

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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FOLIOS: 2

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Señores

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

E. S. D.

REF.: Expediente No. 06 032018 - Solicitud de Patente FASE NACIONAL

Corresp. a la Solicitud Internacional PCT/JP2004/014896

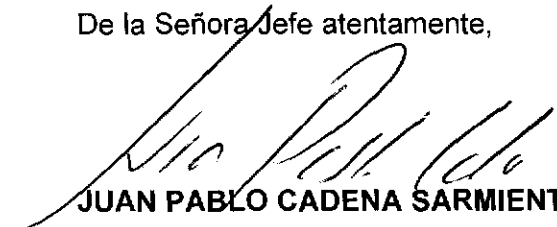
a nombre de: **ONO PHARMACEUTICAL CO., LTD.**

Titulada: PREPARACIÓN DE INFUSIÓN QUE COMPRENDE ÁCIDO (2R)-2-
PROPILOCTANOICO COMO UN INGREDIENTE ACTIVO

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad **ONO PHARMACEUTICAL CO., LTD.**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 08-17,980 por valor de \$420.000.

De la Señora Jefe atentamente,


JUAN PABLO CADENA SARMIENTO

C.C. No. 80.410.337 de Usaquén

T.P. No. 57492 del C.S.J.

Cra 7 No. 71-21 Torre B, Piso 4

Bogotá, 5 de marzo de 2008

MEV/JCN/aac

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SECRETARÍA DE INDUSTRIA Y COMERCIO
 DIRECCIÓN DE REGISTRO DE MARCAS
 BOGOTÁ, D.C.
 Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 00 - 17,900
 FECHA : FEBRERO 28 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3535362	28/02/2008	23,935,600.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-32018

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **580** DE

FECHA **28 DE SEPTIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **27 DE DICIEMBRE DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

portada de la solicitud internacional de D1

121
121

(12) 特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
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(43) 国際公開日
2003年1月30日 (30.01.2003)

PCT

(10) 国際公開番号
WO 03/007992 A1

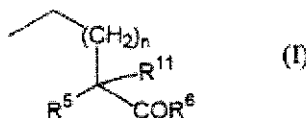
- (51) 国際特許分類: A61K 45/06, 31/19, A61P 9/00, 43/40
- (21) 国際出願番号: PCT/JP02/07212
- (22) 国際出願日: 2002年7月16日 (16.07.2002)
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- (26) 国際公開の言語: 日本語
- (30) 優先権データ:
特願2001-217755 2001年7月18日 (18.07.2001) JP
- (71) 出願人 (米国を除く全ての指定国について): 小野薬品工業株式会社 (ONO PHARMACEUTICAL CO., LTD.) [JP/JP] 〒541-8526 大阪府 大阪市 中央区道修町2丁目1番3号 Osaka (JP).
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- (81) 指定国 (国内): AE, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RU, RW, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) 指定国 (広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW). ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). ユーロッパ特許 (AE, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LI, MC, NL, PT, SE, SK, TR). OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
国際調査報告書

2文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(54) Title: REMEDIES FOR BRAIN ISCHEMIC DISEASES

(54) 発明の名称: 脳虚血疾患治療剤



(57) Abstract: Remedies and/or preventives for brain ischemic diseases comprising two active ingredients, namely, an astrocytic function-improving agent, preferably a compound represented by the following general formula (I), and a thrombolytic agent, preferably a tissue plasminogen activator; (I) wherein R⁶ represents hydroxy, etc.; and (I) n is 1, R¹¹ represents hydrogen, and R⁵ represents alkyl having a fluorine atom as a substituent of a carbon atom-CH₂-; or (2) n is 0 or 1, R¹¹ represents hydrogen, etc., and R⁵ represents alkyl, etc. These drugs show synergistic therapeutic effects compared with the case where an astrocytic function improving agent and a thrombolytic agent are separately administered.

/ 続葉石 /

WO 03/007992 A1

patente perteneciente a la familia de patentes de P1
presentada en EEUU

D1
122
122

United States Patent Application

20040176347

Kind Code

A1

Honjo, Kaneyoshi ; et al.

September 9, 2004

Agent for treatment of cerebral ischemic diseases

Abstract

A pharmaceutical composition for the treatment and/or prevention of cerebral ischemic diseases, which comprises two components, i.e. an astrocyte function-improving agent, preferably a compound represented by the formula (I): 1 (wherein R.sup.6 is hydroxy, etc., (1) n is 1, R.sup.11 is hydrogen and R.sup.5 is (alkyl of which one carbon atom is substituted by fluorine)--CH.sub.2-- or (2) n is 0 or 1, R.sup.11 is hydrogen, etc., and R.sup.5 is alkyl, etc.) and a thrombolytic agent, preferably tissue plasminogen activator, as active ingredients. The pharmaceutical composition of the present invention exhibits a synergistic therapeutic effect compared to independent administration of an astrocyte function-improving agent and a thrombolytic agent.

Inventors: **Honjo, Kaneyoshi;** (*Osaka, JP*) ; **Tateishi, Narito;** (*Osaka, JP*) ; **Katsube, Nobuo;** (*Osaka, JP*)

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Serial No.: **483629**

Series Code: **10**

Filed: **January 14, 2004**

PCT Filed: **July 16, 2002**

PCT NO: **PCT/JP02/07212**

U.S. Current Class: **514/210.01; 514/217.12; 514/237.5;**
514/252.12; 514/317; 514/374; 514/408;
514/561

U.S. Class at Publication: **514/210.01; 514/217.12; 514/317; 514/408;**
514/561; 514/237.5; 514/252.12; 514/374

Intern'l Class: **A61K 031/397; A61K 031/55; A61K**

123
123

Foreign Application Data

Date	Code	Application Number
Jul 18, 2001	JP	2001-217755

Claims

1. A pharmaceutical composition for the treatment and/or prevention of cerebral ischemic diseases, which comprises an astrocyte function-improving agent and a thrombolytic agent as active ingredients.
2. The pharmaceutical composition for the treatment and/or prevention of cerebral ischemic diseases as claimed in claim 1, wherein the astrocyte function-improving agent is a compound represented by the formula (I):

