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E. S. D.

REF: **Expediente 07-008-212**

TÍTULO SOLICITADO: **UNA COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE GABAPENTINA.**

PUBLICACIÓN: **Gaceta 587 de 18 de enero de 2008, Nº de publicación 1395.**

PRIORIDAD: **IT MI2004A001447 de 20/07/2004**

SOLICITANTE: **ZAMBON GROUP S.P.A.**

APODERADO: **DILIA MARÍA RODRÍGUEZ D'ALEMAN**

TRÁMITE: **SUSTENTACION DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**,dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 27 de Septiembre de 2007, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

- La publicación internacional WO 2004/014356 publicada el 19 de febrero de 2004 y titulada "SOLID COMPOSITIONS COMPRISING GABAPENTIN HAVING IMPROVED STABILITY" revela la inclusión de sales de ácidos débiles en formulaciones que contienen gabapentina, las cuales previenen de manera significativa la formación del derivado lactámico -impureza- de gabapentina en formulaciones sólidas para administración oral tipo tableta. Si bien es cierto la solicitud colombiana en trámite hace referencia en su capítulo reivindicatorio a la obtención de cápsulas, no lo es menos que las tabletas de la anterioridad en mención anticipan claramente la solución al problema técnico que propone la solicitud en curso, circunstancia que afecta notoriamente el nivel inventivo de ésta.

  Es importante resaltar que la anterioridad reseñada reconoce y aplica la misma estrategia que ahora emplea el solicitante: estabilizar la gabapentina en una formulación sólida de administración oral a través de sales de ácidos débiles, entre ellos el fosfato tribásico de sodio, siendo este muy similar en comportamiento al fosfato tribásico cálcico de la solicitud colombiana en trámite.

- La publicación internacional WO 02/26263 publicada el 04 de abril de 2003 y titulada "STABLE SOLID DOSAGE FORMS OF AMINOACIDS AND PROCESSES FOR PRODUCING SAME" revela que la presencia de cierta cantidad de aniones en el contexto donde se encuentra la pregabalina, favorece la estabilidad de la misma y previene la formación del derivado lactámico, y que dicha estrategia puede utilizarse en la formulación de composiciones sólidas para administración oral, entre las cuales se mencionan explícitamente distintos tipos de cápsulas. Esto permite desvirtuar sin más el argumento que fundamenta el nivel inventivo de la solicitud colombiana en trámite, ya que como se aprecia en su capítulo reivindicatorio, la utilidad de agentes del tipo sales de calcio de ácido débil puede verse como la aplicación de estos compuestos como donadores de éstas pequeñas cantidades de aniones estabilizadores.

- Finalmente, puede demostrase también, que independientemente de dicha estrategia, el uso y la formulación de gabapentina[1] (que originalmente fue desarrollada para el tratamiento de epilepsia y que actualmente es ampliamente utilizada para aliviar el dolor de origen neuropático), se viene formulando en forma de cápsulas como un medicamento seguro y aprobado por la FDA con bastante anterioridad.

II. COMPLEMENTO DE INFORMACIÓN.

Por si no fuesen suficientes los argumentos dados en la oposición presentada anteriormente, la publicación internacional WO 99/59573 publicada el 25 de Noviembre de 1999 y titulada "STABILIZED PHARMACEUTICAL PREPARATIONS OF GAMMA-AMINOBUTYRIC ACID DERIVATIVES AND PROCESS FOR PREPARING THE SAME" proporciona preparaciones farmacéuticas de un derivado de ácido 4-amino-3-sustituido-butanóico el cual puede ser obtenido por incorporación de un aminoácido como un estabilizante.

Más adelante revela:

> This invention relates to a stabilized solid or liquid pharmaceutical preparation comprising a 4-amino-3-substituted-butanoic acid derivative and a process for the preparation of the same.
>
> More particularly, the invention is concerned with a stabilized solid pharmaceutical preparation of a 4-amino-3-substituted-butanoic acid derivative, including gabapentin, pregabalin or baclofen, in the dosage forms of tablets, powders, granules and capsules and a stabilized liquid pharmaceutical preparation in the dosage forms of
>
> (...)

[1] Literature References: Amino acid structurally related to g-aminobutyric acid (GABA), q.v., designed to cross the blood brain barrier. Prepn: G. Satzinger et al., DE 2460891 (1976 to Gödecke); eidem, US 4024175 (1977 to Warner-Lambert). Pharmacokinetics and metabolism: K.-O. Vollmer et al., Arzneimittel-Forsch. 36, 830 (1986). Clinical pharmacology: B. Saletu et al., Int. J. Clin. Pharmacol. Ther. Toxicol. 24, 362 (1986). GC determn in biological fluids: W. D. Hooper et al., J. Chromatog. 529, 167 (1990). Review of pharmacology and clinical trials in epilepsy: B. Schmidt in Antiepileptic Drugs, R. H. Levy et al., Eds. (Raven Press, New York, 3rd ed., 1989) pp 925-935; K. L. Goa, E. M. Sorkin, Drugs 46, 409-427 (1993). Clinical trial for treatment of pain in diabetic neuropathy: M. Backonja et al., J. Am. Med. Assoc. 280, 1831 (1998). Clinical evaluation in social phobia: A. C. Pande et al., J. Clin. Psychopharmacol. 19, 341 (1999).

7. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in any of claims 1 - 4 wherein it is in the form of solid preparations.

8. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in claim 7 wherein it is in the dosage form of tablets, powders, granules or capsules.

(...)

16. The process as claimed in claim 15 wherein the solid preparation is in the dosage form of tablets, powders, granules or capsules.

(...)

17. The process as claimed in any of claims 10 - 16 wherein the stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative is a gabapentin-containing preparation, a pregabalin-containing preparation, a baclofen-containing preparation, or a preparation containing 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl-pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid.

En esta anterioridad se utilizan diversos aminoácidos para darle estabilidad a la Gabapentina incluida en formulaciones del tipo sólidas como por ejemplo cápsulas, que si bien es cierto no corresponden exactamente a la estrategia de estabilización de la solicitud colombiana en trámite (sal de calcio de un ácido débil), puede verse afectado el nivel inventivo de la misma en el sentido que en el mismo estado de la técnica (elaboración de cápsulas con un contenido estable de gabapentina) ya se había resuelto de manera efectiva dicho problema técnico planteado (conversión de la gabapentina en su derivado lactámico), resultando las características de la formulación de la solicitud colombiana como una simple variación en la formulación basada en la reconocida tendencia de la gabapentina a formar dichos derivados lactámicos.

De otro lado, la publicación internacional WO 99/59572 publicada el 25 de Noviembre de 1999 y titulada "GAMMA-AMINOBUTYRIC ACID DERIVATIVES CONTAINING, SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME" revela una composición sólida estabilizada que contiene un derivado de ácido 4-amino-3-sustituido-butanóico el cual puede ser obtenido por incorporación de un humectante como estabilizante.

