 nm, about 6 nm, about 7 nm, or about 8 nm. Mean iron core size can be, for example, between about 1 nm and about 9 nm; between about 3 nm and about 7 nm; or between about 4 nm and about 5 nm.

[0082] The molecular weight (*i.e.*, the whole molecular weight of the agent) is considered a primary determinant in the pharmacokinetics, or in other words, how quickly it is cleared from the blood stream. The amount of labile (*i.e.*, biologicaly available) iron is inversely correlated with the molecular weight of the iron-carbohydrate complex. Van Wyck (2004) J. Am. Soc. Nephrology 15, S107-S111, S109. That is to say, the magnitude of labile iron effect is greatest in iron-carbohydrate compounds of lowest molecular weight and least in those of the highest molecular weight. Generally, there is a direct relationship between the molecular weight of the agent and the mean diameter of the entire particle (*i.e.*, the iron core along with the carbohydrate shell). In various embodiments, the mean diameter size of a particle of the iron carbohydrate complex is no greater than about 35 nm. For example, the particle mean size can be no greater than about 30 nm. As another example, the particle mean size can be no greater than about 25 nm. As another example, the particle mean size can be no greater than about 20 nm. As another example, the particle mean size can be no greater than about 15 nm. As a further example, the particle mean size can be no greater than about 10 nm. As another example, the particle mean size can be no greater than about 7 nm.

[0083] Absence of Significant Adverse Reaction to the Single Dosage Unit Administration

[0084] Generally, a safe and effective amount of an iron carbohydrate complex is, for example, that amount that would cause the desired therapeutic effect in a patient while minimizing undesired side effects. The dosage regimen will be determined by skilled clinicians, based on factors such as the exact nature of the condition being treated, the severity of the condition, the age and general physical condition of the patient, and so on. Generally, treatment-emergent adverse events will occur in less than about 5% of treated patients. For example, treatment-emergent adverse events will occur in less than 4% or 3% of treated patients. Preferably, treatment-emergent adverse events will occur in less than about 2% of treated patients.

[0085] For example, minimized undesirable side effects can include those related to hypersensitivity reactions, sometimes classified as sudden onset closely related to the time of dosing, including hypotension, bronchospasm, layngospasm, 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

