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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 October 2009 (22.10.2009)

PCT

(10) International Publication Number
WO 2009/128795 A1

(51) International Patent Classification:
A61K 31/375 (2006.01) *A61K 33/30* (2006.01)
A61K 31/505 (2006.01) *A61P 7/06* (2006.01)
A61K 33/26 (2006.01)

(21) International Application Number:
PCT/TR2009/000047

(22) International Filing Date:
30 March 2009 (30.03.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2008/02713 18 April 2008 (18.04.2008) TR

(71) Applicant *(for all designated States except US)*: **BERKO ILAC VE KIMYA SAN. A.S.** [TR/TR]; Yeni Camlica Mah. Baraj Yolu Cad. 9. Özgür Sok., No:16, 34779 ISTANBUL (TR).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **BERAN, M. Berat** [TR/TR]; Yeni Camlica Mah. Baraj Yolu Cad. 9. Özgür Sok., No:16, 34779 ISTANBUL (TR).

(74) Agent: **ERK PATENT LTD. STI.**; Hasanpasa Mah. Uzuncayir yolu, Sarilar Is Merkezi Kat:1 No:24/6, 34722 ISTANBUL (TR).

(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, 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, 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))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2009/128795 A1

(54) Title: IRON AND ZINC BASED PHARMACEUTICAL FORMULATION FOR IRON DEFICIENCY TREATMENT

(57) Abstract: The present invention relates to a pharmaceutical formulation, particularly providing high iron absorption, for use in preventing and treating iron deficiency and iron deficiency anemia of various origins.

IRON AND ZINC BASED PHARMACEUTICAL FORMULATION FOR IRON DEFICIENCY TREATMENT

Field of Invention

The present invention relates to a pharmaceutical formulation, particularly providing high iron absorption, for use in preventing and treating iron deficiency and iron deficiency anemia of various origins.

Background of Invention

Iron, which is incorporated into the basic structure of hemoglobin, a protein providing the transport of oxygen in blood, bears great importance in binding the oxygen taken in the lungs to hemoglobin and transporting it to tissues, and therefore is an essential element with respect to proper tissue development in humans. Iron is not present in foodstuffs in adequate amounts, and if it is taken exogenously, it may cause various disorders, since it is absorbed difficultly. Anemia associated with iron deficiency, for instance, is one of the symptoms frequently encountered in blood diseases, and occurs when the blood hemoglobin level drops below a lower limit.

Iron deficiency is still the most-frequently occurring nutritional problem worldwide and iron deficiency anemia is present in around 30% of the world population. Iron deficiency is still a significant public health problem not only in underdeveloped countries, but in the developed countries' disadvantageous groups (infants, adolescents, pregnant women, and ethnical groups in inadequate socioeconomic conditions) as well. According to the report published by the World Health Organization (WHO), the occurrence rate of iron deficiency anemia in developing and developed countries is 36% and 8%, respectively.

Prevalence of iron deficiency anemia: It is the most common cause of anemia worldwide. Anemia is present in 30% of the world population and at least half of this rate is due to iron deficiency.

Infants and pregnant women compose the groups which are most susceptible to anemia. Anemia prevalence is determined to be as 43% in infants and 51% in pregnant women. Anemia prevalence is 37% in school-age children, 35% in nonpregnant women, and 18% in adult males. No certain prevalence figures are available for adolescents and elder people. The prevalence of adolescents is generally considered to be close to that of adult women.

Although anemia associated with iron deficiency has many causes, it is more frequently seen in societies with lower socioeconomic levels and with bad nutritional habits. The causes of anemia may comprise, *inter alia*, delayed commencement of dietary supplements, excessive caw milk consumption by babies, vegetarian nutrition, misapplied weight-loss diets, and eating disorders. In addition, acute or chronic blood loss, e.g. ulcerative hemorrhage or menstrual bleeding and parasitary infections increase the iron need, particularly during the first year of life and the adolescent period in which rapid growth occurs, resulting in possible anemia cases.

