US008431549B2

(12) **United States Patent**
Helenek et al.

(10) **Patent No.: US 8,431,549 B2**
(45) **Date of Patent: *Apr. 30, 2013**

(54) **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**

(75) Inventors: **Mary Jane Helenek**, Brookville, NY (US); **Marc L. Tokars**, Douglassville, PA (US); **Richard P. Lawrence**, Calverton, NY (US)

(73) Assignee: **Luitpold Pharmaceuticals, Inc.**, Shirley, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 47 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/787,283**

(22) Filed: **May 25, 2010**

(65) **Prior Publication Data**

US 2010/0266644 A1 Oct. 21, 2010

Related U.S. Application Data

(63) Continuation of application No. 11/620,986, filed on Jan. 8, 2007, now Pat. No. 7,754, 702.

(60) Provisional application No. 60/757,119, filed on Jan. 6, 2006.

(51) **Int. Cl.**
A61K 31/721 (2006.01)
A61K 31/718 (2006.01)
A61K 31/295 (2006.01)

(52) **U.S. Cl.**
USPC **514/58**; 514/54; 514/502; 536/113

(58) **Field of Classification Search** 514/54, 514/58, 502
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,100,202	A *	8/1963	Muller et al.	536/113
5,624,668	A	4/1997	Lawrence et al.	
6,599,498	B1	7/2003	Groman et al.	
6,960,571	B2	11/2005	Helenek et al.	
7,612,109	B2	11/2009	Geisser et al.	
2004/0180849	A1	9/2004	Helenek et al.	

FOREIGN PATENT DOCUMENTS

WO	9711711	4/1997
WO	2004037865	5/2004
WO	2007023154	3/2007

OTHER PUBLICATIONS

Hamstra et al. JAMA, 1980, 243(17), p. 1726-1731.*
Australian Office Action dated Sep. 15, 2011 in related Application No. AU2007205167 filed Jan. 8, 2007, 3 pages.
Chinese Office Action dated Apr. 30, 2010 in related Application No. CN200780002006 filed Jan. 8, 2007, English translation, 7 pages.
European Official Communication dated Oct. 5, 2011 in related Application No. EP077163093.5 filed Jan. 8, 2007, 6 pages.
International Search Report and Written Opinion dated Sep. 12, 2007 in related PCT Application No. PCT/US07/00176 filed Jan. 8, 2007, 6 pages.
Andersson, "Clinical investigations on a new intramuscular haematinic", British Medical Journal, 1961, 275-279.
Bailie et al., "Hypersensitivity reactions and deaths associated with intravenous iron preparations", Nephrol Dial Transplant, 2005, 20:1443-1449.
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.
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.
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.
European Search Report issued Oct. 21, 2009, in the related application EP 07716309.5.
Fielding, "Intravenous iron-dextrin in iron-deficiency anaemia", British Medical Journal, 1961, 279-283.
Fishbane, "Safety in iron management", Am J Kidney Dis, 2003, 41(6 Suppl 5):S18-S26.
Geisser et al., "Structure/histotoxicity relationship of parenteral iron preparations", Drug Research, 1992, 42 (12):1439-1452.
Haines et al., "Delayed adverse reactions to total-dose intravenous iron polymaltose", Internal Medicine Journal, 2009, 39:252-255.
Kudasheva et al., "Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanoparticles in parenteral formulations", Journal of Inorganic Biochemistry, 2004, 98:1757-1769.
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.
MacDougall, "Intravenous administration of iron in epoetin-treated haemodialysis patients—which drugs, which regimen?", Nephrol Dial Transplant, 2000, 15:1743-1745.
Newnham et al., "Safety of iron polymaltose given as a total dose iron infusion", Internal Medicine Journal, 2006, 36 (10):672-674.
Nissenson et al., "Controversies in iron management", Kidney International, 2003, 64(Supplement 87):S64-S71.
Sipe et al., "Brain iron metabolism and neurodegenerative disorders", Dev Neurosci, 2002, 24(2-3):188-196.
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.
Spinowitz et al., "The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients", Kidney International, 2005, 68:1801-1807.

(Continued)

Primary Examiner — Shaojia Anna Jiang
Assistant Examiner — Jonathan S Lau
(74) *Attorney, Agent, or Firm* — SNR Denton US LLP

(57) **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.

23 Claims, 2 Drawing Sheets

OTHER PUBLICATIONS

Van Wyck et al., "Making sense: a scientific approach to intravenous iron therapy", J Am Soc Nephrol, 2004, 15 (Suppl 2):S91-S92.
Van Wyck, "Labile iron: manifestations and clinical implications", J Am Soc Nephrol, 2004, 15(Suppl 2):S107-S111.
European Official Communication dated Jun. 4, 2012 in related Application No. EP 07716309.5 filed Jan. 8, 2007, 5 pages.
European Official Communication dated Jun. 4, 2012 in related Application No. EP 07716309.5 filed Jan. 8, 2007, 4 pages.

