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103

Señores
SUPERINTENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Ref: Expediente No. 02.103.710
Solicitud de patente de invención titulada:
"FORMULACIONES ESTABLES, LIQUIDAS Y SOLIDAS.."
Solicitante: SCHERING CORPORATION.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTICULO 44 DE LA DECISION 486, GACETA No. 537

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Dando cumplimiento a lo establecido en el articulo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de $177.000 pesos para cubrir la tasa correspondiente, según la Resolución 37323 del año 2003.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo:Recibo por $177.000 pesos

104 99

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 02103710 00000003 Folios: 2
Fecha (AMD): 2004-07-15 09:35:31
Tramite : 011 PCT-PATENT 379 FASE NACI 538 PETICION
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 55,082
FECHA : JULIO 12 DE 2004

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	23286882	12/07/2004	9,344,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	177,000.00
		TOTAL : $	177,000.00

SON: CIENTO SETENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Industria y Comercio
SUPERINTENDENCIA

100

105

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **02-103710**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION - PCT** FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **537**, DE FECHA **27** DE **FEBRERO** DE **2004**, EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **27** DE **MAYO** DE **2004**.

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ___ _____ NO ___ X ____

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Santa Fe de Bogotá D.C. - Colombia

101 106

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C., 09 de febrero de 2007

Apoderado: Carlos Reinaldo Olarte Oficio: 2610

REFERENCIA: Radicación No. 02-103710
Tramite 002
Evento 001
Actuación 430
Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

◆Capítulo descriptivo, folios 42 a 76;
◆Capitulo reivindicatorio original, 77 a 81;
◆Solicitud PCT/US01/16570 en fase nacional;
◆Solicitud del examen de patentabilidad, folios 103 y 104.

Objeto de la invención:

La presente solicitud cuyo título es "FORMULACIONES ESTABLES, LIQUIDAS Y SÓLIDAS"

El objeto de la solicitud es composiciones que comprenden loratadina y una cantidad de un descongestionante nasal.

El objeto de la invención se puede clasificar según la clasificación internacional como A61K 31/445

Claridad de la solicitud:

En el artículo 30 de la decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

Las reivindicaciones 9 a 12 y 17 a 19 no son claras, puesto que en su redacción se pretende caracterizar la "composición", por características que se desea que tenga la composición, no existe características técnicas de composición se supone le confieren esas propiedades deseables.

Además la reivindicación 19, utiliza términos y frases para restarle claridad tales como "**que sustancialmente no contenga azúcar como glucosa o sacarosa y etanol y sea apropiada para uso pediátrico**" no es claro porque cualquier composición se caracteriza por sus elementos constitutivos, no por lo que no contiene, y además solo se anuncian las propiedades deseables para la composición.

Reivindicaciones de uso

De acuerdo con la legislación colombiana el uso que se reclama en las reivindicaciones 20 a 26 y 18 (que esta después de la 26, fue mal enumerada) reclaman el uso que no se considera para protección por patente, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina"... Los Países Miembros otorgarán patentes para las invenciones sean de **productos o procedimientos** en todos los campos de la tecnología..."; AQUÍ NO se hace alusión al uso o empleo.

Continuando con la última parte del Artículo 14"... (Los Países Miembros otorgarán patentes para las invenciones sean de **productos o procedimientos** en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial." El hecho que se diga que el producto o el procedimiento tengan aplicación industrial no quiere decir que la aplicación industrial sea susceptible de patente.

Así mismo, citando **completamente** el artículo 19 este reza: " Se considerará que una **invención** *(léase producto o procedimiento)* es susceptible de aplicación industrial *(una característica de la invención)* cuando su objeto puede ser producido o utilizado en cualquier clase de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios." Esta diciendo que una invención, producto o procedimiento, debe servir para algo. En ningún momento se dice que un uso pueda ser protegido como patente.

El artículo 21 dice: " Los productos o procedimientos *(o sea, los inventos, nótese que nunca se refieren a nada diferente)* ya patentados comprendidos en el estado

de la técnica de conformidad con el Artículo 21 de la presente Decisión, no serán objeto de nueva patente por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial." Nunca se refieren a una protección para el uso, como erróneamente se podría interpretar. Se trata de no conceder nueva patente a un invento (exclusivamente productos o procedimientos) al que se le ha encontrado nueva función, pero que se trata exactamente del mismo producto o procedimiento. Es decir, sí el compuesto, aparato, etc. o método ya esta dentro del estado de la técnica, el hecho que se haya descubierto una nueva aplicación para el mismo compuesto, aparato, etc. o método, implica que no es merecedor de nueva patente, o que el nuevo uso le reestablezca la novedad. En ningún caso se dice que se esta protegiendo el uso. Simplemente se dice que el producto o procedimiento ya esta dentro del estado de la técnica y una utilización diferente no esta contemplada para permitir conceder patente al producto o al procedimiento nuevamente.

