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**Helenek et al.**

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

7,871,597 B2 1/2011 Groman et al.  
2003/0232084 A1 12/2003 Groman et al.  
2004/0180849 A1\* 9/2004 Helenek et al. .... 514/53

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FOREIGN PATENT DOCUMENTS

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CA 2493806 5/2004  
KR 10-2005-0070014 7/2005  
WO WO 97/11711 4/1997  
WO WO 2004037865 A1\* 5/2004 ..... C08B 31/18  
WO WO 2007/023154 3/2007

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OTHER PUBLICATIONS

(\* ) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
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This patent is subject to a terminal dis-  
claimer.

Hamstra et al., JAMA, 1980, 243(17), p. 1726-1731.\*  
Kabat et al., Journal of Immunology, 1953, 70, p. 514-532.\*  
Andersson, Clinical investigations on a new intramuscular  
haematinic, British Medical Journal, 1961, pp. 275-279, vol. 2.  
Australian Office Action dated Sep. 15, 2011 in related Australian  
Application No. AU2007205167 filed Jan. 8, 2007, 3 pages.  
Bailie et al., Hypersensitivity reactions and deaths associated with  
intravenous iron preparations, Nephrol Dial Transplant, 2005, pp.  
1443-1449, vol. 20.  
Beshara et al., Pharmacokinetics and red cell utilization of <sup>52</sup>Fe/<sup>59</sup>Fe-  
labelled iron polymaltose in anaemic patients using positron emis-  
sion tomography, Br J of Haematol, 2003, pp. 853-859, vol. 120.  
Canadian Office Action dated Jan. 4, 2013 in related Canadian Appli-  
cation No. CA 2,635,894 filed Jan. 8, 2007, 4 pages.  
Canadian Office Action dated Oct. 17, 2013 in related Canadian  
Application No. CA 2,635,894 filed Jan. 8, 2007, 4 pages.  
Chinese Office Action dated Apr. 30, 2010 in related Chinese Appli-  
cation No. CN 200780002006 filed Jan. 8, 2007, English translation,  
7 pages.  
Cisar et al., Binding Properties of Immunoglobulin Combining Sites  
Specific for Terminal or Nonterminal Antigenic Determinants in  
Dextran, J Exp. Med, 1975, pp. 435-459, vol. 142.  
Eschbach et al., NKF-K/DOQI clinical practice guidelines for ane-  
mia of chronic kidney disease: update 2000, Am J Kidney Dis, 2001,  
pp. S182-S238, vol. 37 (Supp 1).

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No. 12/787,283, filed on May 25, 2010, now Pat. No.  
8,431,549, which is a continuation of application No.  
11/620,986, filed on Jan. 8, 2007, now Pat. No.  
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6, 2006.

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USPC ..... **514/502**; 514/53; 514/54; 514/58;  
514/59

(58) **Field of Classification Search**  
USPC ..... 514/53, 54, 58, 59, 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. .... 424/78.17  
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. .... 514/502

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(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 intrave-  
nously to patients in need thereof.

**20 Claims, 2 Drawing Sheets**

(56)

**References Cited**

## OTHER PUBLICATIONS

European Supplementary Search Report issued Oct. 21, 2009 in related European Application No. EP 07716309.5, 9 pages.

European Official Communication dated May 10, 2011 in related European Application No. EP 07716309.5 filed Jan. 8, 2007, 6 pages.

European Official Communication dated Jun. 4, 2012 in related European Application No. EP 07716309.5 filed Jan. 8, 2007, 5 pages.

European Office Action dated Jul. 5, 2013 in related European Application No. EP 07716309.5 filed on Jan. 8, 2007, 5 pages.

European Search Report dated Jul. 8, 2013 in related European Application No. EP 13166988.9 filed May 8, 2013, 8 pages.

Fielding, Intravenous iron-dextrin in iron-deficiency anaemia, *British Medical Journal*, 1961, pp. 279-283, vol. 2.