$$\text{wherein R.sup.6 is hydroxy, C1-4 alkoxy, C1-4 alkoxy substituted by one phenyl group, or NR.sup.9R.sup.10 in which R.sup.9 and R.sup.10 are independently (i) hydrogen, (ii) C1-4 alkyl, (iii) phenyl, (iv) phenyl substituted by C1-4 alkoxy or carboxy (v) 4- to 7-membered heterocycle comprising one nitrogen atom, (vi) C1-4 alkyl substituted by (a) phenyl, (b) phenyl substituted by C1-4 alkoxy or carboxyl or (c) 4- to 7-membered heterocycle comprising one nitrogen atom, (vii) 4- to 7-membered heterocycle comprising one or two nitrogen atoms or 4- to 7-membered heterocycle comprising one nitrogen atom and one oxygen atom, when taken together with the nitrogen atom bonded to R.sup.9 and R.sup.10, or (viii) amino acid residue, when taken together with the nitrogen atom bonded to R.sup.9 and R.sup.10; n, R.sup.11 and R.sup.5 are (1) n is 1; R.sup.11 is hydrogen; R.sup.5 is (C1-10 alkyl of which one carbon atom is substituted by one to three fluorine atoms)--CH.sub.2--, wherein R.sup.5 does not represent --(CH.sub.2).sub.5--, F--(CH.sub.2).sub.6--, F--(CH.sub.2).sub.7-- or F.sub.3C--(CH.sub.2).sub.2--, or (2) n is 0 or 1; R.sup.11 is hydrogen or chlorine; R.sup.5 is: C3-10 alkyl, C3-10 alkenyl, C2-10 alkoxy, C2-10 alkylthio, C3-7 cycloalkyl, phenyl, phenoxy, F--(CH.sub.2).sub.m-- (m is an integer of 5 to 7), F.sub.3C--(CH.sub.2).sub.2--, (C2-10 alkyl substituted by one or two chlorine atoms)--CH.sub.2--, (C1-5 alkyl substituted by one or two substituents selected from the group consisting of C1-4 alkoxy, C3-7 cycloalkyl, phenyl and phenoxy)--CH.sub.2--; or R.sup.5 and R.sup.11, taken together, are C3-10 alkylidene, or a non-toxic salt or hydrate thereof.$$
3. The pharmaceutical composition for the treatment and/or prevention of



US005989531A

United States Patent [19]
Schamper et al.

[11] **Patent Number:** **5,989,531**
 [45] **Date of Patent:** **Nov. 23, 1999**

[54] **ANTIPERSPIRANT FORMULATION FOR POROUS APPLICATOR**

[75] **Inventors:** **Thomas Schamper**, Cranbury;
Bhalchandra Moghe, White House
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 Kendall Park, all of N.J.

[73] **Assignee:** **Colgate-Palmolive Company**, New
 York, N.Y.

[21] **Appl. No.:** **09/191,897**

[22] **Filed:** **Nov. 13, 1998**

[51] **Int. Cl.⁶** **A61K 7/32; A61K 7/34;**
A61K 7/38; A61K 7/00

[52] **U.S. Cl.** **424/65; 424/66; 424/68;**
424/401

[58] **Field of Search** **424/401, 65, 66,**
424/68

[56] **References Cited**

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WO9800097	1/1998	WIPO
WO9800105	1/1998	WIPO

Primary Examiner—Shelley A. Dodson

Assistant Examiner—Marina Lamm

Attorney, Agent, or Firm—Rosemary M. Miano

[57] **ABSTRACT**

The invention comprises a liquid composition which provides a drier feel and reduced leakage when used with certain types of applicators, especially an applicator having a porous surface, which composition is made by combining an active phase and a silicone phase. The active phase is made by combining: (a) 10–70% of a selected glycol; (b) 0.1–10% of a nonionic emulsifier having an HLB greater than 8; (c) 0.01–30% of a cosmetically active ingredient; and (d) 0–20% of ethanol and/or isopropanol. The silicone phase is made by combining: (a) from 0.1–10% of a selected emulsifier; (b) 0–30% of a non-volatile silicone; (c) 0–30% of a volatile silicone; and (d) 0–25% of an organic emollient; provided that: (a) the silicone phase contains at least 10% silicone; (b) the ratio of silicone phase to active phase is in the range of 1:1 to 1:4; and (c) the composition is processed to maintain a viscosity in the range of 2,000–200,000 centipoise ("cps").

18 Claims, No Drawings

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cerebral ischemic diseases as claimed in claim 1 or 2, wherein the astrocyte function-improving agent is (R)-2-propyloctanoic acid, and a non-toxic salt or hydrate thereof.

4. The pharmaceutical composition for the treatment and/or prevention of cerebral ischemic diseases as claimed in any one of claims 1 to 3, wherein the thrombolytic agent is tissue plasminogen activator or urokinogen.

5. The pharmaceutical composition for the treatment and/or prevention of cerebral ischemic diseases as claimed in any one of claims 1 to 4, wherein the thrombolytic agent is tissue plasminogen activator.

6. The pharmaceutical composition for the treatment and/or prevention of cerebral ischemic diseases as claimed in any one of claims 1 to 5, wherein the cerebral ischemic disease is cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage or white matter disorders.

7. The pharmaceutical composition for the treatment and/or prevention of cerebral ischemic diseases as claimed in any one of claims 1 to 5, wherein the cerebral ischemic disease is cerebral infarction.

8. A pharmaceutical composition for the treatment and/or prevention of cerebral infarction, which comprises (R)-2-propyloctanoic acid or a non-toxic salt or hydrate thereof as an astrocyte function-improving agent and tissue plasminogen activator as a thrombolytic agent.

9. A method for treating cerebral ischemic diseases, which comprises simultaneously administering an astrocyte function-improving agent and a thrombolytic agent.

10. A method for treating cerebral ischemic diseases, which comprises administering an astrocyte function-improving agent after the administration of a thrombolytic agent.

Description

TECHNICAL FIELD

[0001] The present invention relates to a pharmaceutical composition for treating cerebral ischemic diseases. More particularly, the present invention relates to a pharmaceutical composition for the treatment and/or prevention of cerebral ischemic diseases, which comprises two components, i.e. an

INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/US 02/21016

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D493/14 A61P25/08

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D 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, PAJ, CHEM ABS 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 00 50020 A (MCELROY SUSAN L ;UNIV CINCINNATI (US)) 31 August 2000 (2000-08-31) cited in the application page 29, table 1 page 8, line 8 -page 8, line 16; claims 1-11 page 1, line 17 -page 1, line 24	1-32

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- *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
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- *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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

16 September 2002

Date of mailing of the international search report

26/09/2002

Name and mailing address of the ISA

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Authorized officer

Schmid, A

hemorrhage and white matter disorders, etc. The target disease which can be anticipated to be more sensitive is cerebral infarction as proved in the experiments mentioned below.

[0070] The present invention includes a method for treating cerebral ischemic diseases by simultaneous administration of an astrocyte function-improving agent and a thrombolytic agent, and also a method for treating cerebral ischemic diseases by administration of a thrombolytic agent, followed by administration of an astrocyte function-improving agent. Since the astrocyte function-improving agent is effective even quite a long time after the occurrence of ischemia and does not suppress thrombolytic activity of the thrombolytic agent, as is apparent from the experiments described hereafter, simultaneous administration is not necessarily required.

[0071] The compounds represented by the formula (I) according to the present invention are known per se, or can be prepared according to the methods as described in the specification of Japanese Patent Unexamined Publication No. H07-316092 (U.S. Pat. No. 6,201,021) or WO 00/48982.

[0072] The thrombolytic agents used in the present invention are known per se and, for example, t-PA and urobinogen are commercially available.

[0073] The compounds represented by the formula (I) of the present invention may be converted into the corresponding salts by the common method. Non-toxic and water-soluble salts are preferable. Suitable salts include, for example, salts of alkali metals (sodium, potassium, etc.), salts of alkaline earth metals (calcium, magnesium, etc.), ammonium salts, salts of pharmaceutically acceptable organic amines (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine, N-methyl-D-glucamine, etc.), among which sodium salt is particularly preferable.

