(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 December 2010 (16.12.2010)

PCT

(10) International Publication Number
WO 2010/143006 A1

(51) International Patent Classification:
A61K 31/4412 (2006.01) *A61K 31/4196* (2006.01)
A61K 31/7012 (2006.01) *A61K 31/15* (2006.01)
A61K 31/427 (2006.01) *A61P 39/04* (2006.01)
A61K 31/426 (2006.01)

(21) International Application Number:
PCT/IB2009/005902

(22) International Filing Date:
10 June 2009 (10.06.2009)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2010/143006 A1

(54) Title: ORALLY BIOAVAILABLE IRON CHELATORS IN THE TREATMENT OF AN INFLAMMATORY BOWEL DISEASE

(57) Abstract: Use of orally bioavailable iron chelators for the manufacturing of a pharmaceutical composition for the treatment of an inflammatory bowel disease. Useful such chelators include deferiprone and deferasirox.

ORALLY BIOAVAILABLE IRON CHELATORS IN THE TREATMENT OF AN INFLAMMATORY BOWEL DISEASE

FIELD OF THE INVENTION

The present invention refers to the use of orally bioavailable iron chelators (OBIC) for the manufacturing of a pharmaceutical composition to treat a subject affected by an inflammatory bowel disease (IBD).

BACKGROUND OF THE INVENTION

Patients with IBD are at risk of development of micronutrient deficiencies including folate, vitamin D and iron deficiencies, hence require a close nutritional monitoring. Anemia is in fact a common in IBD patients, a problem of multifactorial origin that includes blood loss, iron malabsorption, and the so-called anemia of inflammation.

However, iron supplementation reinforces the intestinal inflammation by enhancing the ROS production. The effects of oral ferrous fumarate compared to intravenous iron sucrose on the clinical state of the IBD patients has been investigated, *inter alia*, by Kari et all. (Scandin J Gastroent. 2005, 40(9):1058-65).

An oxidative stress status and a consequent inflammatory cascade is prompted by iron from the heme extravasation within the mucosa and in gut lumen and, additionally, by the increased mucosal permeability to iron (Liu-Brohy et al. Dig Dis Sci. 1996; 41:2078-86). The role of iron in IBD is supported by the beneficial effects of desferoxamine in colitis (Millar et al., Aliment Pharmacol Ther 2000; 14: 1163-8) in *in vitro ex-vivo* assays, as well as by several other models of ulcerative colitis.

The pathogenetic features, epidemiology, diagnosis and therapy of anemia in IBD have been review by Giannini & Martes (Minerva Gastroenterol Dietol. 2006; 52(3):275-91) showed that anemia is also fuelled by inflammatory cytokines, predominantly IL-6, intervening on iron transport in enterocytes and macrophages.

Arnold et al. (Eur J Gastroenterol Hepatol. 2009; 21(4):425-9) have recently confirmed a low level of hepcidin and high level of IL-6 levels in the IBD patients, either with or without an iron-deficiency anaemia status. The low level of hepcidin and its inverse correlation with IL-6 may therefore reflect a causal or perpetuator effect on intestinal inflammation.

This recent study is confirmative of a previous work of Semrin et al. by the title "Impaired intestinal iron absorption in Crohn's disease correlates with disease activity and markers of inflammation" (Inflam Bowel Dis. 2006; 12(12):1101-6).

In the co-pending applications PCT/IB09/005631-56317, and PCT/IB09/005776, a variety of non- or low bioavailable iron chelators have been proposed to treat IBD. Their apparent utility resides in the low interference of the claimed chelators with the iron status of both anemic and anemic-prone IBD subjects.

However, iron chelating drugs with known pharmacology to be readily formulated and adapted to the treatment of non-malignant intestinal disorders could provide an evident advantage for the gastroenterological medical community and their patients.

SUMMARY OF THE INVENTION

It has now surprisingly been found that the inflammatory action by accumulated iron and its effect on the immune-stimulating microflora on intestinal mucosa can be substantially and safely inhibited by orally bioavailable iron chelators (OBIC). The manifestations associated with such inhibition include Crohn's disease, ulcerative colitis, collagenous lymphocytic, ischaemic, indeterminate, and diversion colitis, Behçet's syndrome, proctitis, and proctosigmoiditis.

An aspect of the invention is thus the use of an OBIC for the preparation of a pharmaceutically composition for the treatment of IBD, in particular for the inhibition of the inflammatory iron storage and the pathogenic microflora within the intestinal mucosa.

