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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 August 2010 (12.08.2010)

PCT

(10) International Publication Number
WO 2010/090546 A1

(51) **International Patent Classification**:
A61K 31/197 (2006.01) ***A61P 17/00*** (2006.01)
A61K 9/20 (2006.01)

(21) **International Application Number**:
PCT/RU2009/000701

(22) **International Filing Date**:
18 December 2009 (18.12.2009)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
200900146 26 December 2008 (26.12.2008) EA

(71) **Applicant** *(for all designated States except US)*: **NEKOMMERCHESKOE UCHREZHDENIE "NAUCHNO-ISSLEDOVATEL'SKIJ INSTITUT TSITOKHIMII I MOLEKULYARNOYJ FARMAKOLOGII'** [RU/RU]; ul. 6-ya Radialjnaya, 24-14, Moscow, 115404 (RU).

(72) **Inventors; and**
(75) **Inventors/Applicants** *(for US only)*: **KOMISSAROVA Irina Alekseevna** [RU/RU]; ul. Medikov, 24-47, Moscow, 115304 (RU). **KORSUNSKAYA Irina Markovna** [RU/RU]; ul. 0ktyabr'skaya,16B, Chekhov, 142301 (RU). **NARTSISSOV Yaroslav Ryurikovich** [RU/RU]; ul. Medikov, 24-47, Moscow, 115304 (RU).

(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, SM, 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 2010/090546 A1

(54) **Title**: COMPOSITION OF AMINO ACIDS FOR SUBLINGUAL APPLYING FOR ENHANCED SKIN INTEGUMENT REPIGMENTATION IN VITILIGO AND METHOD OF ITS ADMINISTRATION

(57) **Abstract**: The task of this invention is in use of composition containing natural metabolites - amino acids, and in method of its administration which make it possible to increase skin repigmentation through sulfurcontaining compounds rise and activation of endogenic metabolic reactions, and to get persistent normalization of melanogenesis thus improving skin integument and as a consequence patient's quality of life. Composition includes L cystine, L glutamic acid and glycine in the following quantity, mg: L cystine 85 ± 10%, L glutamic acid 85 ± 10%, Glycine 85 ± 10%. The amino acid composition mentioned above must be administered 3 times a day for 5 weeks independent of meal in accordance with method of increase of skin integument repigmentation in vitiligo. The course can be repeated in 4-5 weeks.

Composition of amino acids for sublingual applying for enhanced skin integument repigmentation in vitiligo and method of its administration

Field of application

The invention relates to medicine, ortho-molecular medicine, pharmaceuticals, nutrition, biochemistry of amino acids, in particular to composition of amino acids for sublingual applying for enhanced repigmentation of skin integument in vitiligo and method of its administration.

Background of invention

Individuals of various ethnicities and races may suffer from chronic dermatosis (vitiligo) characterized by appearance of depigmentation focuses on the skin. Histologic studies of such focuses show absence or reduction of melanine.

Etiology, pathogenesis and vitiligo treatment has been one of the unresolved issues of dermatology. Wide spread of vitiligo in many ethnic groups and areas, its significant influence on psychosocial status, lack of efficient methods of treatment and information about possible interrelation of vitiligo pathogenesis and skin melanoma indicate to topicality of fundamental studies, research and elaboration of new means contributing to normalization of melanogenesis.

Given views of the role of vitiligo genetic disposition, immunopathology (I.M Karsunskaya., Vitiligo Genetic and metabolic features of the disease, treatment method. Abstract for a thesis for a doctor's of medicine degree, Moscow, 2004) of biochemical disorders in the form of decrease of catalase and tiriodin – reductase activity (K.U. Schallreuter, The society for Investigate Dermatology, International journal of derm. 2008, Jul. 47(7): 743-53) inspiring oxidative stress, treatment methods have symptomatic character. They are not efficient enough, may cause traumas and they are quite limited because of adverse by-effects.

There is known vitiligo treatment method characterized by use of ultraviolet radiation, ultraviolet radiation with reflexotherapy and photosensitizing drugs in particular, for melanogenesis stimulation. (D.V. Proshutinskaya, Selective phototherapy of vitiligo-ill children taking into account role of immune changes, abstract of a thesis for a candidate of medicine, Moscow,2004, p.19; R.N.

Voloshin., Clinico-pharmacologic features of complex vitiligo treatment by methods of psoralen ultraviolet radiation of A band) and reflexotherapy, abstract of a thesis for doctor's of medicine degree, 14.0025, Volgograd, 2006; U.N. Koshevenko, Phototherapy of vitiligo: substantiation, characteristics, clinical effect, Russian journal of skin and veneral diseases, 2001, No3., p. 58-66). Contraindications to such exposures in most of coexistent diseases, total and local side effects including increase possibility of squamous cell carcinoma formation restrict using long-wave ultraviolet rays.