Fishbane, Safety in iron management, *Am J Kidney Dis*, 2003, S18-S26, vol. 41, No. 6 (Suppl 5).

Geisser et al., Structure/histotoxicity relationship of parenteral iron preparations, *Drug Research*, 1992, pp. 1439-1452, vol. 42, No. 12.

Haines et al., Delayed adverse reactions to total-dose intravenous iron polymaltose, *Internal Medicine Journal*, 2009, pp. 252-255, vol. 39.

International Search Report and Written Opinion dated Sep. 12, 2007 in related PCT Application No. PCT/US07/00176 filed Jan. 8, 2007, 6 pages.

Korean Office Action (in Korean and English) dated May 28, 2013 in related Application No. 10-2008-701-6352 filed Jul. 4, 2008, 13 pages.

Kudasheva et al., Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanoparticles in parenteral formulations, *Journal of Inorganic Biochemistry*, 2004, pp. 1757-1769, vol. 98.

Landry et al., Pharmacokinetic Study of Ferumoxytol: A New Iron Replacement Therapy in Normal Subjects and Hemodialysis Patients, *Am J Nephrol*, 2005, pp. 400-410, vol. 25.

MacDougall, Intravenous administration of iron in epoetin-treated haemodialysis patients—which drugs, which regimen?, *Nephrol Dial Transplant*, 2000, pp. 1743-1745, vol. 15.

Marchasin et al., The Treatment of Iron-Deficiency Anemia with Intravenous Iron Dextran, *Blood*, 1964, pp. 354-358, vol. 23, No. 3.

Newnham et al., Safety of iron polymaltose given as a total dose iron infusion, *Internal Medicine Journal*, 2006, pp. 672-674, vol. 36, No. 10.

Nissenson et al., Controversies in iron management, *Kidney International*, 2003, pp. S64-S71, vol. 64 (Supp 87).

Sipe et al., Brain iron metabolism and neurodegenerative disorders, *Dev Neurosci*, 2002, pp. 188-196, vol. 24, No. 2-3.

Sofic et al., Increased iron (III) and total iron content in post mortem substantia nigra of parkinsonian brain, *J. Neural Transm*, 1988, pp. 199-205, vol. 74.

Spinowitz et al., The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients, *Kidney International*, 2005, pp. 1801-1807, vol. 68.

Van Wyck et al., Making sense: a scientific approach to intravenous iron therapy, *J Am Soc Nephrol*, 2004, pp. S91-S92, vol. 15 (Supp.2).

Van Wyck, Labile iron: manifestations and clinical implications, *J Am Soc Nephrol*, 2004, pp. S107-S111, vol. 15 (Supp. 2).