The presence of high amounts of iron in the intestine during oral treatment triggers oxidative damage. Therefore, losses are encountered in the formation, destruction, and functions of intestinal mucosal cells. Zinc ensures the stability of intestinal cells and cell walls, thereby providing protection against the peroxidative damage of iron. The studies conducted reports that the presence of zinc in the medium reduces iron-dependent hydroxyl radical formation at intestinal mucosa and protects the cells against iron-dependent lipid peroxidative damage.

In zinc deficiency, however, atrophy, flattening, and blunting occur at intestinal villuses and in result, the absorption functions of intestines start deteriorating. No satisfactory outcomes can be achieved in iron deficiency treatments, which are conducted when zinc deficiency is prominent. As a matter of fact, since iron can

not be absorbed adequately and since iron storages can not be filled entirely, frequent recurrences occur in anemia therapies.

In cases when iron is used together with zinc, it is known to maintain the iron:zinc rate between 1:1 and 2.5:1, in order to avoid the absorption of both elements from interfering each other negatively.

Folic acid cannot be produced in the human body, since PABA cannot be synthesized and the first glutamate cannot be added to the molecule. Folic acid plays role in the cellular DNA synthesis and is absolutely required during the formation stage of new cells. It is also required for erythrocytes to be regenerated during anemia. Deterioration occurs in the metabolism of cells which are rapidly destructed and regenerated in folic acid deficiency. The most-susceptible cells are normoblasts, leukocyte cells, platelet cells, intestinal epithelial cells with the fastest division and regeneration rates. The susceptibility of erythrocytes gives rise to megaloblastic anemia. In folic acid deficiency there may occur megaloblastic anemia, neural tube and other congenital birth defects, hyperhomosysteinemia.

Vitamin C, a water soluble and potent antioxidant that cannot be synthesized by humans, is assistive in iron absorption. It plays roles in carnitine synthesis, the conversion of tryptophan to serotonin and thyroxin, the conversion of corticosteroids and aldosteron cholesterol to bile acids, immune system functions, preventing cancer, and in collagen synthesis.

An effort towards preventing and treating disorders associated with iron deficiency is known from the application WO 2006024241. WO 2006024241 discloses a preparation in the form of tablet or aqueous suspension for preventing or treating iron deficiency, this preparation containing between 6 and 26% ferrous fumarate and between 74 and 94% haemoderivative in powder form, with an ionic iron/haem iron ratio of between 30 and 70% and an amino acid concentration of between 20 and 30 µmol/100µmol of proteins.

The patent JP 2006193428 discloses a prophylactic or ameliorative agent for iron deficiency anemia, comprising an iron compound containing various iron salts, e.g. ferrous fumarate, extracts of *Eleutherococcus Senticosus*, and rutin and/or a rutin derivative.

Description of Invention

The object of the present invention is to provide a pharmaceutical formulation ensuring high iron absorption for efficiently preventing and treating iron deficiency and anemia associated with iron deficiency.

Another object of the present invention is to provide efficient iron, zinc, and folic acid, as essential agents, in proportions which will not interfere the absorption of each other, against malnutrition-associated macrocytes anemias, anemias due to hemorrhage, zinc deficiency co-occurring with iron deficiency, and zinc deficiency co-occurring with megaloblastic anemia.

A further object of the present invention is to provide efficient iron absorption against iron deficiencies during pregnancy, in infants and children, and against latent iron deficiency.