More particularly, the invention is concerned with a stabilized solid pharmaceutical preparation of the 4-amino-3-substituted-butanoic acid derivative, including gabapentin, pregabalin, baclofen, 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid, in the dosage forms of tablets, powders, granules and capsules, as well as a process for the preparation of the same.

(...)

7. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein said humectant is sorbitol.

(...)

10. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein it is a solid pharmaceutical preparation of gabapentin, pregabalin, baclofen, 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid.

11. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 10 wherein it is a solid pharmaceutical preparation in the dosage form of tablets, powders, granules or capsules.

[0082] Examples of suitable tablet or capsule form ingredients, include but are not limited, to oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodiumbenzoate, sodium acetate, sodium chloride, etc. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, etc.

(...)

Example I

[0101] The following is an example of a gelatin capsule composition of the present invention. The capsule is formed by combining and mixing the ingredients of each column using conventional technology and transferring the mixture to an appropriate sized hard gelatin capsule (e.g., #2 size) for oral administration.

Ingredient	%/w/w
Gabapentin	20.000
Trimebutine	20.000
Lactose NF[1]	5.000
Tricalcium Phosphate[2]	55.000

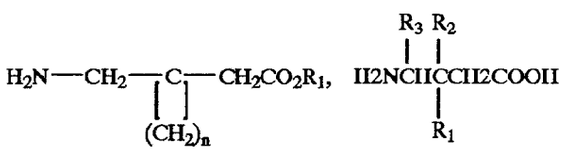
[1]Lactose NF - Lactose Monohydrate, Amresco Inc.
[2]Tricalcium Phosphate - American International Chemical Inc.

(...)

What is claimed is:

1. A composition for treating or preventing gastrointestinal disorders, comprising:

a) a safe and effective amount of a GABA analog of the formula selected from the group consisting of:



(...)

12. A composition according to claim 1, in the form of a tablet, capsule, microcapsule, suspension, solution, injectable, rectal suppository, rectal cream, rectal ointment, rectal gel.

En esta anterioridad se puede observar claramente la existencia previa de formulaciones de cápsulas de gabapentina junto a excipientes tales como fosfato da calcio tribásico, manitol y sacáridos, goma guar y alginato, tal y como lo hace la solicitud colombiana en trámite en sus reivindicaciones 1, 6, 8, 9 y 10.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS

- La publicación internacional WO 99/59573 publicada el 25 de Noviembre de 1999 y titulada "STABILIZED PHARMACEUTICAL PREPARATIONS OF GAMMA-AMINOBUTYRIC ACID DERIVATIVES AND PROCESS FOR PREPARING THE SAME" Pagina 1 y capitulo reivindicatorio.
- La publicación internacional WO 99/59572 publicada el 25 de Noviembre de 1999 y titulada "GAMMA-AMINOBUTYRIC ACID DERIVATIVES CONTAINING, SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME" pagina 1 y capitulo reivindicatorio.
- La patente americana US 2004/010035 publicada el 15 de Enero de 2004 y titulada "GASTROINTESTINAL COMPOSITIONS" paginas 6, 8 y capitulo reivindicatorio.

Señor Superintendente,

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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(54) Title: STABILIZED PHARMACEUTICAL PREPARATIONS OF GAMMA–AMINOBUTYRIC ACID DERIVATIVES AND PROCESS FOR PREPARING THE SAME

(57) Abstract

The present invention provides a stabilized pharmaceutical preparation of a 4–amino–3–substituted–butanoic acid derivative which can be obtained by incorporating an amino acid as a stabilizer.

STABILIZED PHARMACEUTICAL PREPARATIONS OF GAMMA-AMINOBUTYRIC ACID DERIVATIVES AND PROCESS FOR PREPARING THE SAME

FIELD OF THE INVENTION

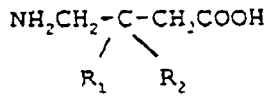
This invention relates to a stabilized solid or liquid pharmaceutical preparation comprising a 4-amino-3-substituted-butanoic acid derivative and a process for the preparation of the same.

Particularly, the invention is concerned with a stabilized solid or liquid pharmaceutical preparation of the 4-amino-3-substituted-butanoic acid derivative, including gabapentin, pregabalin, baclofen, 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid and a process for the preparation of the same.

More particularly, the invention is concerned with a stabilized solid pharmaceutical preparation of a 4-amino-3-substituted-butanoic acid derivative, including gabapentin, pregabalin or baclofen, in the dosage forms of tablets, powders, granules and capsules and a stabilized liquid pharmaceutical preparation in the dosage forms of

What is claimed is:

1. A stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanoic acid derivative which comprises a 4-amino-3-substituted-butanoic acid derivative having the general formula



wherein,

R_1 is a hydrogen atom, a hydroxyl group, a methyl group or an ethyl group;

R_2 is a monovalent group selected from:

a straight or branched alkyl group of 3 - 8 carbon atoms;

a straight or branched alkylene group of 3-8 carbon atoms;

a straight or branched alkyl group of 3 - 8 carbon atoms which is mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkyl group of 3 - 8 carbon atoms;

a cycloalkyl group of 3 - 8 carbon atoms which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an

alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

an alkylcycloalkyl group wherein said cycloalkyl has 3 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

an alkylcycloalkyl group wherein said cycloalkyl has 3 - 8 carbon atoms, is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS- and is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, and one or two of the unsubstituted methylene groups ($-CH_2-$) are mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino

group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$, and one or two of the unsubstituted methylene groups ($-CH_2-$) being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms

wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, said phenyl group being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)2-, said phenyl ring being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

an alkylcycloalkyl group wherein said cycloalkyl has 5 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-, one of the methylene groups ($-CH_2-$) in said cycloalkyl ring being replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

an alkylcycloalkyl group wherein said cycloalkyl has 5 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-, and one of the methylene groups ($-CH_2-$) in said cycloalkyl ring being replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$ and one or two of the unsubstituted methylene groups ($-CH_2-$) being mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a phenyl or naphthyl group;

a phenyl group substituted with a methylenedioxy group;

a phenyl or naphthyl group which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group, a phenoxy

group, a phenylmethoxy group, a phenylmethoxy group wherein said phenyl ring is mono-substituted with a halogen atom, trifluoromethyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group, a cycloalkylmethoxy group having 5 - 8 carbon atoms in the cycloalkyl ring, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring, a cycloalkanedienylmethoxy group having 5 - 8 carbon atoms in the cycloalkanedienyl ring, a cycloalkylmethoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, a cycloalkenylmethoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$, a cycloalkanedienyl-methoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkanedienyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$ group, a cycloalkylmethoxy group having 5 - 8 carbon atoms in the cycloalkyl ring wherein said cycloalkyl ring is mono-substituted with a halogen atom, trifluoromethyl group, a hydroxy group, an alkyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group or a carboalkoxy

group and one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring wherein said cycloalkenyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxy group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring is replaced by -O-, -NH-, -N-, -S-, -SO- or $-S(O)_2-$, or a cycloalkanedienylmethoxy group having 5 - 8 carbon atoms in the cycloalkanedienyl ring wherein said cycloalkanedienyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups ($-CH_2-$) in said cycloalkanedienyl ring is replaced by -O-, -NH-, -N-, -S-, -SO- or $-S(O)_2-$;