* cited by examiner

FIGURE 1

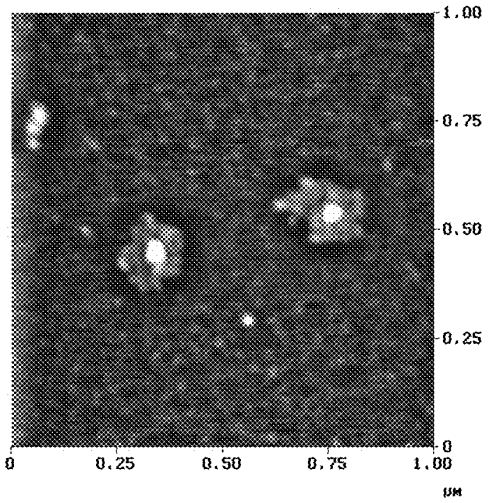


FIG. 1A

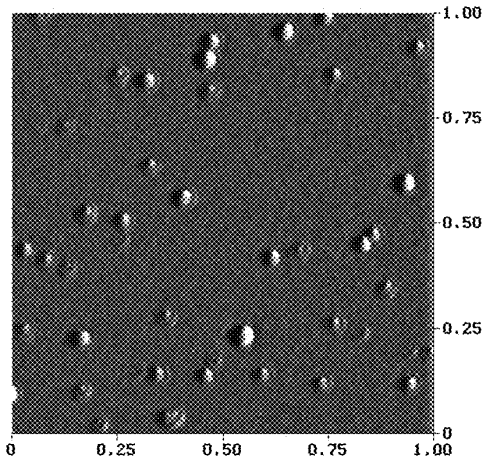


FIG. 1B

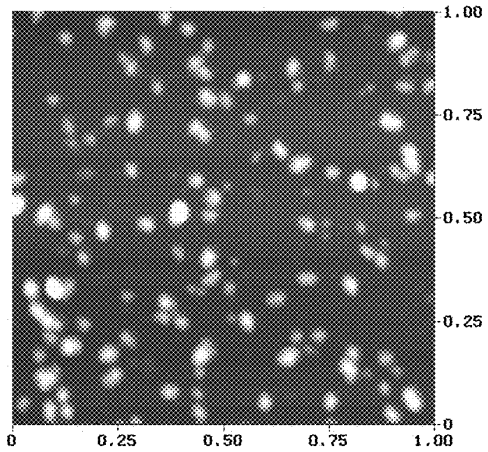
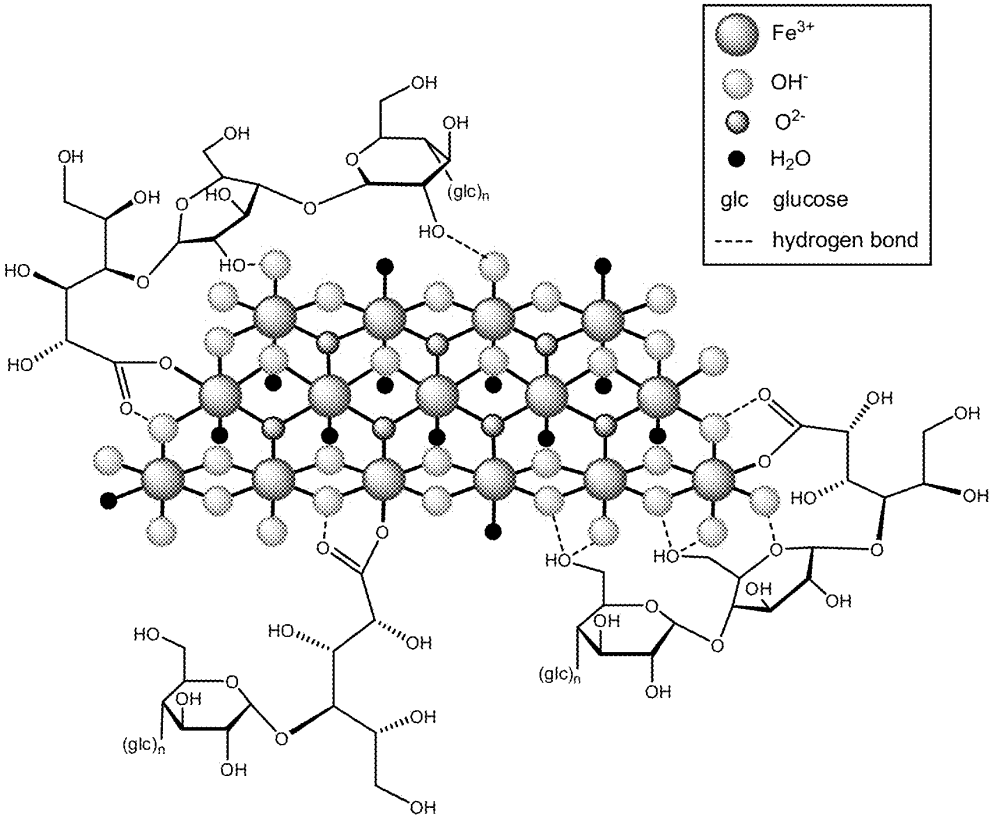


FIG. 1C

FIGURE 2



METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation Application that claims priority to U.S. Non-Provisional application Ser. No. 11/620,986, filed on Jan. 8, 2007, which in turn claims priority from U.S. Provisional Application Ser. No. 60/757,119, filed on Jan. 6, 2006, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention generally relates to treatment of iron-related conditions with iron carbohydrate complexes.

BACKGROUND

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.

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.

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.

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. Pat. No. 6,599,498.

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

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.

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.

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.

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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.