The pharmaceutical formulation according to the present invention preferably comprises 3 to 20 mg/ml iron, 1 to 20 mg/ml zinc, 1.5 to 60 mg/ml vitamin C, and 0.015 to 0.50 mg/ml folic acid. A more preferred pharmaceutical formulation according to the present invention comprises 5 to 12 mg/ml iron, 4 to 10 mg/ml zinc, 5 to 40 mg/ml vitamin C, and 0.08 to 0.40 mg/ml folic acid. The most preferred pharmaceutical formulation according to the present invention comprises 7 to 9 mg/ml iron, 5 to 7 mg/ml zinc, 10 to 20 mg/ml vitamin C, and 0.1 to 0.2 mg/ml folic acid. According to a preferred formulation of the present invention, the fructose amount may be kept between 30 mg/ml and 250 mg/ml, but this amount may be kept in more preferred formulations between 100 mg/ml and 200 mg/ml and in most preferred formulations between 120 mg/ml and 180 mg/ml.

The formulation according to the present invention further comprises excipients, or auxiliary agents, such as sorbitol, sodium saccharin, fructose, sodium hydroxide, nipagin, sodium saccharin, neohesperidin dihidrochalcone, orange, lemon and mandarin essences citric acid, as well as deionized water.

As an alternative to fructose, the formulation according to the present invention may contain mixed saccharide materials, such as sucrose, glucose, mannose, galactose, lactose, or a mixture thereof.

The proportions of fructose given above builds iron-fructose complexes with iron, thereby enhancing the dissolution rate and the absorption of iron.

The excipient citric acid is similarly supportive in iron absorption, but is also pH lowering, as well as maintaining the stability of vitamin C. According to a preferred formulation of the present invention, the citric acid amount may be kept between 1.5 mg/ml and 600 mg/ml, but this amount may be kept in more preferred formulations between 50 mg/ml and 300 mg/ml and in most preferred formulations between 90 mg/ml and 110 mg/ml.

As an alternative to citric acid for use in the formulation according to the present invention, other organic acids, carrying one or more carboxyl groups and organic side chains, e.g. tartaric acid, malic acid, may be included into the formulation.

The iron employed in the pharmaceutical formulation according to the present invention is divalent iron (Fe (II)) based on its high absorption rate, but this fact does not exclude the use of trivalent iron (Fe (II)) from the scope of the present invention. Iron and zinc are included in a formulation according to the present invention preferably in the form of ferrous fumarate ($C_4H_2FeO_4$) iron salt and zinc sulfate ($ZnSO_4$) zinc salt, respectively.

The iron salt may also be in the form of ferrous gluconate, ferrous succinate, ferrous glutamate, ferrous lactate, ferrous citrate, ferrous tartrate, ferrous pyrophosphate. According to a preferred embodiment according to the present

invention, the source of iron may be in the form of iron-EDTA, iron ammonium ortophosphate, iron II ammoniumsulfate iron complexes.

In another formulation according present invention, the source of iron may be in the form of iron III protein succinate, iron III polymaltose, iron III Sodium-EDTA, carbonyl iron, iron chloride.

As for the zinc salt, it may be in the form of zinc sulfate mono or heptahydrate, zinc acetate, zinc carbonate, zinc chloride, zinc gluconate, zinc picolinate.

The formulation according to the present invention is preferably in the form of a syrup, but it can also be prepared in any oral liquid forms, including the aqueous suspension form. Thus, the oral administration thereof may be facilitated as compared to the tablet form, especially for children. Said "liquid form" further comprises effervescent tablet compositions, which are convenient for oral administration once they are dissolved in water.

The constituents making up an exemplary composition according to the present invention are listed as follows:

Constituent	Mass per 5 ml syrup (mg)
Ferrous fumarate	121
Zinc sulfate	66
Folic acid	0.2
Vitamin C	50

Example 2:

Constituent	Mass per 5 ml syrup (mg)
Ferrous fumarate	121
Zinc sulfate	66
Folic acid	0.2

Vitamin C	50
Fructose	750

Example 3:

Constituent	Mass per 5 ml syrup (mg)
Ferrous fumarate	121
Zinc sulfate	66
Folic acid	0.2
Vitamin C	50
Fructose	750
Citric acid	500 mg

Example 4:

Constituent	Mass per 5 ml syrup (mg)
Ferrous fumarate	121
Zinc sulfate	66
Folic acid	0.2
Vitamin C	50
Sorbitol	1500
Propylene glycol	250
Ethyl alcohol	250
Nipagin M sodium	5

Example 5:

Constituent	Mass per 5 ml syrup (mg)
Ferrous fumarate	121
Zinc sulfate	66
Folic acid	0.2
Vitamin C	50

Sorbitol	1500
Neohesperidin dihydrochalcone	5
Citric acid	500
Propylene glycol	250
Ethyl alcohol	250
Nipagin M sodium	5
Sodium saccharine	5
Sunset yellow	0.03
Orange essence	2
Lemon essence	2
Mandarin essence	2
Grapefruit essence	2
Deionized water	*quantum sufficit* to complete to 5 ml

Example 6:

Constituent	Mass per 5 ml syrup (mg)
Ferrous fumarate	121
Zinc sulfate	66
Folic acid	0.2
Vitamin C	50
Sorbitol	1500
Propylene glycol	250
Ethyl alcohol	250
Nipagin M sodium	5
Sodium saccharine	5
Sunset yellow	0.03
Orange essence	2
Lemon essence	2
Mandarin essence	2
Grapefruit essence	2
Deionized water	*quantum sufficit* to complete to 5 ml

The proportion between iron and zinc in a formulation according to the present invention is preferably 1 to 2.5; the proportion between vitamin C and iron is preferably 0.5 to 3; and the proportion between folic acid and iron is preferably between 0.005 to 0.025. In another preferred formulation according to the present invention, the proportion between iron and fructose is preferably 0.04 to 0.1 and the proportion between vitamin C and citric acid is 1 to 10.

CLAIMS

1. A pharmaceutical formulation for use in preventing and treating iron deficiency and iron deficiency anemia, characterized by comprising 3 to 12 mg/ml iron, 1 to 12 mg/ml zinc, and 1.5 to 36 mg/ml vitamin C, as active agent.

2. A formulation according to Claim 1, characterized by further comprising 0.015 to 0.3 mg/ml folic acid.

3. A formulation according to claims 1 and 2, wherein the amount of iron is between 5 to 10 mg/ml, of zinc between 4 to 9 mg/ml, of vitamin C between 5 to 30 mg/ml, and of folic acid between 0.08 to 0.25 mg/ml.

4. A formulation according to claims 1 and 2, wherein the amount of iron is between 7 to 9 mg/ml, of zinc between 5 to 7 mg/ml, of vitamin C between 10 to 20 mg/ml, and of folic acid between 0.1 to 0.2 mg/ml.

5. A formulation according to any of the preceding claims, further comprising fructose, preferably in an amount between 30 to 300 mg/ml, more preferably in an amount between 100 to 200 mg/ml, and most preferably in an amount between 120 to 180 mg/ml.

6. A formulation according to any of the preceding claims, further comprising citric acid, preferably in an amount between 1.5 to 600 mg/ml, more preferably in an amount between 50 to 300 mg/ml, and most preferably in an amount between 90 to 110 mg/ml.

7. A formulation according to any of the preceding claims, characterized in that iron is included into the formulation in the form of an iron salt, selected from the group consisting of ferrous fumarate, ferrous gluconate, ferrous succinate, ferrous glutamate, ferrous lactate, ferrous citrate, ferrous tartrate, ferrous pyrophosphate.

8. A formulation according to any of the preceding claims, characterized in that iron is included into the formulation in the form of an iron complex, selected from the group consisting of iron-EDTA, iron ammonium ortophosphate, iron II amonniumsulfate.

9. A formulation according to any of the preceding claims, characterized in that iron is selected from the group consisting of iron III protein succinate, iron III polymaltose, iron III Sodium-EDTA, carbonyl iron, iron chloride.