[0074] The compounds represented by the formula (I) of the present invention may be converted into the corresponding acid addition salts by the common method. Non-toxic and water-soluble acid addition salts are preferable. Suitable acid addition salts include, for example, inorganic acid salts (hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, nitrate, etc.) and organic acid salts (acetate, lactate, tartrate, oxalate, fumarate, maleate, citrate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, isethionate, glucuronate, gluconate, etc.).

[0075] The compounds of the formula (I) or salts thereof according to the present invention may be converted into the hydrates by the known method.

TREATING DISORDERS BY APPLICATION OF INSULIN-LIKE GROWTH FACTORS AND ANALOGS

BACKGROUND OF THE INVENTION

This application is a continuation of application Ser. No. 07/958,903 filed on Oct. 7, 1992, now U.S. Pat. No. 5,652,214, which is a continuation in part of Lewis et al. U.S. Ser. No. 07/869,913, filed Apr. 15, 1992, now abandoned; which is in turn a continuation in part of Lewis et al. U.S. Ser. No. 534,139, filed on Jun. 5, 1990; which is in turn a continuation in part of Lewis et al. U.S. Ser. No. 361,595 filed on Jun. 5, 1989 now U.S. Pat. No. 5,093,317.

The present invention relates to therapeutic polypeptides useful, e.g., for the treatment of neurological and other disorders.

Insulin-like growth factors (IGFs) have been identified in various animal species as polypeptides that act to stimulate growth of cells in a variety of tissues (see Baxter et al., *Comp. Biochem. Physiol.* 91B:229-235 (1988); and Daughaday et al., *Endocrine Rev.* 10:68-91 (1989) for reviews), particularly during development (see D'Ercole, J. *Devel. Physiol.* 9:481-495 (1987) for review). The IGFs, each of which has a molecular weight of about 7,500 daltons, are chemically related to human proinsulin: i.e. they possess A and B domains that (1) are highly homologous to the corresponding domains of proinsulin, and (2) are connected by a smaller and unrelated C domain. A carboxyl-terminal extension, the D domain, is also present in IGFs but is not found in proinsulin.

Certain polypeptide fragments of the IGFs have proven to be useful as antigens to raise antibodies specific for each of the IGFs (see, e.g., Japanese Patent Application No. 59065058; Hintz and Liu, *J. Clin. Endocr. Metab.* 54:442-446 (1982); Hintz et al., *Horm. Metab. Res.* 20:344-347 (1988)). Using labelled IGF-specific antibodies as a probe, IGF-I and IGF-II (sometimes respectively termed "somatomedin C" and "somatomedin A") have been found in a variety of tissues, including the mammalian central nervous system (CNS); the presence in the CNS of mRNAs encoding these polypeptides suggests local synthesis in the CNS (see Baskin et al., *TINS* 11:107-111 (1988) for review). In addition, IGF-III (or "brain IGF"), a truncated form of IGF-I lacking the latter protein's three N-terminal amino acid residues, has been found in fetal and adult human brain (Sara et al., *Proc. Natl. Acad. Sci. USA* 83:4904-4907 (1986), as well as in colostrum (Francis et al., *Biochem. J.* 251:95-103 (1988)). Two different IGF receptors have been identified in the adult human CNS (Baskin et al., 1988, *supra*), including in the brain (Sara et al., *Neurosci. Lett.* 34:39-44 (1982)). In addition, European Patent No. 227,619 describes evidence for a third type of IGF receptor located in human fetal membranes. Complicating research in this area are (1) evidence that the insulin receptor of brain membranes recognizes not only insulin but also the IGFs; (2) the finding that one of the two types of adult IGF receptors exhibits some affinity for insulin as well as for both IGF-I and II, and (3) current uncertainty as to the physiological significance of binding of IGF-II to the second type of adult IGF receptor (Baskin et al., 1988, *supra*).

IGF-I and IGF-II appear to exert a stimulatory effect on development or proliferation of a wide range of susceptible cell types (see Daughaday et al., 1989, *supra*, for review). Treatment with the IGFs or with certain polypeptide fragments thereof has been variously suggested as a bone repair and replacement therapy (European Patent Application No.

289 314), as a means to counteract certain harmful side effects of carcinostatic drugs (Japanese Patent No. 63196524), and as a way to increase lactation and meat production in cattle and other farm animals (Larsen et al., U.S. Pat. No. 4,783,524). Each of the IGFs also appears to enhance the survival, proliferation and/or neurite outgrowth of cultured embryonic neurons (which, unlike mature neurons, have not yet lost their ability to undergo cell division) from various parts of the CNS (Aizenman et al., *Brain Res.* 406:32-42 (1987); Fellows et al., *Soc. Neurosci. Abstr.* 13:1615 (1987); Onifer et al., *Soc. Neurosci. Abstr.* 13:1615 (1987); European Patent No. 227,619 and from the peripheral nervous system (Bothwell, *J. Neurosci. Res.* 8:225-231 (1982); Recio-Pinto et al., *J. Neurosci.* 6:1211-1219 (1986)). In addition, the IGFs have been shown to affect the development of undifferentiated neural cells: human neuroblastoma tumor cells were shown to respond to added IGFs by extending neurites (Recio-Pinto and Ishii, *J. Neurosci. Res.* 19:312-320 (1988)) as well as by undergoing mitosis (Mattson et al., *J. Cell Biol.* 102:1949-54 (1986)). As the induction of the enzyme ornithine decarboxylase has been shown to correlate with the stimulation of mitotic activity of these cells, an assay for cell proliferation has been developed based upon measuring the level of activity of this enzyme (Mattson et al., 1986).

Developing forebrain cholinergic neurons (cultured rat septal neurons) are sensitive to a variety of growth factors in vitro. Addition of nerve growth factor (NGF) to the culture medium increases the number of cells positive for the expression of transmitter-specific enzymes (acetyl choline esterase (AChE) and choline acetyl transferase (ChAT)) (Hariikka and Hefti, *J. Neuroscience* 8:2967-2985 (1988)). Thyroid hormone also increases the level of ChAT in cultured septal neurons and thyroid hormone in combination with NGF results in a stimulation of ChAT activity much greater than the sum of the effects of individual addition of these two substances (Hayashi and Patel, *Dev. Brain Res.* 36:109-120 (1987)). IGF-I, IGF-II, and insulin also induce ChAT activity in cultured septal neurons (Knusel et al., *J. of Neuroscience* 10:558-570 (1990)). When NGF and insulin are both added to the culture medium the effect on ChAT activity is additive, but the effects of IGF-I or IGF-II in combination with insulin are not additive (Knusel et al., 1990, *supra*).

In vivo studies also support the hypothesis that the IGFs play a role in development and differentiation of the immature peripheral and central nervous systems (Sara et al., *J. Dev. Physiol.* 1:343-350 (1979); Philipps et al., *Pediatr. Res.* 23:298-305 (1988); Sara et al., *Prog. Brain Res.* 73:87-99 (1988)), although the physiological nature of this role remains uncertain. Once the neuronal cells of the CNS reach maturity, they do not undergo further cell division.