\* cited by examiner

FIGURE 1

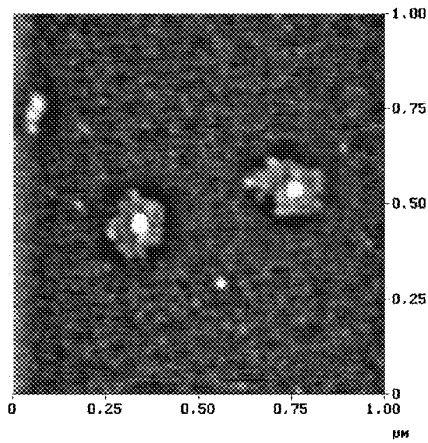


FIG. 1B

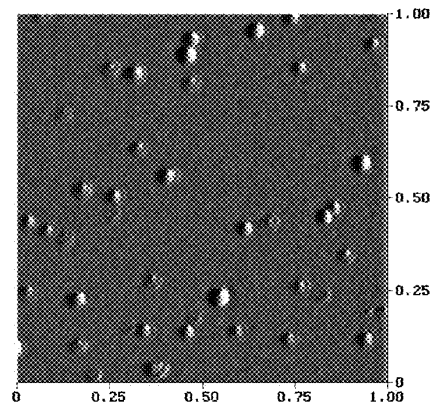


FIG. 1A

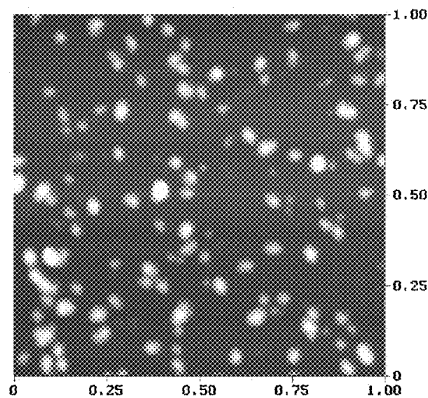
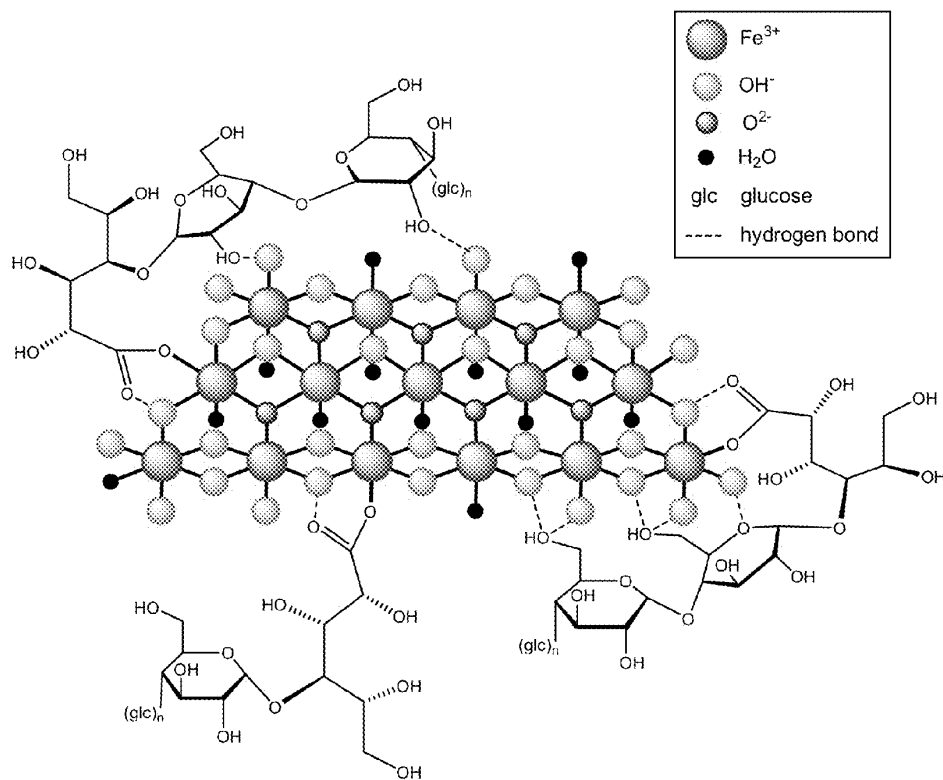


FIG. 1C

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. 13/847,254, filed 19 Mar. 2013; U.S. Non-Provisional application Ser. No. 12/787,283, filed 25 May 2010, issued as U.S. Pat. No. 8,431,549 on 30 Apr. 2013; and U.S. Non-Provisional application Ser. No. 11/620,986, filed 8 Jan. 2007, issued as U.S. Pat. No. 7,754,702 on 13 Jul. 2010, both of which claim priority to U.S. Provisional Application Ser. No. 60/757,119, filed 6 Jan. 2006, each of which is incorporated herein by reference in their entireties.

### 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, Dexferum), 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(5 Suppl), 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(5 Suppl), 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-steroidal 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; Sjogren'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

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