Los usos o segundos usos no son patentables, de conformidad con la sentencia del TJAC 89-AI-2000, los usos en general no son patentables.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: "*El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*
Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

No	Documento No.	Título	Fecha de Publicación
D1	Rev. Alergia Mex. Vol.	Antihistamínicos de Nueva Generación y descongestionantes nasales en rinitis	1993

	40(1); pags. 16-20	alérgicas	
D2	WO8808302	Cough/cold mixtures comprising non-sedating antihistamina drugs	03-nov-1988
D3	WO9507103	Composition containing an amino acid salt of propionic acid non-steroidal anti-inflamatory angent and least one of a edscongestionant, an expectorant, an antihistamine and an antitissive	16-mar-1995
D4	WO9962516	A stabilized antihistamina syrup containing aminopolycarboxylic acid as stabilizer	09-dic-1999

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*

En cumplimiento de este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad:

El Art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica." "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida".*

La solicitud en estudio reclama como nueva una composición farmacéutica que comprende una cantidad efectiva de loratadina o una de sus sales aceptable para uso farmacéutico y una cantidad efectiva de un descongestionante nasal o una de sus sales aceptable para uso farmacéutico, y en forma opcional, una cantidad efectiva de un expectorante o una de sus sales aceptables para uso farmacéutico y, por lo menos un vehículo aceptable para uso farmacéutico.

-La anterioridad D1 describe composiciones que comprenden un antihistamínico de nueva generación y descongestionante nasales, donde se encuentra específicamente loratadina+ Pseudoefedrina y donde se muestran todos las mediciones de reacciones clínicas, tolerancia, efectos secundarios, inicio de acción y efectos colaterales, entonces lo que se observa es que en la solicitud en estudio se hizo una generalización de los estudios publicados en el presente anterioridad.

-La anterioridad D2 describe composiciones farmacéuticas que comprende un antihistamínico no sedante con descongestionante nasales, antiinflamatorio , con vehículos farmaceuticamente aceptables; lo que indica que la materia reclamada como nueva es del estado de la técnica.

-La anterioridad D3 describe formas farmacéuticas, que comprenden un antihistamínico loratadina junto con descongestionante nasal, que pueden contener expectorante y con vehículos farmaceuticamente aceptables para adaptarlos a la forma farmacéutica deseable. Se puede ver que D3 destruye categóricamente la novedad la solicitud en estudio, puesto que esta anterioridad enseña la misma mezcla de loratadina con un descongestionante nasal y opcionalmente un expectorante; por lo tanto "el medicamento" que se reclama como nuevo en la solicitud donde la novedad de basa en una mezcla de "loratadina con cualquier descongestionante nasal" y tal como se puede ver esa mezcla ya era conocida en el estado de la técnica.

-La anterioridad D4 describe una composición liquida que comprende loratadina con Pseudoefedrina sulfato, y el ejemplo 9, es una composición especifica que destruye categóricamente la "composición" que se reclama como nueva en la solicitud en estudio, lo cual nos muestra claramente que "La composición en estudio se encuentra materializada específicamente en la anterioridad D4. Por lo cual la composición reclamada en la presente solicitud no nueva, ni es la primera vez que se encuentra en una composición loratadina y un descongestionante nasal.

Se debe tener claro que cualquier solicitud afectada por novedad, menos tiene nivel inventivo.

No.	Documento	Reivindicaciones Afectadas	Requisito que afecta
D1	Re. Alergia Mex	1 a 20	Novedad
D2	WO8808302	1 a 20	Novedad

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D3	WO9507103	1 a 20	Novedad
D4	WO9962516	1 a 20	Novedad

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

Notifíquese conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5° del título 1° de la Circular Única n° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL.
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 23 FEB. 2007.