A further aspect of the invention is the use of an OBIC, preferably in low doses, for the prevention, delay of progression or treatment of patients with IBD.

A further aspect of the invention is the use of an OBIC for the treatment or prevention of a intestinal pathology related to a dysfunction, in particular a reduction or inhibition of accumulated iron in the intestinal tract.

A further aspect of the invention is a method to treat IBD by attenuating the inflammatory-immune response by accumulated iron, and/or the iron dependent iperproliferative microflora within the intestinal tract, whereby a therapeutically effective amount of an OBIC is administered to the subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

Useful active ingredients are bidentate and tridentate orally bioavailable iron chelators (OBIC), preferably those listed herewith after.

Suitable bidentate OBIC include l,2-dimethyl-3-hydroxypyridin-4-one (deferiprone, L1, or Ferriprox™), analogs thereof, e.g. in formula (I) of the U. S. Pat. 6,534,528; and 2-deoxy-2-(N-carbamoylmethyl-[N'-2'-methyl-3'-hydroxypyridin-4'-one])-D-glucopyranose (feralex-G).

Tridentate OBIC include pyridoxal isonicotinyl hydrazone (PIH), 4,5- dihydro-2-(2,4-dihydroxyphenyl)-4-methylthiazole-4-carboxylic acid (deferitrin), 4,5-dihydro-2-(3'-hydroxypyridin-2'-yl)-4-methylthiazole-4-carboxylic acid (desferrithiocin, DFT) or the desferrithiocin derivatives as disclosed in WO2005034949; and 4-[3,5-bis(2-hydroxyphenyl)-[l,2,4]triazol-l-yl]benzoic acid (deferasirox). Substituted 3,5-diphenyl-l,2,4-triazoles in free acid form, salts and its crystalline forms are disclosed in WO 97/49395. An advantageous pharmaceutical preparation in the form of dispersible tablets is disclosed in WO 2004/035026.

Preferred OIBC are deferiprone and deferasirox due to their known safety profile.

If an increase of biotolerability or solubility is desired, the hydrated forms and/or the physiologically acceptable salts of OBIC are employed. Exemplary such salts are formed with Li^+, K^+, Na^+, Ca^{2+}, Mg^{2+}, $NH4^+$, substituted ammines, or lysine, etc.; or with anions of inorganic acid such as HCl and organic acids such as citric acid.

The compositions of invention can be conceived in a variety of oral dosage forms including, but not limited to, tablets, soft gelatin capsules, and hard shell capsules.

In one embodiment the compositions of invention have a prompt release delivery.

In another embodiment the compositions of invention are orally administered in a controlled release dosage form. An example of such form is disclosed in EP1183014, describing a multi-matrix controlled-release technique known as MMX™ where the OBIC are dispersed in three different layers; as well as in description and examples of the co-pending application PCT/IB09/005776.

The compositions of invention can also be in rectal forms including, but not limited to, suppository, enema, foam, gel, spry, suspension, solution, and emulsion.

These compositions typically include a pharmaceutically acceptable carrier and optionally one or more pharmaceutically acceptable excipients, including diluents, binders, plasticizers, lubricants, disintegrants, colorants, stabilizers, surfactants, etc.

As generally used herein "carrier" includes, but is not limited to, diluents, binders, lubricants, disintegrators, fillers, solubilizing agents, pH modifying agents, preservatives, stabilizers, such as anti-oxidants, wetting or emulsifying agents, suspending agents, and coating agents. Carrier also includes pigments, colorants, stabilizing agents, glidants, pore formers, and the like.

Diluents, also referred to as "fillers," are typically necessary to increase the bulk of a solid dosage form so that a practical size is provided for compression of tablets or formation of beads and granules. Suitable diluents include lactose, sucrose, mannitol, sorbitol, cellulose, microcrystalline cellulose, kaolin, sodium chloride, dry starch, hydrolyzed starches, pregelatinized starch, silicone dioxide, and powdered sugar.

Binders are used to impart cohesive qualities to a solid dosage formulation, and thus ensure that a tablet or bead or granule remains intact after the formation of the dosage forms. Suitable binder materials include, but are not limited to, starch, pregelatinized starch, gelatin, sugars (including sucrose, glucose, dextrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums such as acacia, tragacanth, sodium alginate, cellulose, including hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, and veegum, and synthetic polymers such as acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, aminoalkyl methacrylate copolymers, polyacrylic acid/polymethacrylic acid and polyvinylpyrrolidone.