Neurotrophic factors other than the IGFs have been proposed as a potential means of enhancing neuronal survival, for example as a treatment for the neurodegenerative diseases amyotrophic lateral sclerosis (using skeletal muscle-derived proteins having apparent molecular weights in the 20,000-22,000 dalton and 16,000-18,000 dalton ranges: PCT Application No. PCT/US88/01393), and Alzheimer's disease (using phosphoethanolamine: PCT Application No. PCT/US88/01693). Sara et al., although finding a "significant elevation" in serum and cerebrospinal fluid somatomedin (IGF) levels in patients suffering from Alzheimer's disease compared to normal controls, nevertheless conclude:

Whether somatomedins play a casual (sic) role in the etiology of the dementia disorders of the Alzheimer

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[0083] When the compounds of the present invention are administered, they are used as solid compositions, liquid compositions or other compositions for oral administration, and as injections, external compositions or suppositories, etc. for parenteral administration.

[0084] The solid compositions for oral administration include tablets, pills, capsules, dispersible powders, granules, and the like. The oral compositions also include gargles which are to be stuck to oral cavity and sublingual tablets. The capsules include hard capsules and soft capsules.

[0085] In such solid compositions for oral use, one or more of the active compound(s) may be admixed solely or with diluents (such as lactose, mannitol, glucose, microcrystalline cellulose, starch, etc.), binders (such as hydroxypropyl cellulose, polyvinylpyrrolidone, magnesium aluminometasilicate, etc.), disintegrators (such as cellulose calcium glycolate, etc.), lubricants (such as magnesium stearate etc.), stabilizers, solubilizers (such as glutamic acid, aspartic acid, etc.), and then formulated into a preparation in a conventional manner. When necessary, such preparations may be coated with a coating agent such as sucrose, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate, etc.) or they may be coated with two or more coating layers. Furthermore, the solid compositions for oral use include capsules of absorbable materials like gelatin.

[0086] The liquid compositions for oral administration include pharmaceutically acceptable aqueous solutions, suspensions, emulsions, syrups, elixirs, and the like. In such compositions, one or more of the active compound(s) may be dissolved, suspended or emulsified in a commonly used diluent (such as purified water, ethanol or a mixture thereof, etc.). Besides such diluents, said compositions may also contain wetting agents, suspending agents, emulsifiers, sweetening agents, flavoring agents, perfumes, preservatives and buffers and the like.

[0087] Injections for parenteral administration include solutions, suspensions, emulsions, and solid injectable compositions which are dissolved or suspended in a solvent immediately before use. The injections are used by dissolving, suspending or emulsifying one or more of the active compounds in a diluent. Examples of said diluents are distilled water for injection, physiological saline, vegetable oil, alcohol (such as propylene glycol, polyethylene glycol, ethanol, etc.), and a combination thereof. Further, the injections may contain stabilizers, solubilizers (such as glutamic acid, aspartic acid, polysorbate 80 (registered trade mark), etc.), suspending agents, emulsifiers, soothing agents, buffers, preservatives, etc. The injections are sterilized in the final formulation step or prepared by sterile procedure. The

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cholinergic neurons of the brain or spinal cord of said mammal, said neurons being at risk of dying due to such disease, said method comprising administering to said mammal a therapeutically effective amount of insulin-like growth factor I.

4. A method of treating a mammal subjected to a head or spinal cord injury by enhancing the survival of non-mitotic neurons of the brain or spinal cord of said mammal, said neurons being at risk of dying due to such injury, said method comprising administering to said mammal a therapeutically effective amount of insulin-like growth factor I.

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5. The method of claim 4 wherein said neurons are cholinergic.

6. A method of treating a mammal subjected to a head or spinal cord injury by enhancing the survival of non-mitotic cholinergic neurons of the brain or spinal cord of said mammal, said neurons being at risk of dying due to such injury, said method comprising administering to said mammal a therapeutically effective amount of insulin-like growth factor I.

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injections may also be formulated into sterile solid preparations, for example, by freeze-drying, and may be used after sterilized or dissolved in sterile injectable water or other sterile diluent(s) immediately before use.

BEST MODE FOR CARRYING OUT THE INVENTION

[0088] The following Examples are provided to illustrate the present invention, but are not to be construed as limiting the invention.

EXAMPLE 1

Effects of the Present Invention in Thrombin-induced Focal Cerebral Ischemic Model

Experiment

[0089] 1) Preparation of ischemic model

[0090] Twenty male Wistar rats (8-weeks age) were used as one group. The rats were anesthetized with halothane, followed by incision and then subjected to carotid artery shunting. A polyethylene catheter containing thrombin (10 international units) was catheterized into the carotid artery, and 10 ml of blood was sucked and reserved in the catheter for 10 minutes. Then, thrombus formed in the catheter was infused into the carotid artery together with thrombin (J. Cereb. Blood Flow Metab., 17 123 (1997)).

[0091] The neurological symptoms of said rats were scored according to the method as described in Brain Res., 452, 323 (1988). The evaluation of score was carried out at 6 hours, 24 hours, 48 hours and 72 hours after infusion of thrombin, and the scores were accumulated. The survival period was determined by monitoring surviving or dead rats at intervals of one hour for the first 72 hours after the infusion of thrombin.

[0092] 2) Administration of agent

[0093] From forty minutes after thrombin infusion, t-PA (Activacin 100,000 international units, product of Kyowa Hakko Kogyo Co., Ltd.) was continuously administered in an amount of 33 μ L/min to the anesthetized rats for 15 minutes. (R)-2-propyloctanoic acid (hereinafter referred to as compound A) in an amount of 10 mg/mL/kg was administered through tail vein of the rats three times at 6 hours, 24 hours and 48 hours after the infusion of thrombin. A physiological saline solution was given to the single drug group and the control group in the same manner, respectively. * indicates that the result is significantly different from the control group (Log-

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(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8
- (B) TYPE: amino acid
- (C) STRANDEDNESS: Not Relevant
- (D) TOPOLOGY: Not Relevant

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Leu Glu Thr Tyr Cys Ala Thr Pro
1 5

(2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8
- (B) TYPE: amino acid
- (C) STRANDEDNESS: Not Relevant
- (D) TOPOLOGY: Not Relevant

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Cys Ala Thr Pro Ala Lys Ser Glu
1 5

(2) INFORMATION FOR SEQ ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8
- (B) TYPE: amino acid
- (C) STRANDEDNESS: Not Relevant
- (D) TOPOLOGY: Not Relevant

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Tyr Cys Ala Pro Ala Lys Ser Glu
1 5

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5
- (B) TYPE: amino acid
- (C) STRANDEDNESS: Not Relevant
- (D) TOPOLOGY: Not Relevant

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

Tyr Cys Ala Pro Ala
1 5

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 6
- (B) TYPE: amino acid
- (C) STRANDEDNESS: Not Relevant
- (D) TOPOLOGY: Not Relevant

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

Thr Tyr Cys Ala Pro Ala
1 5

What is claimed is:

1. A method of treating a mammal subjected to a neurological disease by enhancing the survival of non-mitotic neurons of the brain or spinal cord of said mammal, said neurons being at risk of dying due to such disease, said

method comprising administering to said mammal a therapeutically effective amount of insulin-like growth factor I.