CONCEPTO TÉCNICO No. 263	EXAMINADOR TÉCNICO Código: 202012

D1 107 H2

Artículo en Inglés

González GJG, Díaz AG, Topete RE, García RG

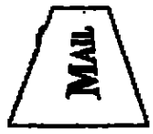
Antihistamínicos de nueva generación y descongestionantes nasales en rinitis alérgica

Rev Alergia Mex 1993; 40(1) 16-20.

RESUMEN

Con el propósito de evaluar la reacción clínica a las nuevas preparaciones de antihistamínicos y pseudoefedrina se estudiaron 160 pacientes con rinopatía alérgica activa; se separaron al azar en cuatro grupos diferentes: 1) loratadina + pseudoefedrina; 2) astemizol + pseudoefedrina; 3) terfenadina + pseudoefedrina; 4) placebo. A cada pacience se le entregó un cuestionario para autoevaluación y medición de la reacción clínica, tolerancia, inicio de acción y efectos colaterales. Se encontró mejoría importance en 87% de los pacientes del grupo 1, 85% en el grupo 2, 70% en el grupo 3 y 3% en el grupo 4. Se observaron efectos colaterales en 24% del grupo 1 y 48% en el grupo 2 y 47% en el grupo 3. El conocimiento de la reacción clínica a las diferentes combinaciones permite individualizar el tratamiento y ofrecer a los pacientes el mejor medicamento para su caso.

Palabras clave: Antihistamínicos, loratadina, evaluación.



Regresar al índice | Clave Alx 9105 | HOME

[Indice principal | | Regresar al índice | | H O M E | Solicitud de artículos | Búsqueda]

DZ 1/13

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 31/445, 31/54, 31/455 A61K 31/62 // (A61K 31/445 A61K 31:19) (A61K 31/54 A61K 31:455, 31:445)

A1

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(31) Priority Application Number: 042,120

(32) Priority Date: 24 April 1987 (24.04.87)

(33) Priority Country: US

(71)(72) Applicants and Inventors: SUNSHINE, Abraham [US/US]; 254 East 68th Street, Apt. 12D, New York, NY 10021 (US). LASKA, Eugene, M. [US/US]; 34 Dante Street, Larchmont, NY 10538 (US). SIEGEL, Carole, E. [US/US]; 1304 Colonia Court, Mamaroneck, NY 10543 (US).

(74) Agents: STEPNO, Norman, H. et al.; Burns, Doane, Swecker & Mathis, The George Mason Building, Washington & Prince Streets, P.O. Box 1404, Alexandria, VA 22313-1404 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COUGH/COLD MIXTURES COMPRISING NON-SEDATING ANTIHISTAMINE DRUGS

(57) Abstract

Pharmaceutical compositions and methods of using same comprising a non-steroidal anti-inflammatory drug in combination with a non-sedating antihistamine and optionally one or more other active components selected from a decongestant, cough suppressant (antitussive) or expectorant are provided for the relief of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, headache, fever and general malaise associated therewith.

H_1-histamine receptors, the lesser penetration of the non-sedating antihistamines into the central nervous system may be responsible for their apparent lack of central nervous system effects. In addition, as a general rule, the non-sedating antihistamines possess minimal or no antiserotoninergic, anticholinergic or antiadrenergic activity. Psychomotor and visual function tests in man have shown that the non-sedating antihistamines do not impair psychomotor performance or adversely affect subjective feelings, in contrast to conventional antihistamines which were active in these tests. The non-sedating antihistamines neither affect the EEG as sedative antihistamines are known to do, nor interact with other depressant drugs (such as alcohol or benzodiazepines) to produce enhanced depressant effects.

The lack of sedative effects from the non-sedating antihistamines may be especially useful in children, where prescribing of conventional antihistamines is often hindered because of the daytime sedation they produce.

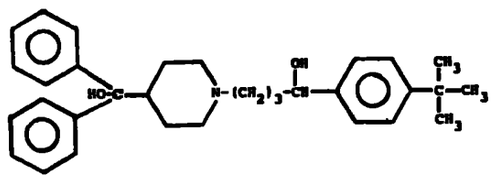
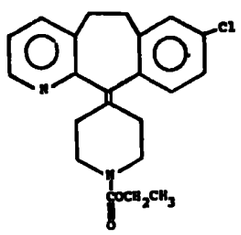
The non-sedating antihistamines include but are not limited to acrivastine, AHR-11325, astemizole, azatadine, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine and terfenadine. Representative chemical structures for many of the non-sedating antihistamines are presented in Table I.