Lubricants are used to facilitate tablet manufacture. Examples of suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, glycerol behenate, polyethylene glycol, talc, and mineral oil.

Disintegrants are used to facilitate dosage after administration, and generally include starch, sodium starch glycolate, sodium carboxymethyl starch, sodium carboxymethylcellulose, hydroxypropyl cellulose, pregelatinized starch, clays, cellulose, alginates, gums or cross linked polymers, such as Polyplasdone™ XL.

Further embodiments of the present invention further comprise one or more additional therapeutic such as, e.g., an immunosuppressive, an anti-inflammatory, a steroid, an immunomodulatory agent, a cytokine, and a TNF-antagonist.

Exemplary immunosuppressives include azathioprine, methotrexate, cyclosporine, FIL506, rapamycin, and mycophenolate mofetil. Exemplary anti-inflammatories include 5-aminosalicylic acid, sulfasalazine and olsalazine. Exemplary steroids include corticosteroids, glucocorticosteroids, prednisone, prednisolone, hydrocortisone, methylprednisolone, dexamethasone and ACTH. Exemplary immunomodulatory agents include PVAC, anti-CD40 ligand, anti-CD40, natalizumab (Antegren™), anti-VCAMI and anti-ICAMl. Exemplary cytokines include IL-10. Exemplary TNF antagonists include infliximab (Remicade™), etanercept (Enbrel™), adalimumab (Humira™), and CDP870.

In an other embodiment provided a pharmaceutical composition comprising a OBIC in association with an effective amount of a further active ingredient(s), e.g. metronidazole, vancomycine, imipenem, vancomycin, ciprofloxacin, octreotide, corticosterois, azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, lidocaine, and carbocaine; or short-chain fatty acids (SCFA) such as sodium acetate, sodium butyrate, and sodium propionate, and combination thereof.

The weight ratio of the OBIC to the further active ingredient(s) may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a OBIC is combined with a second active ingredient the weight ratio in range from about 1000:1 to about 10:1. Combinations of a OBIC and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active is used.

In a further embodiment is provided a method for the treatment of a subject with an inflammatory bowel disease (IBD) such as ulcerative colitis, Crohn's disease, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behçet's syndrome, infective colitis, proctitis, proctosigmoiditis, indeterminate colitis, and spastic colitis.

In the method of this embodiment, the subject is a mammalian, typically a human.

In a method of this embodiment, the OBIC may be taken once, twice, three times a day. The dosages of OBIC may vary from 10 mg through to 1 g per day, more typically 20 mg to 500 mg per day, still more typically 50 mg to 250 mg per day.

In another embodiment, OBIC is administered to an iron-deficient anemic IBD patient in conjunction with parenteral or oral iron supplement. In the latter case, the OBIC is administered at least 6 hours after or 3 hours before iron supplementation.

Usually, the OBIC are administered once a daily. As a general rule for long term therapy the dosage may commence at a low level, such as daily and may be elevated to a higher dosage, such as twice or three times daily if required. Administration is typically over a period of from 30 days to 60 days or more, e.g. from 60 days to 120 days. After relief or symptoms is achieved, administration of the OBIC may be ceased, tapered, or reduced to lower maintenance dosages for an indefinite period.

EXAMPLES

The serendipity observation of the thalassemic community in Milan confirm the present findings. Patients undergoing oral chelation, or switching from subcutaneous to oral chelation, despite the initial signs of gastric intolerance, experience an overall improvement of their intestinal status.

Assumedly, the use of OBIC can decrease the pro-inflammatory concentration of iron (Fe^{3+}) in the intestinal mucosa of IBD patients. Furthermore, the use of OBIC provide the ancillary suppression of the abnormal, pro-pathogenic microflora.

Prototype formulations

For immediate-release oral use, an IBD patient is administered with a halved Ferriprox™ 500 mg tablet; or with 15 ml of Ferriprox™ solution at 100 mg/ml; or with a halved tablet of Exjade™ 250 mg.

For controlled release oral use, an IBD patient is administered with a enteric-coated hard capsule of size 1 (Coni-Snap™, Capsugel, Bornem, Belgium) filled with half portion of a previously crushed Exjade™ 250 mg tablet.

For rectal administration, a 500 ml bottles of Ferriprox™ solution are thickened with xanthan gum under stirring, the resulting solution is then packaged in 100 ml doses in Wheaton enema bottles and administered to a IBD patient.