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

an alkyl-O-, -S- or -SS-phenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms via -O-, -S- or -SS-;

an -O-, -S- or -SS-phenyl group;

a diphenylamino group;

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS- and mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, a alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

an alkyl-O-, -S- or -SS-phenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms via -O-, -S- or -SS- and mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

an -O-, -S- or -SS-phenyl group wherein said phenyl group is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

or

R_1 and R_2, together with the carbon atom to which they are attached, may form a divalent group selected from:

a cycloalkylidene group of 5 - 8 carbon atoms;

a cycloalkylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group or a carboxyl group;

a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$ group and one or more of the unsubstituted methylene groups ($-CH_2-$) in said cycloalkyl ring are mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$ group and one or more of the unsubstituted methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring are mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an

alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms, said phenyl ring being mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms, said phenyl ring being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

an α-amino acid; and, if necessary, an auxiliary agent for manufacturing a pharmaceutical preparation.

2. The stabilized pharmaceutical preparation containing the 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein said α-amino acid is one or more selected from

the L-, D- and DL-forms of neutral α-amino acids;

alkali salts, acid amides, alkyl-substituted derivatives of acid amides or alkyl esters of the L-, D- and DL-forms of acidic α-amino acids;

acid addition salts or monoacylated derivatives of the L-, D- and DL-forms of basic α-amino acids;

α,ω-diaminodicarboxylic acids; and

acidic amino acid-basic amino acid adducts of the L-, D- and DL-forms of acidic α-amino acids and the L-, D- and DL-forms of basic α-amino acids.

3. The stabilized pharmaceutical preparation containing the 4-amino-3-substituted-butanoic acid derivative as claimed in claim 2 wherein said α-amino acid is one or more selected from

neutral α-amino acids consisting of glycine, phenylglycine, hydroxyphenylglycine, dihydroxyphenylglycine, L-alanine, hydroxy-L-alanine, L-leucine, hydroxy-L-leucine,

dihydroxy-L-leucine, L-norleucine, methylene-L-norleucine, L-ketonorleucine, L-isoleucine, hydroxy-L-isoleucine, dihydroxy-L-isoleucine, L-valine, hydroxy-L-valine, L-isovaline, L-norvaline, hydroxy-L-norvaline, hydroxy-L-ketonorvaline, L-methionine, L-homomethionine, L-ethionine, L-threonine, acetyl-L-threonine, L-tryptophan, hydroxy-L-tryptophan, methyl-L-tryptophan, L-tyrosine, hydroxy-L-tyrosine, methyl-L-tyrosine, bromo-L-tyrosine, dibromo-L-tyrosine, 3,5-diiodo-L-tyrosine, acetyl-L-tyrosine, chloro-L-tyrosine, L-m-tyrosine, L-levodopa, L-methyldopa, L-thyroxine, L-serine, acetyl-L-serine, L-homoserine, acetyl-L-homoserine, ethyl-L-homoserine, propyl-L-homoserine, butyl-L-homoserine, L-cystine, L-homocystine, methyl-L-cysteine, allyl-L-cysteine, propyl-L-cysteine, L-phenylalanine, dihydro-L-phenylalanine, hydroxymethyl-L-phenylalanine, L-aminobutyric acid, L-aminoisobutyric acid, L-ketoaminobutyric acid, dichloro-L-aminobutyric acid, dihydroxy-L-aminobutyric acid, phenyl-L-aminobutyric acid, L-aminovaleric acid, L-aminohydroxyvaleric acid, dihydroxy-L-aminovaleric acid, L-aminoisovaleric acid, L-aminohexanoic acid, methyl-L-aminohexanoic acid, L-aminoheptanoic acid, L-aminooctanoic acid and citrulline and the D- and DL-forms thereof;

acidic α-amino acids consisting of L-aspartic acid, L-glutamic acid, L-carbocysteine, L-aminoglutaric acid, L-aminosuccinic acid, L-aminoadipic acid, L-aminopimelic acid, hydroxy-L-aminopimelic acid, methyl-L-aspartic acid, hydroxy-L-aspartic acid, methyl-L-glutamic acid, methyl-hydroxy-L-glutamic acid, L-methyleneglutamic acid, hydroxy-L-glutamic acid, dihydroxy-L-glutamic acid and hydroxy-L-aminoadipic acid and the D- and DL-forms thereof;

basic α-amino acids consisting of L-arginine, L-lysine, L-ornithine, L-canavanine, L-canaline, hydroxy-L-lysine, L-homoarginine, hydroxy-L-homoarginine, hydroxy-L-ornithine, L-diaminopropionic acid, L-diaminohexanoic acid, L-diaminobutyric acid, L-diaminovaleric acid, L-diaminoheptanoic acid, and L-diaminooctanoic acid and the D- and DL-forms thereof; and

α,ω-diaminodicarboxylic acids consisting of diaminosuccinic acid, diaminoglutaric acid, diaminoadipic acid and diaminopimelic acid;

provided that, when said α-amino acid is an adipic α-amino acid, it is used in the form of the corresponding alkali salt, acid amide, alkyl-substituted derivative of acid amide or alkyl ester thereof, or

when said α-amino acid is a basic α-amino acid, it is used in the form of the corresponding acid addition salt or monoacylated derivative thereof, or

said acidic α-amino acid and said basic α-amino acid are also used in the form of the corresponding acidic amino acid-basic amino acid adduct.

4. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in any of claims 1 - 3 wherein a total amount of said α-amino acid is in the range of 0.001 - 80 moles per mole of the 4-amino-3-substituted-butanic acid derivative.

5. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in any of claims 1 - 4 wherein it is in the form of liquid preparations.

6. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in claim 5 wherein it is in the dosage form of liquid preparations, syrups or injections.

7. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in any of claims 1 - 4 wherein it is in the form of solid preparations.

when said α-amino acid is a basic α-amino acid, it is used in the form of the corresponding acid addition salt or monoacylated derivative thereof, or

said acidic α-amino acid and said basic α-amino acid are also used in the form of the corresponding acidic amino acid-basic amino acid adduct.

4. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in any of claims 1 - 3 wherein a total amount of said α-amino acid is in the range of 0.001 - 80 moles per mole of the 4-amino-3-substituted-butanic acid derivative.

5. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in any of claims 1 - 4 wherein it is in the form of liquid preparations.

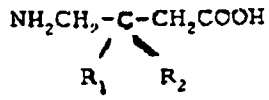
6. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in claim 5 wherein it is in the dosage form of liquid preparations, syrups or injections.

7. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in any of claims 1 - 4 wherein it is in the form of solid preparations.

8. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in claim 7 wherein it is in the dosage form of tablets, powders, granules or capsules.

9. The stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative as claimed in any of claims 1 - 8 wherein it is a gabapentin-containing preparation, a pregabalin-containing preparation, a baclofen-containing preparation, or a preparation containing 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl-pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid.

10. A process for the preparation of a stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanoic acid derivative having the general formula



wherein,

R_1 is a hydrogen atom, a hydroxyl group, a methyl group or an ethyl group;

R_2 is a monovalent group selected from:

a straight or branched alkyl group of 3 - 8 carbon atoms;

a straight or branched alkylene group of 3-8 carbon atoms;

a straight or branched alkyl group of 3 - 8 carbon atoms which is mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkyl group of 3 - 8 carbon atoms;

a cycloalkyl group of 3 - 8 carbon atoms which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an

amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

an alkylcycloalkyl group wherein said cycloalkyl has 3 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

an alkylcycloalkyl group wherein said cycloalkyl has 3 - 8 carbon atoms, is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS- and is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group,

a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, and one or two of the unsubstituted methylene groups ($-CH_2-$) are mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$, and one or two of the unsubstituted

methylene groups ($-CH_2-$) being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, said phenyl group being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)2-, said phenyl ring being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

an alkylcycloalkyl group wherein said cycloalkyl has 5 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-, one of the methylene groups ($-CH_2-$) in said cycloalkyl ring being replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

an alkylcycloalkyl group wherein said cycloalkyl has 5 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-, and one of the methylene groups ($-CH_2-$) in said cycloalkyl ring being replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$ and one or two of the unsubstituted methylene groups ($-CH_2-$) being mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl

group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a phenyl or naphthyl group;

a phenyl group substituted with a methylenedioxy group;

a phenyl or naphthyl group which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group, a phenoxy group, a phenylmethoxy group, a phenylmethoxy group wherein said phenyl ring is mono-substituted with a halogen atom, trifluoromethyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group, a cycloalkylmethoxy group having 5 - 8 carbon atoms in the cycloalkyl ring, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring, a cycloalkanedienylmethoxy group having 5 - 8 carbon atoms in the cycloalkanedienyl ring, a cycloalkylmethoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, a cycloalkenylmethoxy group wherein one of the methylene groups ($-CH_2-$) in said

cycloalkenyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$, a cycloalkanedienylmethoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkanedienyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$ group, a cycloalkylmethoxy group having 5 - 8 carbon atoms in the cycloalkyl ring wherein said cycloalkyl ring is mono-substituted with a halogen atom, trifluoromethyl group, a hydroxy group, an alkyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group and one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring wherein said cycloalkenyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxy group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$, or a cycloalkanedienylmethoxy group having 5 - 8 carbon atoms in the cycloalkanedienyl ring wherein said cycloalkanedienyl ring is mono-substituted with a halogen atom, a

trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups ($-CH_2-$) in said cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

an alkyl-O-, -S- or -SS-phenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms via -O-, -S- or -SS-;

an -O-, -S- or -SS-phenyl group;

a diphenylamino group:

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS- and mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, a alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

an alkyl-O-, -S- or -SS-phenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms via -O-, -S- or -SS- and mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl

group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

an -O-, -S- or -SS-phenyl group wherein said phenyl group is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

or

R_1 and R_2, together with the carbon atom to which they are attached, may form a divalent group selected from:

a cycloalkylidene group of 5 - 8 carbon atoms;

a cycloalkylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group or a carboxyl group;

a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring

is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$ group and one or more of the unsubstituted methylene groups ($-CH_2-$) in said cycloalkyl ring are mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms wherein

one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$ group and one or more of the unsubstituted methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring are mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms, said phenyl ring being mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms, said phenyl ring being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group, which comprises combining the 4-amino-3-substituted-butanoic acid derivative with an α-amino acid and, if necessary, an auxiliary agent for manufacturing a pharmaceutical preparation.

11. The process as claimed in claim 10 wherein said α-amino acid is one or more selected from

the L-, D- and DL-forms of neutral α-amino acids;

alkali salts, acid amides, alkyl-substituted derivatives of acid amides or alkyl esters of the L-, D- and DL-forms of acidic α-amino acids;

acid addition salts or monoacylated derivatives of the L-, D- and DL-forms of basic α-amino acids;

α,ω-diaminodicarboxylic acids; and

acidic amino acid-basic amino acid adducts of the L-, D- and DL-forms of acidic α-amino acids and the L-, D- and DL-forms of basic α-amino acids.

12. The process as claimed in claim 10 wherein said α-amino acid is one or more selected from

neutral α-amino acids consisting of glycine, phenylglycine, hydroxyphenylglycine, dihydroxyphenylglycine, L-alanine, hydroxy-L-alanine, L-leucine, hydroxy-L-leucine, dihydroxy-L-leucine, L-norleucine, methylene-L-norleucine, L-ketonorleucine, L-isoleucine, hydroxy-L-isoleucine, dihydroxy-L-isoleucine, L-valine, hydroxy-L-valine, L-isovaline, L-norvaline, hydroxy-L-norvaline, hydroxy-L-ketonorvaline, L-methionine, L-homomethionine, L-ethionine, L-threonine, acetyl-L-threonine, L-tryptophan, hydroxy-L-tryptophan, methyl-L-tryptophan, L-tyrosine, hydroxy-L-tyrosine, methyl-L-tyrosine, bromo-L-tyrosine, dibromo-L-tyrosine, 3,5-diiodo-L-tyrosine, acetyl-L-tyrosine, chloro-L-tyrosine, L-m-tyrosine, L-levodopa, L-methyldopa, L-thyroxine, L-serine, acetyl-L-serine, L-homoserine, acetyl-L-homoserine, ethyl-L-homoserine, propyl-L-homoserine, butyl-L-homoserine, L-cystine, L-homocystine, methyl-L-cysteine, allyl-L-cysteine, propyl-L-cysteine, L-phenylalanine, dihydro-L-phenylalanine, hydroxymethyl-L-phenylalanine, L-aminobutyric acid, L-aminoisobutyric acid, L-ketoaminobutyric acid, dichloro-L-aminobutyric acid, dihydroxy-L-aminobutyric acid, phenyl-L-aminobutyric acid,