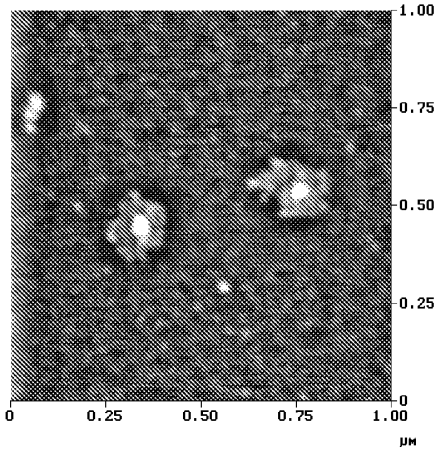


FIG. 1B

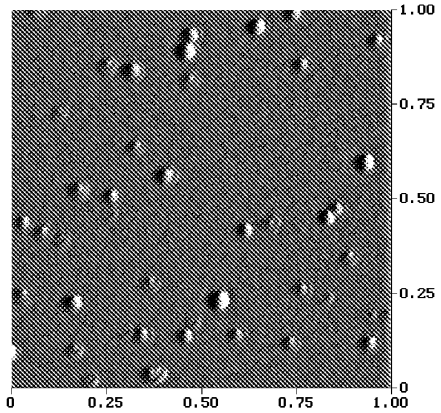


FIG. 1A

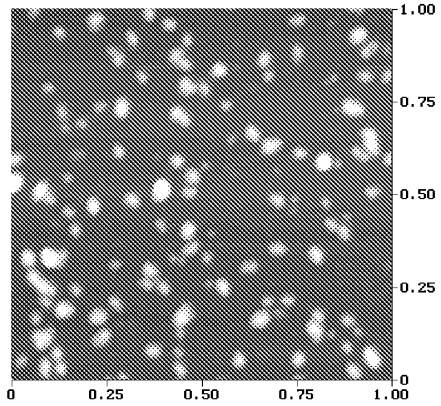
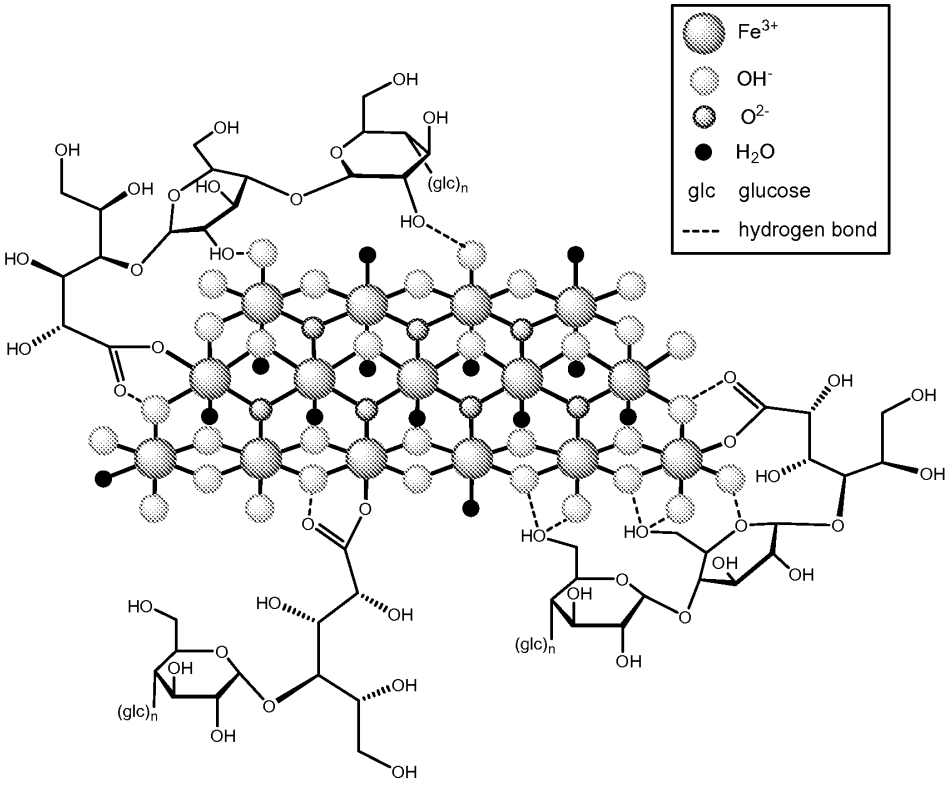


FIGURE 2



Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON
First Named Inventor/Applicant Name:	Mary J Helenek
Filer:	George H. Blosser/Dennis Harney
Attorney Docket Number:	30015730-0053
Filed as Small Entity	

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Utility Search Fee	2111	1	270	270
Utility Examination Fee	2311	1	110	110
Pages:				
Claims:				
Miscellaneous-Filing:				
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
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		Total in USD ($)		**462**

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1	Application Data Sheet	ADS_30015730-0053_May25_2010.pdf	1147466 1281215f38253e0787d13daec70a35a74c2f0193	no	5
Warnings:					
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2		CONT_30015730-0053_May25_2010.pdf	1036618 c8b1ec428dbaa0696fa79c92cf1fb966f0547069	yes	48

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Document Description	Start	End
Specification	1	41
Claims	42	45
Abstract	46	46
Drawings-other than black and white line drawings	47	48

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3	Fee Worksheet (PTO-875)	fee-info.pdf	32998 8b368cbd711836c922f3c3b2f4ba983dba69b86f	no	2
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PTO/SB/06 (12-04)

Approved for use through 7/31/2006. OMB 0651-0032

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/787,283

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	82		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	110		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =		x$26		OR	x$52	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x$110			x$220	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195			390	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	462		TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

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