2. The method of claim 1 wherein said neurons are cholinergic.

3. A method of treating a mammal subjected to a neurological disease by enhancing the survival of non-mitotic,

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(19) 日本国特許庁 (J P)

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(22) 出願日	平成6年(1994)5月30日	(72) 発明者	矢澤 一良 神奈川県相模原市鶴野森571
(31) 優先権主張番号	特願平5-201967	(72) 発明者	藤原 道弘 福岡県福岡市中央区鳥飼1丁目7-1
(32) 優先日	平5(1993)7月23日		
(33) 優先権主張国	日本 (J P)		

(54) 【発明の名称】 抗痴呆薬

(57) 【要約】

【目的】 本発明は、脳虚血により生じる脳機能障害、例えば、脳の遅発性神経細胞壊死を抑制し、また空間認知障害を速やかに改善する副作用のない抗痴呆薬を提供することにある。

【構成】 ドコサヘキサニン酸を有効成分として含有することを特徴とする抗痴呆薬。

(11)Publication number : 07-082146
(43)Date of publication of application : 28.03.1995

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C07C 57/03

(21)Application number : 06-115750 (71)Applicant : SAGAMI CHEM RES
CENTER
(22)Date of filing : 30.05.1994 (72)Inventor : YAZAWA
KAZUYOSHI
FUJIWARA
MICHIIRO

(30)Priority
Priority number 05201967 Priority date 23.07.1993 Priority country JP
: : :

(54) AGENT FOR ALLEVIATING DEMENTIA

(57)Abstract:

PURPOSE: To obtain an agent for alleviating dementia free from side effects, suppressing cerebral function disorder caused by brain ischemia, such as slow neurocyte necrosis of brain, rapidly improving space perception disorder.

CONSTITUTION: This agent for alleviating dementia comprises docosahexaenoic acid which is an unsaturated aliphatic acid much contained in an excitable member of brain and retina and is known to have inhibitory action on arachidonic acid cascade as an active ingredient. The agent for alleviating dementia is orally or parenterally administered. A solid preparation such as powder, granule or tablet and a liquid preparation such as syrup or elixir may be cited as the oral medicine and injection as the parenteral medicine.

JP 7082146 (A)

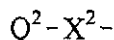
PURPOSE: To obtain an agent for alleviating dementia free from side effects, suppressing cerebral function disorder caused by brain ischemia, such as slow neurocyte necrosis of brain, rapidly improving space perception disorder. CONSTITUTION: This agent for alleviating dementia comprises docosahexaenoic acid which is an unsaturated aliphatic acid much contained in an excitable member of brain and retina and is known to have inhibitory

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C≡C wherein R⁵ is hydrogen or (1-6C)alkyl or, when the inserted group is N(R⁵), R⁵ may also be

5 (2-6C)alkanoyl,

and wherein any CH₂=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl or from

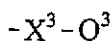
10 a group of the formula :



wherein X² is a direct bond or is selected from CO and N(R⁶)CO, wherein R⁶ is hydrogen or (1-6C)alkyl, and Q² is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

15 and wherein any CH, CH₂ or CH₃ group within a R^1 substituent optionally bears on each said CH, CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,

20 N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino or from a group of the formula :



25 wherein X³ is a direct bond or is selected from O, S, SO, SO₂, N(R⁷), CO, CH(OR⁷), CON(R⁷), N(R⁷)CO, SO₂N(R⁷), N(R⁷)SO₂, C(R⁷)₂O, C(R⁷)₂S and N(R⁷)C(R⁷)₂, wherein R⁷ is hydrogen or (1-6C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

30 and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl,

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action on arachidonic acid cascade as an active ingredient. The agent for alleviating dementia is orally or parenterally administered. A solid preparation such as powder, granule or tablet and a liquid preparation such as syrup or elixir may be cited as the oral medicine and injection as the parenteral medicine.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention controls the cerebral dysfunction by brain ischemia, and it is related with the antidementia drug characterized by containing docosahexaenoic acid as an active principle in more detail about the antidementia drug which improves the shape of dementia accompanying it.

[0002]

[Description of the Prior Art] Also medically, development of the drugs to dementia has been a technical problem more important social still with aging of population in recent years. Although the drugs of the conventional versatility have been developed as an antidementia drug, the expectation for the more outstanding antidementia drug is great. Docosahexaenoic acid is unsaturated fatty acid mostly contained in the excitable membrane of a brain or the retina, and having the operation which checks an arachidonate cascade is known. Although it is thought that the metabolite of this arachidonate cascade is also participating in the cell damage by brain ischemia, it has not been clarified yet. It is known that docosahexaenoic acid has some useful physiological functions other than the above, For example, a cerebral function improvement constituent, a learning ability enhancement agent, a mneme enhancement agent, dementia preventive, Patent application which has a dementia treating agent or a cerebral function improvement effect, such as functional food (JP,2-49723,A), cholinergic drugs (JP,1-279830,A), and an antithrombotic therapy agent (JP,57-35512,A), is made. In these, JP,2-49723,A only clarifies enhancement of the learning ability by docosahexaenoic acid, or mneme, and depressant action of platelet aggregation. It is related with the amount of delivery to the brain of the physostigmine which is a cholinesterase inhibitor increasing JP,1-279830,A by docosahexaenoic acid.

[0003]

[Problem(s) to be Solved by the Invention] There is this invention in providing an antidementia drug without the side effects that control the cerebral dysfunction produced by brain ischemia, for example, a cerebral tardive neuronal necrosis, and a spatial perception obstacle is improved promptly.

[0004]

[Means for Solving the Problem] This invention persons about a spatial perception obstacle induced by transient forebrain ischemia of a rat. As a

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result of repeating examination wholeheartedly using Pulsinelli & Brierly's and others 4 blood-vessel ligation, chronic administration of docosahexaenoic acid completed this invention based on the new knowledge of preventing a hippocampus, a line object, especially a cell damage by hypoxia of a hippocampus. That is, an antidementia drug of this invention is applied to symptoms accompanied to dementia produced by brain ischemia, multiinfarct dementia, cerebrovascular dementia, dementia by cerebral dysfunction, and such dementia.

[0005]Docosahexaenoic acid used for this invention means the salt, ester, glyceride, phospholipid, the Kolin compound, an ascorbic acid compound, amino acid compounds including free acid, etc. Not less than 10% of thing has a good rate that docosahexaenoic acid in total fatty acid occupies preferably as an oil containing this docosahexaenoic acid (as free acid). If an example of such a thing is raised, fats and oils of marine-products origin extracted from fish oil of eye socket fat origin of large-sized marine fish, such as fish oil extracted from blue-skinned fish, such as a sardine, a mackerel, a horse mackerel, a salmon, and a Pacific saury, a tuna, and a bonito, fats and oils from microorganism, krill oil, and 'Tara and cuttlefish liver, etc. will be mentioned as a desirable example.