L-aminovaleric acid, L-aminohydroxyvaleric acid, dihydroxy-L-aminovaleric acid, L-aminoisovaleric acid, L-aminohexanoic acid, methyl-L-aminohexanoic acid, L-aminoheptanoic acid, L-aminooctanoic acid and citrulline and the D- and DL-forms thereof;

acidic α-amino acids consisting of L-aspartic acid, L-glutamic acid, L-carbocysteine, L-aminoglutaric acid, L-aminosuccinic acid, L-aminoadipic acid, L-aminopimelic acid, hydroxy-L-aminopimelic acid, methyl-L-aspartic acid, hydroxy-L-aspartic acid, methyl-L-glutamic acid, methyl-hydroxy-L-glutamic acid, L-methyleneglutamic acid, hydroxy-L-glutamic acid, dihydroxy-L-glutamic acid and hydroxy-L-aminoadipic acid and the D- and DL-forms thereof;

basic α-amino acids consisting of L-arginine, L-lysine, L-ornithine, L-canavanine, L-canaline, hydroxy-L-lysine, L-homoarginine, hydroxy-L-homoarginine, hydroxy-L-ornithine, L-diaminopropionic acid, L-diaminohexanoic acid, L-diaminobutyric acid, L-diaminovaleric acid, L-diaminoheptanoic acid, and L-diaminooctanoic acid and the D- and DL-forms thereof; and

α,ω-diaminodicarboxylic acids consisting of diaminosuccinic acid, diaminoglutaric acid, diaminoadipic acid and diaminopimelic acid;

provided that, when said α-amino acid is an acidic α-amino acid, it is used in the form of the corresponding alkali salt, acid amide, alkyl-substituted derivative of acid amide or alkyl ester thereof, or

when said α-amino acid is a basic α-amino acid, it is used in the form of the corresponding acid addition salt or monoacylated derivative thereof, or

said acidic α-amino acid and said basic α-amino acid are also used in the form of the corresponding acidic amino acid-basic amino acid adduct.

13. The process as claimed in any of claims 10 - 12 wherein the stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanoic acid derivative is in the form of liquid preparations.

14. The process as claimed in claim 5 wherein the liquid preparation is in the dosage form of liquid preparations, syrups or injections.

15. The process as claimed in any of claims 10 - 12 wherein the stabilized pharmaceutical preparation is in the form of solid preparations.

16. The process as claimed in claim 15 wherein the solid preparation is in the dosage form of tablets, powders, granules or capsules.

17. The process as claimed in any of claims 10 - 16 wherein the stabilized pharmaceutical preparation containing a 4-amino-3-substituted-butanic acid derivative is a gabapentin-containing preparation, a pregabalin-containing preparation, a baclofen-containing preparation, or a preparation containing 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl-pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid.

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(57) Abstract

The present invention provides a stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative which can be obtained by incorporating a humectant as a stabilizer.

GAMMA-AMINOBUTYRIC ACID DERIVATIVES CONTAINING, SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME

FIELD OF THE INVENTION

This invention relates to a stabilized solid composition comprising a 4-amino-3-substituted-butanoic acid derivative and a process for the preparation of the same.

Also, this invention relates to a solid pharmaceutical preparation of the 4-amino-3-substituted-butanoic acid derivative comprising the stabilize solid composition and a process for the preparation of the same.

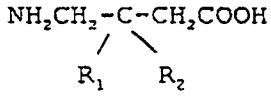
More particularly, the invention is concerned with a stabilized solid pharmaceutical preparation of the 4-amino-3-substituted-butanoic acid derivative, including gabapentin, pregabalin, baclofen, 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid, in the dosage forms of tablets, powders, granules and capsules, as well as a process for the preparation of the same.

BACKGROUND OF THE INVENTION

1-(Aminomethyl)cyclohexaneacetic acid, one of the 4-amino-3-substituted-butanoic acid derivatives, having the

What is claimed is:

1. A stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative which comprises a 4-amino-3-substituted-butanoic acid derivative having the general formula



wherein,

R_1 is a hydrogen atom, a hydroxyl group, a methyl group or an ethyl group;

R_2 is a monovalent group selected from:

a straight or branched alkyl group of 3 - 8 carbon atoms;

a straight or branched alkylene group of 3-8 carbon atoms;

a straight or branched alkyl group of 3 - 8 carbon atoms which is mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkyl group of 3 - 8 carbon atoms;

a cycloalkyl group of 3 - 8 carbon atoms which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an

alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

an alkylcycloalkyl group wherein said cycloalkyl has 3 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

an alkylcycloalkyl group wherein said cycloalkyl has 3 - 8 carbon atoms, is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS- and is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, and one or two of the unsubstituted methylene groups ($-CH_2-$) are mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino

group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$, and one or two of the unsubstituted methylene groups ($-CH_2-$) being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms

wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, said phenyl group being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)2-, said phenyl ring being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

an alkylcycloalkyl group wherein said cycloalkyl has 5 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-, one of the methylene groups ($-CH_2-$) in said cycloalkyl ring being replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

an alkylcycloalkyl group wherein said cycloalkyl has 5 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-, and one of the methylene groups ($-CH_2-$) in said cycloalkyl ring being replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$ and one or two of the unsubstituted methylene groups ($-CH_2-$) being mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a phenyl or naphthyl group;

a phenyl group substituted with a methylenedioxy group;

a phenyl or naphthyl group which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group, a phenoxy

group, a phenylmethoxy group, a phenylmethoxy group wherein said phenyl ring is mono-substituted with a halogen atom, trifluoromethyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group, a cycloalkylmethoxy group having 5 - 8 carbon atoms in the cycloalkyl ring, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring, a cycloalkanedienylmethoxy group having 5 - 8 carbon atoms in the cycloalkanedienyl ring, a cycloalkylmethoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring having 5 - 8 carbon atoms is replaced by $-O-$, $-NH-$, $-S-$, $-SO-$ or $-S(O)_2-$, a cycloalkenylmethoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring having 5 - 8 carbon atoms is replaced by $-O-$, $-NH-$, $=N-$, $-S-$, $-SO-$ or $-S(O)_2-$, a cycloalkanedienyl-methoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkanedienyl ring having 5 - 8 carbon atoms is replaced by $-O-$, $-NH-$, $=N-$, $-S-$, $-SO-$ or $-S(O)_2-$ group, a cycloalkylmethoxy group having 5 - 8 carbon atoms in the cycloalkyl ring wherein said cycloalkyl ring is mono-substituted with a halogen atom, trifluoromethyl group, a hydroxy group, an alkyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group or a carboalkoxy

group and one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring wherein said cycloalkenyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxy group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$, or a cycloalkanedienylmethoxy group having 5 - 8 carbon atoms in the cycloalkanedienyl ring wherein said cycloalkanedienyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups ($-CH_2-$) in said cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

an alkyl-O-, -S- or -SS-phenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms via -O-, -S- or -SS-;

an -O-, -S- or -SS-phenyl group;

a diphenylamino group;

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS- and mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, a alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

an alkyl-O-, -S- or -SS-phenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms via -O-, -S- or -SS- and mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

an -O-, -S- or -SS-phenyl group wherein said phenyl group is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

or

R_1 and R_2, together with the carbon atom to which they are attached, may form a divalent group selected from:

a cycloalkylidene group of 5 - 8 carbon atoms;

a cycloalkylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group or a carboxyl group;

a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$ group and one or more of the unsubstituted methylene groups ($-CH_2-$) in said cycloalkyl ring are mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$ group and one or more of the unsubstituted methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring are mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an

alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms, said phenyl ring being mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms, said phenyl ring being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a humectant; and, if necessary, an auxiliary agent for manufacturing a pharmaceutical preparation.

2. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein said humectant comprises one or more of the compounds selected from ethylene glycol, propylene glycol, butylene glycol, sorbitol and glycerol and an aliphatic acid ester thereof.

3. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein said humectant is ethylene glycol.

4. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein said humectant is propylene glycol.

5. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein said humectant is butylene glycol.

6. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein said humectant is glycerol or an aliphatic acid ester thereof.

7. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein said humectant is sorbitol.

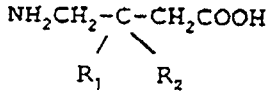
8. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein a total amount of said humectant is 0.01 - 25% by weight relative to the 4-amino-3-substituted-butanoic acid derivative.

9. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein a total amount of said humectant is 0.01 - 25% by weight relative to a total amount of the 4-amino-3-substituted-butanoic acid derivative and an auxiliary agent for manufacturing a pharmaceutical preparation.

10. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein it is a solid pharmaceutical preparation of gabapentin, pregabalin, baclofen, 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid.

11. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 10 wherein it is a solid pharmaceutical preparation in the dosage form of tablets, powders, granules or capsules.

12. A process for the preparation of a solid composition containing a 4-amino-3-substituted-butanoic acid derivative having the general formula



wherein,

R_1 is a hydrogen atom, a hydroxyl group, a methyl group or an ethyl group;

R_2 is a monovalent group selected from:

a straight or branched alkyl group of 3 - 8 carbon atoms;

a straight or branched alkylene group of 3-8 carbon atoms;

a straight or branched alkyl group of 3 - 8 carbon atoms which is mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkyl group of 3 - 8 carbon atoms;

a cycloalkyl group of 3 - 8 carbon atoms which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an

alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

an alkylcycloalkyl group wherein said cycloalkyl has 3 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

an alkylcycloalkyl group wherein said cycloalkyl has 3 - 8 carbon atoms, is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS- and is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, and one or two of the unsubstituted methylene groups ($-CH_2-$) are mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino

group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$, and one or two of the unsubstituted methylene groups ($-CH_2-$) being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms

wherein one of the methylene groups ($-CH_2-$) is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, said phenyl group being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)2-, said phenyl ring being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

an alkylcycloalkyl group wherein said cycloalkyl has 5 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-, one of the methylene groups ($-CH_2-$) in said cycloalkyl ring being replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

an alkylcycloalkyl group wherein said cycloalkyl has 5 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-, and one of the methylene groups ($-CH_2-$) in said cycloalkyl ring being replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$ and one or two of the unsubstituted methylene groups ($-CH_2-$) being mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a phenyl or naphthyl group;

a phenyl group substituted with a methylenedioxy group;

a phenyl or naphthyl group which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group, a phenoxy

group, a phenylmethoxy group, a phenylmethoxy group wherein said phenyl ring is mono-substituted with a halogen atom, trifluoromethyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group, a cycloalkylmethoxy group having 5 - 8 carbon atoms in the cycloalkyl ring, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring, a cycloalkanedienylmethoxy group having 5 - 8 carbon atoms in the cycloalkanedienyl ring, a cycloalkylmethoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, a cycloalkenylmethoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$, a cycloalkanedienyl-methoxy group wherein one of the methylene groups ($-CH_2-$) in said cycloalkanedienyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$ group, a cycloalkylmethoxy group having 5 - 8 carbon atoms in the cycloalkyl ring wherein said cycloalkyl ring is mono-substituted with a halogen atom, trifluoromethyl group, a hydroxy group, an alkyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group or a carboalkoxy

group and one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring wherein said cycloalkenyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxy group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$, or a cycloalkanedienylmethoxy group having 5 - 8 carbon atoms in the cycloalkanedienyl ring wherein said cycloalkanedienyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups ($-CH_2-$) in said cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

an alkyl-O-, -S- or -SS-phenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms via -O-, -S- or -SS-;

an -O-, -S- or -SS-phenyl group;

a diphenylamino group:

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS- and mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, a alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

an alkyl-O-, -S- or -SS-phenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms via -O-, -S- or -SS- and mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

an -O-, -S- or -SS-phenyl group wherein said phenyl group is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

or

R_1 and R_2, together with the carbon atom to which they are attached, may form a divalent group selected from:

a cycloalkylidene group of 5 - 8 carbon atoms;

a cycloalkylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group or a carboxyl group;

a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$;

a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or $-S(O)_2-$ group and one or more of the unsubstituted methylene groups ($-CH_2-$) in said cycloalkyl ring are mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$;

a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms wherein one of the methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or $-S(O)_2-$ group and one or more of the unsubstituted methylene groups ($-CH_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring are mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an

alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms, said phenyl ring being mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms, said phenyl ring being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group, which comprises combining the 4-amino-3-substituted-

butanoic acid derivative with a humectant and, if necessary, an auxiliary agent for manufacturing a pharmaceutical preparation.

13. The process as claimed in claim 12 wherein said humectant comprises one or more of the compounds selected from ethylene glycol, propylene glycol, butylene glycol, sorbitol and glycerol and an aliphatic acid ester thereof.

14. The process as claimed in claim 13 wherein said composition is a solid preparation of gabapentin, pregabalin, baclofen, 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid.

15. The process as claimed in claim 14 wherein a solid pharmaceutical preparation containing a 4-amino-3-substituted-butanoic acid derivative is a pharmaceutical preparation in the dosage form of tablets, powders, granules or capsules.

16. A stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein it is further combined with a neutral amino acid.

17. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 16 wherein said neutral amino acid is one or more of the neutral amino acids selected from L-leucine, L-isoleucine, L-valine, L-alanine, D-leucine, D-isoleucine, D-valine, D-alanine, DL-leucine, DL-isoleucine, DL-valine, DL-alanine and glycine.