In the pharmaceutical compositions and methods of the present invention, the foregoing active ingredients will typically be administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, i.e., oral tablets, capsules, elixirs, syrups, suspensions, etc. and consistent with conventional pharmaceutical practices. For instance, for oral administration in the form of tablets or capsules, the active drug components may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, ethyl alcohol (liquid forms) 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, sodium benzoate, sodium acetate, sodium chloride, etc. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, etc. Sweetening and flavoring agents and preservatives can also be included where appropriate.

Of course, additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate

TABLE I (continued)

Non-Sedating Antihistamines

Common Name or Generic Name	Chemical Structure	Chemical Name
terfenadine		alpha-(4-(1,1-dimethylethyl)phenyl)-4-(hydroxydiphenylmethyl)-1-piperidinebutanol
loratidine		(8-chloro(6,11-dihydro-11-(1-carboethoxy-4-piperidylidene)-5-H-benzo(5,6]cyclohepta(1,2-b]-pyridine)

P3
112 H7

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: A61K 45/06, 31/19, 31/445, 31/485 | A1

(11) International Publication Number: WO 95/07103

(43) International Publication Date: 16 March 1995 (16.03.95)

(21) International Application Number: PCT/US94/09581

(22) International Filing Date: 24 August 1994 (24.08.94)

(30) Priority Data:
08/116,927 7 September 1993 (07.09.93) US

(71) Applicants: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).

(72) Inventor: MITRA, Sekhar; 7305 Denner Road, Cincinnati, OH 45243 (US).

(74) Agents: REID, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).

(81) Designated States: AU, BR, CA, CN, JP, PL, RU, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: COMPOSITIONS CONTAINING AN AMINO ACID SALT OF PROPIONIC ACID NON-STEROIDAL ANTI-INFLAMMATORY AGENT AND AT LEAST ONE OF A DECONGESTANT, AN EXPECTORANT, AN ANTIHISTAMINE AND AN ANTITUSSIVE

(57) Abstract

The present invention relates to compositions and methods for providing improved treatment, management or mitigation of cold, cold-like and/or flu symptoms by administering a safe and effective amount of a composition comprising certain amino acid salts of propionic acid non-steriodal anti-inflammatory agents along with at least one of (a) a decongestant, (b) an expectorant, (c) an antihistamine and (d) an antitussive.

detailed disclosure of the chemical structure, synthesis, side effects, etc., of non-steroidal anti-inflammatory agents, reference may be had to standard texts, including Anti-inflammatory and Anti-Rheumatic Drugs, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and Anti-inflammatory Agents, Chemistry and Pharmacology, 1, R. A. Scherrer, et al., Academic Press, New York (1974), both of which are incorporated by reference herein.

The preferred non-steroidal anti-inflammatory agents useful in the composition of the present invention include the amino acid salts of the propionic acid derivatives such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic. Mixtures of these non-steroidal anti-inflammatory agents may also be employed. Of these propionic acid NSAIDs, ibuprofen, naproxen and ketoprofen are most preferred.

Most preferred for use herein is the S(+) isomer of these NSAID salts. The term "S(+)" as applied to the analgesic agents herein is intended to encompass the dextrorotatory or S(+) isomer of the amino acid salt derivatives thereof. The expression "substantially free of the R(-) antipode" as used in conjunction with the term "S(+)" means that the S(+) enantiomer is sufficiently free it is R(-) antipode to exert the desired onset-hastened and enhanced analgesic effect. Practically speaking, this means that the active ingredient should contain at least 90% by weight of the S(+) enantiomer and 10% or less weight R(-) enantiomer. Preferably, the weight ratio of S(+) enantiomer to R(-) enantiomer is greater than 20:1, more preferably greater than 97:3. Most preferably the S(+) enantiomer is 99 or more % by weight free of R(-) enantiomer, i.e., the weight ratio of S to R is approximately equal to or greater than 99:1.

The safe and effective amount of the amino acid salts of ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic generally ranges from about 7.5 mg to about 1000mg, and are generally the same as their acid derivatives counterparts. Useful dosage of these agents can be found in The Physicians' Desk Reference, 47th Edition (1993) and in U.S. Patent 4,552,899 to Sunshine et al., issued November 12, 1985, both of which are incorporated by reference herein.