[0006]An oral target or a parenteral target can be medicated with an antidementia drug of this invention for a therapy. It can be considered as liquid preparations, such as solid preparations, such as an orally administered drug, powder medicine, a granule, a capsule, and a tablet, or syrups, and elixirs. It can be considered as injections as a parenteral administration agent. These pharmaceutical preparation is manufactured in accordance with a conventional method by adding a manufacture auxiliary agent admitted to an active ingredient pharmacologically and in galenical pharmacy. It is also possible to consider it as durability pharmaceutical preparation by publicly known art. When using the manufacture auxiliary agent concerned, loadings of docosahexaenoic acid (as free acid) in an antidementia drug of this invention are usually 50 to 100 % of the weight preferably ten to 100% of the weight.

[0007]As the above-mentioned manufacture auxiliary agent, it is used from a suitable ingredient for pharmaceutical preparation according to a route of administration of internal application pharmaceutical preparation (oral agent), lumbar for injection (injections), mucosal administration agents (buccal, troches, suppositories, etc.), external preparations (ointment, patches, etc.), etc.

[0008]For example, if it is in an oral agent and a mucosal administration agent, an excipient (example: -- starch, milk sugar, crystalline cellulose, milk sugar calcium, and magnesium aluminometasilicate.) A silicic acid anhydride, disintegrator (example: carboxymethyl-cellulose, carboxymethyl-cellulose calcium), Ingredients for pharmaceutical preparation, such as lubricant (example: stearic acid a mug NESHIMU, talc), a coating agent (example:

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hydroxyethyl cellulose, white soft sugar, hydroxypropylcellulose, polyvinyl pyrrolidone), and corrigent, are used. a granule -- manufacturing -- a wet type - or -- carrying out dry granulation -- a tablet -- manufacturing -- these powder medicine and granules -- as it is -- or what is necessary is to add lubricant, such as magnesium stearate and talc, and just to tablet These granulation or tablets can be covered with enteric bases, such as hydroxypropylmethylcellulose phthalate, methacrylic acid, and a methyl methacrylate copolymer, can be covered with an enteric coated preparation or ethyl cellulose, a carnauba wax, hydrogenated oil, etc., and can also be considered as durability pharmaceutical preparation. After being filled up with powder medicine or a granule for manufacturing a capsule at a hard filled capsule or dissolving an active ingredient in glycerin, a polyethylene glycol, sesame oil, olive oil, etc., it can cover with gelatin film and can be considered as an elastic capsule. Liquid preparations for internal use to manufacture An active ingredient, white soft sugar, sorbitol, It is good also as an emulsion or suspension to consider it as elixirs or add [sweetening agents, such as glycerin, are dissolved in water and add transparent syrups and also oil refinement, ethanol, etc.,] gum arabic, tragacanth, polysorbate 80, carboxymethylcellulose sodium, etc. Corrigent, colorant, a preservative, etc. may be added to such liquid preparations by request.

[0009]a resolvent thru/or a solubilizing agent (example: -- distilled water for injection.) which can constitute aqueous injections if it is in injections Ingredients for pharmaceutical preparation, such as a physiological saline, propylene glycol, a suspending agent (example: surface-active agents, such as polysorbate 80), a pH adjuster (example: organic acid or its metal salt), and stabilizer, are used. An active ingredient if needed to manufacture injections Chloride, sodium hydroxide, PH adjusters, such as an emulsion, sodium lactate, phosphoric acid 1 hydrogen sodium, and a sodium dihydrogenphosphate, It dissolves in distilled water for injection with isotonicizing agents, such as sodium chloride and grape sugar, Whether sterile filtration is carried out and an ampul is filled up Mannitol, dextrin, adding cyclodextrin, gelatin, etc. and freeze-drying under a vacuum -- business -- the time -- a dissolved type -- good also as injections -- it can carry out, and you can add lecithin, polysorbate 80, polyoxyethylene hydrogenated castor oil, etc. to an active ingredient, and make it able to emulsify underwater, and it can also be considered as an emulsion for injection.

[0010]If it is furthermore in external preparations, ingredients for pharmaceutical preparation, such as a water thru/or oily resolvent thru/or a solubilizing agent (example: alcohol and fatty acid ester), a binder (example: a carboxyvinyl polymer, polysaccharide), and an emulsifier (example: surface-active agent), are used. A rectum administration agent to manufacture Tori of an active ingredient and cacao oil, and fatty acid, JI, and monoglyceride, What is necessary is just to cover with gelatin film, after humidifying and fusing bases for suppositories, such as a polyethylene glycol, pouring into a mold,

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and cooling or dissolving an active ingredient in a polyethylene glycol, soybean oil, etc. An active ingredient to manufacture skin external preparations White vaseline, yellow bees wax, a liquid paraffin, After in addition to a polyethylene glycol etc. humidifying and kneading, considering it as an ointment or kneading with binders, such as rosin and an acrylic-acid-alkyl-ester polymer, if necessary, it spreads to nonwoven fabrics, such as polyethylene, and is considered as a tape. For manufacturing inhalations, an active ingredient is dissolved or distributed to propellants, such as chlorofluocarbon, a resisting pressure container is filled up, and it carries out with aerosols.

[0011]In addition, an antimentia drug of this invention which has the above-mentioned composition can be manufactured also by a method which added a publicly known manufacturing method, for example, a method given in 10th edition of Pharmacopoeia of Japan general rules for preparations, thru/or a suitable improvement. Hereafter, an example explains this invention in detail.

[0012]

[Example]

The elevated type 8 direction radial maze was used for training for spatial perception acquisition at the example of examination 1 examination using the 7-week old Wistar system male rat (280 to 300 g weight). The rat was put into the central platform which closed the entrance to eight directions, and it measured by opening an entrance wide. All the times of finishing taking or 10 minutes after a measurement start passing were considered for the food which has a rat at the tip of eight directions as the end of trial, and one trial was performed on the 1st. The total when the first number to visit in the eight directions was visited twice or more in the direction visited the number of right selections and once was made into the number of false drops. What in authorization of spatial perception acquisition the number of right selections showed seven or more continuously, and the number of false drops showed three trial of the last of training of a rat for one or less, Or in 5 trial before the last training, the number of right selections showed seven or more, in the number of false drops, the number of right selections should show four or less by 4 trial example and the last trial, and the number of false drops should show one or less or more by seven. In accordance with the method of Pulsinelli & Brierly and others, electrocauterization cutting of the vertebral artery was carried out at bilaterality by making this rat into a spatial perception acquisition rat. The rat ligated the both-sides common carotid artery for 10 minutes after checking having recovered the influence of a vertebral-artery cautery operation using the clip for ligation. The rat in which a righting reflex did not disappear was excepted from the experiment after ligation. The experiment of regenerative trial is one-day trial [1] ***** during seven days from 24 hours after blood-flow resumption. Docosahexaenoic acid under examination It carries out in kg and 1mg /per weight of a rat, and the dose of [ethyl ester and 97% of purity] is docosahexaenoic acid. [Ethyl ester and 97%

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R

of purity] were diluted and used just before use with purified water. Before common-carotid-artery ligation, the solution which gave a diet and carried out dilution adjustment 1 to 2 hours afterward was administered orally for 21 days and for after-ligation seven days, and they administered it orally 1 hour before common-carotid-artery ligation only on the ligation day. The test result for after-ligation five days of the number of false drops and the number of right selections is shown in Table 1 (drawing 1) and Table 2 (drawing 2). The average value of $n=5$ showed the test result.

