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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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TITLE OF INVENTION (500 characters max)

Methods and Compositions for Administration of Iron

ENCLOSED APPLICATION PARTS

☒ Specification [Total Pages 32]
☐ CD(s), Number of CDs [Total _____]
☒ Drawing(s) [Total Sheets 1]
☒ Other: Return Postcard
☒ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES

☐ Applicant claims small entity status. See CFR 1.27.

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Dated: January 6, 2006

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METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

FIELD OF THE INVENTION

[0001] The present invention generally relates to treatment of iron-related conditions with iron carbohydrate complexes.

BACKGROUND

[0002] 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.

[0003] 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.

[0004] 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.

[0005] 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.

[0006] 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

[0007] 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.

[0008] 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.

[0009] Other objects and features will be in part apparent and in part pointed out hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] 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.

[0011] 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 (Iron Dextran). FIG 1B is an electron micrograph depicting the particle size of Venofer (Iron Sucrose). FIG 1C is an electron micrograph depicting the particle size of Vit -45 (Iron Carboxymaltose).

DETAILED DESCRIPTION OF THE INVENTION

[0012] 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.

[0013] 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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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

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