CLAIMS

1. Use of an orally bioavailable iron chelator (OBIC) for the manufacturing of a pharmaceutical composition to treat an inflammatory bowel disease (IBD).
2. Use according to claim 1 wherein said OBIC is a bidentate chelator selected from the group consisting of deferiprone and feralex-G.
3. Use according to claim 1 wherein said OBIC is a tridentate chelators selected from the group consisting of deferasirox, pyridoxal isonicotinyl hydrazone (PIH), deferitrin, desferrithiocin.
4. Use according to any of claims 2 to 3 wherein said OBIC is present in an amount from 10 to 500 mg per unit dose.
5. Use according to any of claims 2 to 3 wherein said OBIC is present in an amount from 100 to 250 mg per unit dose.
6. Use according to any of claims 2 to 3 wherein said pharmaceutical composition is a rectal, an oral, or an oral controlled release dosage form.
7. A pharmaceutical composition for the treatment of an IBD comprising a OBIC according to any of claims 2 to 6.
8. The composition of claim 7 wherein said IBD is selected from the group consisting of Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behçet's syndrome, proctitis, proctosigmoiditis, indeterminate colitis, and spastic colitis.
9. The composition according to claims 7 and 8 in a oral dosage form such as tablets, granules, capsule, micropellets, or sachets further, said composition further comprising pharmacologically acceptable excipients.
10. The composition according to claim 9 wherein the oral dosage form is a controlled release dosage form.
11. The composition according to claims 7 and 8 in the rectal dosed form such as suppository, enema, foam, cream, ointment, or gel, said composition further comprising pharmacologically acceptable excipients.
12. The composition according to any of claims 7 to 11 wherein the OBIC is deferiprone or deferasirox.

13. The composition according to claims 12 wherein said deferiprone or deferasirox is comprised from 50 to 250 mg per unit dose.
14. A method for the treatment of IBD including administering to a mammal a pharmaceutical composition comprising an effective amount of an OBIC of according to any of claims 2 to 7.
15. The method of claim 14 wherein said mammal is a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 2009/005902

A. CLASSIFICATION OF SUBJECT MATTER

IPC[8]: ***A61K 31/4412*** (2006.01); ***A61K 31/7012*** (2006.01); ***A61K 31/427*** (2006.01); ***A61K 31/426*** (2006.01); ***A61K 31/4196*** (2006.01); ***A61K 31/15*** (2006.01); ***A61P 39/04*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[8]: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, TXTE, TXTG, registry, HCAplus, embase, xpesp

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0044220 A1 (BERGERON, JR.) 04 March 2004 (04.03.2004) *paragraphs [0049],[0058]-[0067]; claims 8,9* --	1,3-5,7-9,11, 13-15
X	WO 2000/016765 A1 (UNIVERSITY OF FLORIDA) 30 March 2000 (30.03.2000) *pages 15-18; claim 1* --	1,3-5,7-9,11, 13-15
X	WO 2006/114630 A1 (AQ+PLC) 02 November 2006 (02.11.2006) *claims 1,2,4,5,21,31*	1,7-9,11,14,15
Y	--	2-5,12,13

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* 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
25 March 2010 (25.03.2010)	13 April 2010 (13.04.2010)

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Continuation of first sheet

Continuation 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:

Claims Nos.: 14,15 because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14 and 15 refer to a method of treatment of the human/animal body by therapy, a search has been carried out and bases on the alleged effects.

Claims Nos.: 6,10 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:

A Swiss-type claim may not contain therapeutical recommendations (e.g. "rectal", "oral", etc.). Said terms should be replaced by the name of the unit dosage form (e.g. suppository) which is actually applied.
Claim 10 describes a mere desiderata ("controlled release dosage form") without disclosing how said controlled release is achieved.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 2009/005902

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/015021 A1 (NOVARTIS AG) 07 February 2008 (07.02.2008) *claims 1,4-6*	2-5,12,13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IB 2009/005902

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
US	A	2004044220		US	A1	2008255081	2008-10-16
				US	A1	2005234113	2005-10-20
				WO	A2	2004017959	2004-03-04
				US	A1	2004132789	2004-07-08
				AU	A1	2003263948	2004-03-11
				US	A1	2004044220	2004-03-04
WO	A	0016765		WO	A1	0016765	2000-03-30
				JP	T	2003517443T	2003-05-27
				EP	A1	1113789	2001-07-11
				CA	A1	2344438	2000-03-30
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WO	A	2008015021		JP	T	2009545547T	2009-12-24
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				EP	A1	2049108	2009-04-22