[0013]

[Table 1]

	血流再開後（日）の誤選択数				
	1	2	3	4	5
虚血コントロール	7.0	6.2	4.1	3.0	1.6
DHA 1mg/kg	5.2	6.0	2.5	2.5	1.5

訓練最後の3試行の誤選択数 0.4

[0014]

[Table 2]

	血流再開後（日）の正選択数				
	1	2	3	4	5
虚血コントロール	5.8	6.3	6.7	6.8	7.2
DHA 1mg/kg	6.8	6.7	6.9	7.4	7.7

訓練最後の3試行の正選択数 7.8

[0015] Although a significant difference with contrast was not accepted about a false drop by 21 1 mg/kg administration in docosahexaenoic acid before common-carotid-artery ligation, the tendency of the improvement was accepted in right selection.

[0016] Example of examination 2 docosahexaenoic acid The dose of [ethyl ester and 97% of purity] was made into 10 mg/kg per weight of a rat, and also it carried out like the example 1 of an examination. The result was shown in drawing 3 and drawing 4. The tendency of the improvement was accepted in 21 docosahexaenoic acid 10 mg/kg administration.

[0017] Example of examination 3 docosahexaenoic acid The dose of [ethyl ester and 97% of purity] was made into 100 mg/kg per weight of a rat, and also it carried out like the example 1 of an examination. The result was shown in drawing 5 and drawing 6. Docosahexaenoic acid Although the improvement effect was not accepted to the spatial perception obstacle 24 hours after the ischemia by 21 100 mg/kg administration in [ethyl ester and 97% of purity], also in the false drop, the recovery process of the subsequent spatial perception obstacle was intentionally early also in right selection.

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[0018]Example of examination 4 docosahexaenoic acid The dose of [ethyl ester and 97% of purity] was made into 200 mg/kg per weight of a rat, and also it carried out like the example 1 of an examination. The result was shown in drawing 7 and drawing 8. Docosahexaenoic acidAlso in [although the improvement effect was not accepted / in [ethyl ester and 97% of purity] / to the spatial perception obstacle 24 hours after the ischemia like the case of 21 100 mg/kg administration by 21 200 mg/kg administration | right selection the recovery process of a subsequent spatial perception obstacle, Also in the false drop, it was intentionally early.

[0019]Although change of the lactate dehydrogenase (LDH) in the inside of example of examination 5 blood serum does not necessarily reflect a certain specific disease, it is supposed that the rise of this value can be *(ed) if diseases, such as acute myocardial infarction and cerebral thrombosis, are expected, for example.

Generally it becomes a rule of thumb of the cell damage in an anoxia state. For the examination, oxygen pressure low Shimonaka and the both-sides common carotid artery of the rat were ligated using the clip for ligation using the 7-week old Wistar system male rat (280 to 300 g weight), and the LDH activity of the hippocampus for 0 to 30 minutes, for 30 to 60 minutes, and for 0 to 30 minutes after reperfusion was measured. Docosahexaenoic acid under examination It carries out in kg and 100mg /per weight of a rat, and the dose of [ethyl ester and 97% of purity] is docosahexaenoic acid. [Ethyl ester and 97% of purity] were diluted and used just before use with purified water. Before common-carotid-artery ligation, the solution which gave between-meal snack food on the 21st, and carried out dilution adjustment 1 to 2 hours afterward was administered orally, and it administered orally 1 hour before common-carotid-artery ligation only on the ligation day. Measurement of LDH was performed using the LDH mono- test (the Wako Pure Chem make, product number 1087 592) based on the recommendation of the German clinical chemistry meeting (GSCC), and LDH activity set LDH activity for 10 minutes in front of hypoxia to 100, and showed it to drawing 9.

Docosahexaenoic acid before common-carotid-artery ligation in 21 100 mg/kg administration. Although there was no difference in hippocampus LDH activity [in after-ligation 0 to 30 minutes / between / comparison and contrast], 0 to 30 minutes [from after reperfusion] afterward, the fall of significant hippocampus LDH activity was seen by the DHA administration group [in after-ligation 30 to 60 minutes] as compared with the control group. This shows that it has an improving action which shows that DHA has controlled intentionally the cell damage of the hippocampus by ligation by hypoxia pressing down, and brings recovery of a spatial perception obstacle forward.

[0020]

CLAIMS

12/3
RDP

[Claim(s)]

[Claim 1]An antidementia drug containing docosahexaenoic acid as an active principle.

[Claim 2]The antidementia drug according to claim 1 whose antidementia drugs are cerebral dysfunction prevention and improvement medicine.

[Claim 3]The antidementia drug according to claim 2 which are cerebral dysfunction prevention, cerebral dysfunction prevention according [improvement medicine] to brain ischemia, and improvement medicine.

[Claim 4]The antidementia drug according to claim 2 cerebral dysfunction prevention and whose improvement medicine are cerebral tardive neuronal-necrosis prevention and improvement medicine.

[Claim 5]The antidementia drug according to claim 4 which is cerebral tardive neuronal-necrosis prevention, tardive neuronal-necrosis prevention according [improvement medicine] to brain ischemia, and improvement medicine.

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado:
✓ **JUAN PABLO CADENA SARMIENTO**

ASUNTO:	Radicación No.	06 03 2018
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	10864
	Folios	

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados:

Descripción:	Folios 52 a 85 modificada en fase Internacional.
Reivindicaciones:	Folios 86 a 88 modificada en fase Internacional.
Prioridad:	JP 2003-345125 (2003-10-03)

2. Objeto de la Invención

Titulo de la invención: "Preparación de infusión que comprende ácido (2R)-2-propiloctanoico como un ingrediente activo"

Problema Técnico Planteado: "Necesidad de una infusión para uso intravenoso en el tratamiento de enfermedades neurodegenerativas"

Solución: "Proporcionar una composición farmacéutica que comprende ácido (2R)-2- propiloctanoico o una sal del mismo en una concentración alta, resistente a fluctuaciones de pH y un proceso de producción de la misma."

IPC: A61K 31/20, A61K 9/08, A61K 47/02

3. Excepciones a la Patentabilidad (Art 20 D 486 literal d)

Las reivindicaciones 15 y 13 no son patentables pues se refieren a un método de tratamiento

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

La reivindicación 16 no es materia patentable por que se refiere a un uso de los compuestos de la solicitud.

5. Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Claridad:

La reivindicación 4 presenta la relación de la proporción de equivalentes químicos entre el ácido y el ión metálico, sin definir claramente los rangos para los mismos.

La reivindicación 9 se refiere a un recipiente que está caracterizado por contener la preparación de la invención y adicionalmente define como características esenciales el volumen que dicho recipiente contiene de solución, pero no agrega características esenciales a la composición, ni caracteriza el empaque por condiciones físicas, químicas o del diseño del mismo.