10. A formulation according to any of the preceding claims, characterized in that zinc is included into the formulation in the form of a zinc salt, selected from the group consisting of zinc sulfate mono or heptahydrate, zinc acetate, zinc carbonate, zinc chloride, zinc gluconate, zinc picolinate.

11. A formulation according to any of the preceding claims, further comprising excipient or auxiliary agent selected from the group consisting of sorbitol, propylene glycol, ethyl alcohol, sodium saccharin, fructose, sodium hydroxide, nipagin, sodium saccharin, neohesperidin dihidrochalcone, orange, lemon and mandarin essences, subset yellow, as well as deionized water.

12. A formulation according to any of the preceding claims, characterized in that said formulation is in oral liquid form, including syrup and aqueous suspension forms.

13. A formulation according to Claim 12, characterized in that said oral liquid form also comprises liquid compositions, which result when effervescent tablets are dissolved in water for oral administration.

14. A formulation according to any of the preceding claims, characterized in that the proportion of iron : zinc in said formulation is preferably 1 to 2.5; the proportion of vitamin C : iron is preferably 0.5 to 3; and the proportion of folic acid : iron is preferably between 0.005 to 0.025.

15. A formulation according to any of the preceding claims, characterized in that the proportion of iron : fructose in said formulation is between 0.04 and 0.1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2009/000047

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/375 A61K31/505 A61K33/26 A61K33/30 A61P7/06

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)
A61K A61P

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 practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/042218 A (TRIS PHARMA INC [US]; MEHTA KETAN [US]; TU YU-HSING [US]; SHAH MAHENDR) 10 April 2008 (2008-04-10) page 20, line 30 - page 21, line 14 page 25, line 12 - line 17	1-15
A	EP 1 810 682 A (CT NAC DE BIOPREPARADOS [CU]; MEDSOL LAB [CU]) 25 July 2007 (2007-07-25) claim 1	1-15
A	WO 93/13783 A (HOLM CHRISTENSEN BOERGE [DK]) 22 July 1993 (1993-07-22) claims 4,56	1-15

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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
31 July 2009	25/08/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Werner, Doris

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2009/000047

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/24165 A (NYCOMED PHARMA AS [NO]; COCKBAIN JULIAN [GB]; SCHLYTER JIMMY HIRSCHSPR) 28 March 2002 (2002-03-28) page 41 - page 42; example 4	
A	US 2003/206969 A1 (NIDAMARTY PRASAD [US] ET AL) 6 November 2003 (2003-11-06) paragraphs [0053], [0062]	1-15
A	US 5 807 586 A (JACKSON SHERRY D [US] ET AL) 15 September 1998 (1998-09-15) claims	1-15

2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2009/000047

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008042218 A	10-04-2008	NONE	
EP 1810682 A	25-07-2007	BR PI0515598 A	26-08-2008
		WO 2006024241 A1	09-03-2006
		PA 8643701 A1	03-08-2006
		SV 2007002213 A	20-03-2007
WO 9313783 A	22-07-1993	AU 3449193 A	03-08-1993
		DE 69311306 D1	10-07-1997
		ES 2105219 T3	16-10-1997
		NZ 246866 A	26-07-1995
WO 0224165 A	28-03-2002	AT 380541 T	15-12-2007
		AU 8791801 A	02-04-2002
		BG 107738 A	30-01-2004
		CN 1461210 A	10-12-2003
		CZ 20030808 A3	13-08-2003
		DK 1320356 T3	28-01-2008
		EE 200300109 A	15-04-2005
		EP 1320356 A2	25-06-2003
		HU 0301250 A2	28-11-2003
		NO 20031249 A	20-05-2003
		PL 365047 A1	27-12-2004
		PT 1320356 E	03-01-2008
		SK 3232003 A3	03-02-2004
		US 2004043043 A1	04-03-2004
US 2003206969 A1	06-11-2003	AU 2003231249 A1	17-11-2003
		WO 03092674 A1	13-11-2003
US 5807586 A	15-09-1998	NONE	