For immune disorders correction there are used polyoxidonium and amixin. However administration of the mentioned drugs does not ensure full, intense and persistent repigmentation. Polyoxidonium is administered in the form of injections which is attended by undesirable everyday (10-week) injury of skin integuments and risk of local infection. Amixin is administered only since 14 years of age and is contraindicated in affected thyroid.

Substance of invention

The task of this invention is in use of composition containing natural metabolites – amino acids, and in method of its administration which make it possible to increase skin repigmentation through sulfurcontaining compounds rise and activation of endogenic metabolic reactions, and to get persistent normalization of melanogenesis thus improving skin integument and as a consequence patient's quality of life.

The given task is accomplished by composition of amino acids for sublingual applying for enhanced skin integument repigmentation in vitiligo which includes L cystine, L glutamic acid and glycine in the following quantity, mg:

L cystine	85 ± 10%,
L glutamic acid	85 ± 10%,
Glycine	85 ± 10%

The amino acid composition mentioned above must be administered 3 times a day during 5 weeks independent of meal in accordance with method of increase of skin integument repigmentation in vitiligo.

The course can be repeated in 4-5 weeks. Composition can be administered in the form of a tablet or powder obtained by tablet porphyrizing.

Composition in the form of a tablet contains additionally ether of cellulose and stearate as adjuncts in the quantity of 1%-10% of tablet weight for each agent.

Realization of invention

For quite a long time there have been conducted studies of medical possibilities of amino acids composition of L cystine, L glutamic acid and glycine. Amino acids composition of L cystine, L glutamic acid and glycine is known to be used in components mass ratio 1:1:1 and with quantity content of 0.1 g. for each component as a means inducing glutathione biosynthesis, glutathione transferase activity and having detoxifying, antiradiation and antihypoxic action (RU 2096034 C1, IPC 6 A61K 31/195, 1997).

However as a means of persistent repigmention in vitiligo achievement amino acids composition of L cystine, L glutamic acid and glycine in the form of monoimpact was first offered by the authors of the present invention Irina .Alekseevna Komissarova, Irina Markovna Korsunskaya and Yaroslav Riurikovich Nartsissov. Clinical research and estimation of medicine efficiency were carried out through mediation of Marina Alexandrovna Gornostaeva and Ekaterina Viktorovna Zhavoronkova.

After the course of administration of elaborated composition there is reached an effect which induces changes in color of depigmentation focuses, appearance of pigmented areas akin to disseminations. Such result could not be achieved in such short terms and by use of other known methods earlier.

Further pigmentation augment takes place even after discontinuation of drugs in contrast to Polyoxidonium and Amixin treatment methods which require refresher treatment course in order to maintain the result.

The effect attained on composition administration is persistent and lasts for 2 years. Resolution of cosmetic problems in such period makes it possible to improve quality of life and social adaptation of a patient.

Composition does not have any contraindications or side effects and can be administered to a wide range of vitiligo-patients without limitations as well as to patients with concomitant and confounding pathologies.

Since each of composition amino acids is introduced in quantity 3-10 times less than its daily requirement its administration does not provoke any allergic or

toxic reactions typical of various vitiligo treatment methods. Moreover there is no danger of squamous cell skin carcinoma, melanoma, cataract, and photoageing.

Composition influence has been tested on a group of 15 patients with vitiligo of spread and bounded form. Patients' age varied from 12 to 31. The group consisted of 9 women and 6 men. Depigmentation focuses were mostly on limbs and body.

Composition was taken 3 times a day in the form of a tablet or powder after tablet porphyrizing sublingually independent of meal in the morning, afternoon and evening. The course took 5 weeks.

Substantial life quality improvement and evident repigmentation can be considered as an effect which was attained by each patient on administration of this composition and lasted for 2 years. There were observed no side effects and complications.

Efficiency of this composition can be demonstrated on the following examples of particular patients.

Example 1

Patient A, 14 years of age diagnosed with vitiligo was under hospital treatment. When she was admitted to hospital there were noticed clear-cut sharply marginated spots on knees, elbows and periorbital region. Composition was administered in accordance with the suggested method.

Composition was administered in the form of a tablet or powder after its porphyrizing 3 times a day for 5 weeks.

Chemistry panel before composition administration: cholesterol – 2.2, total bilirubin – 4.0, AST (Aspartate aminotransferase) – 11.7 u., AlT (Alanine aminotransferase) – 7.6 u., gamma GTP (gamma glutamyl transpeptidase) – 20.3 mol/l., ALP – 111.1 (Alkaline phosphatase) u/l, Trg – 0.7 (Triglycerides) mol/l, protein – 62.2, glucose – 3.1.