Concisión:

La reivindicación 1 hace referencia a una preparación para infusión caracterizada por que contiene ácido propiloctanoico y un ión metálico, para este último el grupo abarca una cantidad amplia de opciones que incluyen algunas que no están soportadas por los ejemplos.

La reivindicación 3, adiciona materiales a la preparación nombrando 4 grupos de moléculas: i. electrolitos, ii. sacáridos, iii. vitaminas y iv. aminoácidos de proteína. Respecto a los grupos, ninguno se encuentra delimitado, resultando en la adición de 4 grupos ilimitados a una preparación que contiene dos componentes, donde uno de ellos tampoco ha sido definido, haciendo que el alcance de esta reivindicación sea muy amplio, cobijando incluso preparaciones que no han sido ensayadas por el solicitante.

La reivindicación 14 presenta rangos de pH de la siguiente manera: "pH de aproximadamente 8,4 a aproximadamente 9.0", de lo cual se anota que este no define concisamente dicho rango.

6. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación 2003-10-03 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO03007992	Remedies for brain ischemic diseases	30.01.2003
D2	JP 07 082146	Agent for alleviating dementia	28.03.1995

7. Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

1. Respecto a la solicitud en estudio

La reivindicación 1 dice: "Una preparación de infusión que comprende ácido (2R)-2-propionolactónico o una sal del mismo y un ion metálico básico."

La reivindicación 14 dice: "Un proceso para producir una preparación de infusión que comprende ácido 2R-2-propiloctanoico o una sal del mismo y un ión metálico básico, el cual consiste en disolver el ácido o la sal del mismo, una o al menos

dos sales seleccionadas de una sal metálica de ácido fosfórico, una sal metálica de ácido carbónico, una sal metálica de ácido sulfuroso, una sal metálica de ácido carbónico, una sal metálica de ácido sulfuroso, una sal metálica de ácido orgánico sulfónico y una sal metálica de ácido orgánico C2-C6 y opcionalmente hidróxido metálico en un medio acuoso para de este modo preparar una disolución que comprende adicionalmente de aproximadamente 2.5 a aproximadamente 100 mg/ml de ácido 2R 2-propiloctanoico o una sal del mismo y que tiene un pH de aproximadamente 8,4 a aproximadamente 9,0; diluyendo la solución preparada con uno o al menos dos ingredientes seleccionados de i.) Electrolitos, ii.) Sacáridos, iii.) Vitaminas y iv.) Aminoácidos de proteína para de este modo ajustar la concentración de ácido 2R 2 propiloctanoico o una sal del mismo en la disolución de aproximadamente 0.1 a aproximadamente 20 mg/ml y cargar un recipiente para infusión con la disolución diluida."

2. Estado de la Técnica más cercano:

D1 enseña composiciones para tratar la isquemia cerebral (Folios 122 y 123), específicamente algunas que contienen ácido (2R)-2- propiloctanoico, sales o hidratos no tóxicos del mismo (folios 123 y 124, reivindicaciones 3 y 8).

D1 revela que las composiciones pueden administrarse por vía parenteral (folio 126, párrafo 0083) y enseña el proceso para su preparación (folio 126, párrafo 0087) donde incluye soluciones reguladoras de pH, estabilizadores, agentes suspensores, la inclusión de solución salina para uso fisiológico

D1 enseña que las sales derivadas del compuesto de fórmula i pueden ser sales de metales alcalinos (sodio, potasio, etcétera) o sales derivadas de lisina, arginina y N-methyl-D-glucamina entre otras (folio 125, párrafo 73 y 74).

La solicitud se diferencia de D1 en que la preparación contiene un ión metálico básico que proviene de una cierta cantidad de sal metálica de ácido débil como fosfato trisódico o carbonato sódico (folio 54, líneas 5-20).

El Efecto Técnico que logra la inclusión de un ión metálico básico es la obtención de una infusión para administración intravenosa que contiene una alta cantidad de ácido (2R)-2- propiloctanoico resistente al enturbiamiento de la solución debido a fluctuaciones del pH.

El Problema Técnico Objetivo de esta solicitud es proveer infusiones para administración intravenosa que contengan una alta cantidad de ácido (2R)-2-propiloctanoico resistente al enturbiamiento de la solución debido a fluctuaciones del pH.

D2 revela composiciones para tratar la demencia y enseña un proceso de elaboración donde sugiere: la disolución del activo, el uso agentes reguladores del pH, (lactato de sodio, fosfato mono sódico, o di sódico), hidróxido de sodio (folio 132, párrafo 9), y sacáridos como el manitol.

3. Así las cosas, la persona versada estaría motivada a añadir un ión metálico a la composición revelada por D1 para llegar a la composición de la reivindicación 1.

En relación al proceso de preparación de la infusión de la reivindicación 1, D1 y D2 sugerían a la persona versada a preparar la composición por disolución del activo, y por la adición de reguladores de pH, sales de ácidos orgánicos, sacáridos y la inclusión de aminoácidos de proteína.

Las demás reivindicaciones no presentan materia que la hagan inventiva.

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4. Se concluye que el objeto de la invención carece de nivel inventivo.

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO03007992	1, 2, 3, 4, 5, 8, 11, 12	Nivel inventivo
D2	JP 07 082146	1, 3, 5, 6, 14	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____ 2009

OK

CONCEPTO TECNICO NUMERO: 2603	EXAMINADOR TÉCNICO Código: 202092
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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 14541

Por la cual se niega una patente de invención

Rad. PCT/06-32018

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 3, numeral 30 del decreto 3523 de 2009, y

CONSIDERANDO:

PRIMERO: Que la solicitud de patente de invención titulada "PREPARACION DE INFUSION QUE COMPRENDE ACIDO (2R)-2-PROPILOCTANOICO COMO UN INGREDIENTE ACTIVO", que corresponde a la solicitud internacional PCT/JP2004/014896 de fecha 01 de octubre del 2004, fue radicada en esta Superintendencia el 31 de marzo del 2006 bajo el número 06-032018 -00000-0000, para que se dé comienzo a la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un período de treinta días adicionales.(...) Si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente"*.

CUARTO: Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 121 a 140 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del solicitante, por lo cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 14547

Por la cual se niega una patente de invención

Rad. PCT/06-32018

RESUELVE:

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "PREPARACION DE INFUSION QUE COMPRENDE ACIDO (2R)-2-PROPILOCTANOICO COMO UN INGREDIENTE ACTIVO", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Juan Pablo Cadena Sarmiento, en su calidad de apoderado de ONO PHARMACEUTICAL CO LTD., o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 16 MAR 2010

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


GUSTAVO VALBUENA QUIÑONES

Doctor
JUAN PABLO CADENA SARMIENTO
Calle 70 A No. 4-41
Bogotá D.C.

M

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

EL SECRETARIO GENERAL

Certifica que el(la) señor(a) JUAN PABLO CADENA
SARMIENTO

identificado con CC No. 80410337.0

se notificó de la resolución 14547 de fecha 16/03/2010

por INTERNET el 24/03/2010