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(54) **GASTROINTESTINAL COMPOSITIONS**

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(57) **ABSTRACT**

The invention relates to compositions and methods for treating and/or preventing lower gastrointestinal (GI) disorders in mammalian patients, more particularly for alleviating and/or preventing the lower GI symptoms associated with such disorders.

compositions of the present invention can be found in the Drug Facts and Comparisons (54th Ed. 2000), pp. 918-928; the cited pages of which are herein incorporated by reference. Mixtures of the above selective serotonin reuptake inhibitors can also be used.

[0079] Further dosage information concerning the disclosed actives is summarized in the table below:

Generic Name	Suitable Strengths and Dosage Forms (Brand Names)	Usual Adult Dosage
Bulk-Foaming Laxatives		
Calcium polycarbophil	625-mg tablets that provide 500 mg of polycarbophil (Konsyl Fiber)	1–6 g/day as polycarbophil in divided doses
Methylcellulose	2 g/Tbsp oral powder (Citrucel)	4–6 g/day in divided doses
Psyllium	3.4 g/tsp or 3.4 g/Tbsp oral powder; 1.7 g wafer (Metamucil)	2.5–30 g/day in divided doses
Antidiarrheals (opiate and anticholinergic agents)		
Diphenoxylate	2.5-mg tablets; 2.5 mg/5 mL oral liquid (Lomotil)	2.5–5 mg four times daily as needed for diarrhea
Loperamide	2-mg tablets and capsules; 1 mg/5 mL oral liquid (Imodium)	2–4 mg up to four times daily as needed.
Dicyclomine	10-mg capsules; 20-mg tablets; 10 mg/5 mL syrup (Bentyl)	10–20 mg three or four times daily
Hyoscyamine	0.125-mg tablets; 0.125 mg/mL; 0.125 mg/5 mL elixir (Levsin)	0.15–0.3 mg up to four times daily
Tincture of belladonna	Tincture with 0.3 mg/mL alkaloids of belladonna leaf	0.6–1 mL three or four times daily
Peristaltic Stimulants		
Cisapride	10-, 20-mg tablets; 5 mg/mL oral suspension (Propulsid)	5–10 mg three times daily
Metoclopramide	5-, 10-mg tablets; 5 mg/5 mL oral liquid	
Selective Serotonin Reuptake Inhibitors		
Fluoxetine	20-mg capsules; 20 mg/5 mL oral solution (Prozac)	
Fluvoxamine	50-, 100-mg tablets (Luvox)	
Paroxetine	10 mg/5 mL oral suspension; 10-, 20-, 30-, 40-mg tablets (Paxil)	
Sertraline	25-, 50-, 100-mg tablets (Zoloft)	
Serotonin ($5HT_3$) Receptor Antagonist		
Alosetron	1-mg tablets (Lotronex)	1 mg twice daily
Granisetron	1-mg tablets (Kytril)	
Ondansetron	4-, 8-mg tablets (Zofran)	4 mg three times daily
Gastric Secretion Inhibitors		
Octreotide	50, 100, 200, 500, 1000 μg/mL sterile solution for s.c. or i.v. injection (Sandostatin); 10-, 20-, 30-mg sterile suspensionfor i.m. injection (Sandostatin LAR Depot)	

[0080] Carriers

[0081] In accordance with the practices of the present invention, the gastrointestinal compositions may be administered in admixture with suitable pharmaceutical diluents, carriers or other excipients (collectively referred to as "carrier" materials) suitably selected with respect to the intended route of administration and conventional pharmaceutical practices. The gastrointestinal compositions of the present invention are typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid and the type is generally chosen based on the type of administration being used. The actives can be coadministered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents.

[0082] Examples of suitable tablet or capsule form ingredients, include but are not limited, to oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodiumbenzoate, sodium acetate, sodium chloride, etc. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, etc.

[0083] Of course, additionally, the compositions of the present invention may be formulated in sustained release

methods known for administering gastrointestinal actives. For example, the composition may be adapted for topical administration in the form of rectal preparations such as a rectal cream, gel, ointment, or suppository.

[0096] Method of Treatment

[0097] The method of treatment can be any suitable method which is effective in the treatment of the particular type of lower gastrointestinal disorder that is being treated. Treatment may be oral, rectal, parenteral, intravenous administration or injection. The method of applying an effective amount also varies depending on the lower gastrointestinal disorder being treated. It is believed that oral treatment by tablet, capsule or liquid will be the preferred method of administering the compounds to warm blooded mammals.

[0098] The method of treating lower gastrointestinal disorders may also be by rectal, parenteral, or intravenous administration. The actual time and dosage will depend on the type of the lower gastrointestinal disorder being treated and the desired blood levels.

EXAMPLES

[0099] The compositions in the following illustrate specific embodiments of the gastrointestinal compositions of the present invention, but are not intended to be limiting thereof. Other modifications can be undertaken by the skilled artisan without departing from the spirit and scope of this invention.

[0100] All exemplified compositions can be prepared by conventional formulation and mixing techniques. Component amounts are listed as weight percents and exclude minor materials such as diluents, filler, and so forth. The listed formulations, therefore, comprise the listed components and any minor materials associated with such components.

Example I

[0101] The following is an example of a gelatin capsule composition of the present invention. The capsule is formed by combining and mixing the ingredients of each column using conventional technology and transferring the mixture to an appropriate sized hard gelatin capsule (e.g., #2 size) for oral administration.

Ingredient	%/w/w
Gabapentin	20.000
Trimebutine	20.000
Lactose NF[1]	5.000
Tricalcium Phosphate[2]	55.000

[1]Lactose NF - Lactose Monohydrate, Amresco Inc.
[2]Tricalcium Phosphate - American International Chemical Inc.

Example II

[0102] The following is an example of a rectal ointment of the present invention.

Ingredient	% w/w
Gabapentin	2.500
Trimebutine	5.000
White Wax NF[1]	5.000
Petrolatum USP[2]	87.500
	100.000

[1]Beeswax, Bleached supplied by Strahl & Pitsch Inc.
[2]White Petrolatum supplied by Witco Corporation

[0103] In a suitable vessel equipped with a heat source and a cover or lid for sealing the vessel, the white wax and petrolatum are added and heated with mixing to a melt temperature of between 85-90° C. C. using a suitable turbine blade agitator. The Gabapentin and Trimebutine are slowly added to the molten petrolatum mixture. The mixture is cooled to a temperature of about 60 degrees C. and then poured into a suitable container.

[0104] The rectal ointment is applied in an appropriate amount (e.g., two to four grams) to the rectal area.

Example III

[0105] The following is an example of an sterile liquid composition of the present invention.

Ingredients	% w/v
Gabapentin	2.500
Trimebutine	1.500
Methyl Paraban[1]	0.020
Water for Injection USP	q.s

[1]Supplied by Universal Preserv-A-Chem, Inc.