Vitiligo-patients suffered no hormonal or biochemical changes. There were noted interleukin IL-1 variations within normal limits.

There were revealed no side or any adverse effects on administration of the composition.

Amid 5-week composition administration partial repigmentation in depigmentated focuses has been recorded.

The patient was discharged from hospital with significant improvements. The patient's follow-up has shown further pigmentation augment that testifies to intensity and durability of the effect achieved. Administration of composition was repeated in 5 months to nail down the result attained.

Example 2

Patient 26 years of age, vitiligo-patient since 1997. He sought medical attention about vitiligo in December of 2004. First examination showed multiple focuses sized from 1 to 10 cm. in diameter on facial skin, upper and lower limbs.

Concomitant diseases: chronic gastritis, cholangitis, reactive pancreatits, syndrome of vegetative disfunction.

Thyroid ultrasound – norm.

Abdominal ultrasound revealed moderate hepatomegaly with diffusive change of vascular pattern. Moderate diffusive changes of pancreas.

Arterial blood pressure jumps up to 160/100 mmhg.

HBs –Ag (test for diagnosis and confirmation of hepatitis C), anti – HCV, IgM k HAV (immunoglobulins to hepatitis A) – none.

Total protein – 77, cholesterol – 4.6, total bilirubin – 13.5, ALP – 330, AST – 64.2, gamma GTP – 2.6, urea – 69, creatinine – 5.3.

Composition was administered in the form of a tablet or powder after its porphyrizing 3 times a day for 5 weeks. There were noted no side or any adverse effects on administration of composition.

After the first course progression of the process stopped that confirms composition high efficiency. However given process prevalence it was decided to repeat composition administration. After the third course positive dynamics was recorded. Pigment in focuses on facial skin and upper limbs appeared and grew that indicated to efficiency of its impact.

Claim

1. Use of composition of amino acids which includes L cystine, L glutamic acid and glycine in the following quantity, mg:

L cystine	85 ± 10%,
L glutamic acid	85 ± 10%,
Glycine	85 ± 10%

as a means for sublingual applying for enhanced skin integument repigmentation in vitiligo.

2. The use according to point 1 characterized by composition in the form of a tablet, additionally containing ether of cellulose and stearate as adjuncts in quantity of 1%-10% of tablet weight for each agent.

3. Method of repigmentation increase of skin integument in vitiligo, including 3–times-a-day 5-weeks-long sublingual applying of amino acid composition consisting of L cystine, L glutamic acid and glycine in the following quantity, for single dose, mg:

L cystine	85 ± 10%,
L glutamic acid	85 ± 10%,
Glycine	85 ± 10%

4. Method according to point 3, notable for repeated course of composition administration in 4-5 months.

5. Method according to point 3 characterized by composition administration in the form of a tablet or powder obtained by tablet porphyrizing.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/RU 2009/000701

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/197 *(2006.01)*
A61K 9/20 *(2006.01)*
A61P 17/00 *(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)
A61K 31/197, 31/195, 9/20, 9/00, A61P 17/00

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)
PAJ, Esp@cenet, USPTO DB, RUPAT, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ORECCHIA G. et al., "Cystine in the treatment of vitiligo", G ital Dermatol Venereol. 1998, Nov-Dec;124(11-12):529-31, abstract, [on-line]. [Retrieved 05.05.2010]. Retrieved from PubMed PMID: 2638646	1-5
A	RU 2096034 C1 (OBSCHESTVO S OGRANICHENNOY OTVETSTVENNOST'YU "MEDITSINSKIY NAUCHNO-PROIZVODSTVENNIY KOMPLEKS "BIOTIKI") 20.11.1997, description, p. 2, claims	1-5
A	US 2004/0258717 A1 (GERHARD SAUERMANN et al.) 23.12.2004, abstract, claims	1-5
A	ISHIKAWA M. et al., "Combination of amino acids reduces pigmentation in B16F0 melanoma cells", Biol Pharm Bull. 2007 Apr, 30(4):677-81	1-5

[X] 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 nit 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
06 May 2010 (06.05.2010)	20 May 2010 (20.05.2010)

Name and mailing address of the ISA/RU FGU FIPS
Russia, 123995, Moscow, G-59, GSP-5,
Berezhkovskaya nab., 30-1
Facsimile No. 243-3337

Authorized officer
I. Agapitova
Telephone No. (495) 730-7675

INTERNATIONAL SEARCH REPORT

International application No.
PCT/RU 2009/000701

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	REISH O. et al., "Tyrosinase inhibition due to interaction of homocyst(e)ine with copper: the mechanism for reversible hypopigmentation in homocystinuria due to cystathionine beta-synthase deficiency", Am J Hum Genet. 1995 Jul;57(1):127-32	1-5