[0106] In a suitable vessel, equipped with a suitable turbine agitator, the water for injection is added. While providing moderate agitation, the remaining ingredients are then added and mixed with the water. The mixture is stirred until a homogenous, clear solution is formed. The solution is filtered, aseptically, through a 0.22 micron filter into a sterile container suitable for vial filling. The solution is then aseptically transferred to appropriately sized sterile vials and sealed.

[0107] The injectable is administered hypodermically.

Example IV

[0108] The following is an example of an oral solution of the present invention. The solution is formed by combining and mixing the ingredients of each column using conventional technology and transferring the mixture to an appropriate containers (e.g., HDPE or brown glass). The oral solution is administered orally at dosage amounts of about 5 ml.

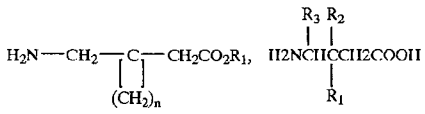
Ingredients	% w/v
Gabapentin	0.025
Trimebutin	0.020
Famotidine	0.002
Alcohol USP (190)[1]	20.000
Purified Water USP	89.955

[1]Ethanol 190 USP, Grain Processing Corporation

What is claimed is:

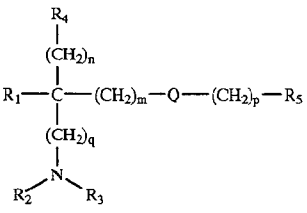
1. A composition for treating or preventing gastrointestinal disorders, comprising:

a) a safe and effective amount of a GABA analog of the formula selected from the group consisting of:



and mixtures thereof; and

b) a safe and effective amount of an amino-ether and/or -ester oxide having the formula:



in which: R_1 is a lower alkyl, R_2 and R_3 which are the same or different are hydrogen or lower alkyl, R_4 is a phenyl or phenoxy nucleus optionally monosubstituted to trisubstituted by substituents which are identical or different, halogen or lower alkoxy, R_5 is a phenyl radical optionally monosubstituted to trisubstituted by substituents which are the same or different, halogen, lower alkyl, lower alkoxy or nitro, a pyridyl radical or a lower alkyl radical, Q is —O— or —COO—, n is equal to zero, 1 or 2, m and q are, independently of one another, equal to zero or to 1, p is an integer ranging from 0 to 9.

2. A composition according to claim 1, further comprising an active is selected from the group consisting of antiinflammatory agents, laxatives, antidiarrheals, antibiotics, antiulceratives, gastric secretion inhibitors, peristaltic stimulants, serotonin ($5HT_3$) receptor antagonists, serotonin ($5HT_4$) receptor agonists, selective serotonin reuptake inhibitors and mixtures thereof.

3. A composition according to claim 2, wherein the serotonin ($5HT_4$) receptor agonist is selected from the group consisting of tegaserod, prucalopride and mixtures thereof.

4. A composition according to claim 2, wherein the selective serotonin reuptake inhibitor is selected from the group consising of fluoxetine, fluvoxamine, paroxetine, sertraline and mixtures thereof.

5. A composition according to claim 2, wherein the laxative is selected from the group consisting of methylcellulose, carboxymethylcellulose sodium, malt soup extract, polyacrylic resin, plantago seeds, dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, dioctyl sodium sulfosuccinate, mineral oil, magnesium citrate, magnesium hydroxide, magnesium sulfate, dibasic sodium phosphate, monobasic sodium phosphate, sodium biphosphate, glycerin, anthraquinones, diphenylmethanes, castor oil and mixtures thereof.

6. A composition according to claim 2, wherein the antidiarrheal is selected from the group consisting of natural opiates, synthetic opiates, anticholinergics, acetyltannic acid, albumin tannate, alkofanone, aluminum salicylates, catechin, lidamidine, mebiquine, trillium, uzarin and mixtures thereof.

7. A composition according to claim 2, wherein the antiulcerative is selected from the group consisting of aceglutamide aluminum complex, ε-acetamidocaproic acid zinc salt, acetoxolone, arbaprostil, benexate hydrochloride, bismuth subcitrate sol (dried), carbenoxolone, cetraxate, cimetidine, enprostil, esaprazole, famotidine, ftaxilide, gefarnate, guaiazulene, irsogladine, nizatidine, omeprazole, omoprostil, γ-oryzanol, pifarnine, pirenzepine, plaunotol, ranitidine, rioprostil, rosaprostol, rotraxate, roxatidine acetate, sofalcone, spizofurone, sucralfate, teprenone, trimoprostil, thrithiozine, troxipide, zolimidine and mixtures thereof.

8. A composition according to claim 2, wherein the gastric secretion inhibitor is selected from the group consisting of enterogastrone, octreotide and mixtures thereof.

9. A composition according to claim 2, wherein the peristaltic stimulant is selected from the group consisting of metoclopromide, cisapride, domperidone and mixtures thereof.

10. A composition according to claim 2, wherein the serotonin ($5HT_3$) receptor antagonist is selected from the group consisting of renzapride, cilansetron, ondansetron, alosetron and mixtures thereof.

11. A composition according to claim 2, wherein the antibiotic is selected from the group consisting of nitroimidazole antibiotics, tetracyclines, pencillins, cephalosporins, carbopenems, amino-glycosides, macrolide antibiotics, lincosamide antibiotics, 4-quinolones, rifamycins, nitrofurantoin and derivatives of 10-(1-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0.3.8]undec-2-ene-2-carboxylic acid and mixtures thereof.

12. A composition according to claim 1, in the form of a tablet, capsule, microcapsule, suspension, solution, injectable, rectal suppository, rectal cream, rectal ointment, rectal gel.

13. A composition according to claim 1, wherein the amino-ether and/or -ester oxide selected from the group consisting of trimebutine, fedotozine and mixtures thereof.

14. A composition according to claim 5, wherein the laxative is a bulk forming laxative.

15. A composition according to claim 14, wherein the laxative is selected from the group consisting of polycarbophil, calcium polycarbophil and mixtures thereof.

16. A composition according to claim 1, in the form of a tablet, capsule, microcapsule, suspension, solution, injectable, rectal suppository, rectal cream, rectal ointment, rectal gel.

17. A composition for treating or preventing gastrointestinal disorders, comprising: a GABA analog selected from the group consisting of (1-aminomethyl-3-methylcyclohexyl) acetic acid, (1-aminomethyl-3-methylcyclopentyl)acetic acid, (1-aminomethyl-3,4-dimethylcyclopentyl)acetic acid, 3-(1-aminoethyl)-5-methylhexanoic acid, 3-aminomethyl-5-methyl-hexanoic acid, and (S)-3-(aminomethyl)-5-methylhexanoic acid and mixtures thereof; and an amino-ether and/or -ester oxide selected from the group consisting of trimebutine, fedotozine and mixtures thereof.

18. A method of treating or preventing gastrointestinal disorders, comprising the step of administering to a mammal in need of such treatment a safe and effective amount of the composition of claim 1.

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