For example, the safe and effective amount of the amino acid salt of ibuprofen used in the compositions of the present invention generally ranges from about 50 to about 800 mg, preferably from about 50 to about 400 mg, more preferably from about 50 to about 200 mg and most preferably from about 50 to

about 100 mg. The safe and effective amount of the amino acid salt of flurbiprofen used in the compositions of the present invention generally ranges from about 12.5 to about 300 mg, preferably from about 12.5 to about 200 mg, more preferably from about 12.5 to about 100 mg and most preferably from about 12.5 to about 50 mg. The safe and effective amount of the amino acid salt of ketoprofen used in the compositions of the present invention generally ranges from about 5 to about 100 mg, preferably from about 5 to about 75 mg, more preferably from about 5 to about 50 mg and most preferably from about 5 to about 25 mg. Generally, the amount of the S(+) isomers of these agents will be about half of the amount of the racemic mixture.

The compositions of the present invention also include at least one other pharmacological active selected from the following class: (a) a decongestant, (b) an expectorant (c) an antihistamine and (d) an antitussive. The decongestants useful in the compositions of the present invention include pseudoephedrine, phenylpropanolamine, phenylephrine and ephedrine, their pharmaceutically acceptable salts, and mixtures thereof. The antitussives useful in the present invention include those such as dextromethorphan, chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts, and mixtures thereof. The antihistamines useful in the present invention include those such as chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, azatadine, doxylamine, tripelennamine, cyproheptadine, hydroxyzine, clemastine, carbinoxamine, phenindamine, bromodiphenhydramine, pyrilamine, their pharmaceutically acceptable salts, as well as the non-sedating antihistamines which include acrivastine, AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, and terfenadine, their pharmaceutically acceptable salts and mixtures thereof. The expectorants (also known as mucolytic agents) useful in the present invention include glyceryl guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and bromhexine, ambroxol, their pharmaceutically acceptable salts, and mixtures thereof. All of these components, as well as their acceptable dosage ranges are described in the following: U.S. Patent 4,783,465 to Sunshine et al., issued November 8, 1988, U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, which are incorporated by reference herein.

Preferably, the pharmaceutical compositions of the present invention comprise the analgesic agent and other pharmacological active in a ratio of anal-

gesic agent:pharmacological active of from about 200:1 to about 1:1, preferably from about 50:1 to about 1:1 and most preferably from about 10:1 to about 1:1.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules, lozenges and bulk powders and liquid forms such as syrups and suspensions. These oral forms comprise a safe and effective amount, usually at least about 5% of the active component. Solid oral dosage forms preferably contain from about 5% to about 95%, more preferably from about 10% to about 95%, and most preferably from about 25% to about 95% of the active component. Liquid oral dosage forms preferably contain from about 1% to about 50% and more preferably from about 1% to about 25% and most preferably from about 3% to about 10% of the active component.

Tablets can be compressed, triturated, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives and flow-inducing agents. Also useful are soft gelatin capsules.

Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, pseudo emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, taste-masking agents, coloring agents, and flavoring agents. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms, are described in U.S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," Modern Pharmaceutics, Vol. 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (1980), incorporated herein by reference.

In preparing the liquid oral dosage forms, the active component is incorporated into an aqueous-based orally acceptable pharmaceutical carrier consistent with conventional pharmaceutical practices. An "aqueous-based orally acceptable pharmaceutical carrier" is one wherein the entire or predominant solvent content is water. Typical carriers include simple aqueous solutions, syrups, dispersions and suspensions, and aqueous based emulsions such as the oil-in-water type. The most preferred carrier is a suspension of the pharmaceutical composition in an aqueous vehicle containing a suitable suspending agent. Suitable suspending agents include

Avicel RC-591 (a microcrystalline-cellulose/sodium carboxymethyl cellulose mixture available from FMC), guar gum and the like. Such suspending agents are well known to those skilled in the art. While the amount of water in the compositions of this invention can vary over quite a wide range depending upon the total weight and volume of the active component and other optional non-active ingredients, the total water content, based on the weight of the final composition, will generally range from about 20 to about 75%, and, preferably, from about 20 to about 40%, by weight/volume.

Although water itself may make up the entire carrier, typical liquid formulations preferably contain a co-solvent, for example, propylene glycol, glycerin, sorbitol solution and the like, to assist solubilization and incorporation of water-insoluble ingredients, such as flavoring oils and the like into the composition. In general, therefore, the compositions of this invention preferably contain from about 5 to about 25 volume/volume percent and, most preferably, from about 10 to about 20 volume/ volume percent, of the co-solvent.

The compositions of this invention may optionally contain one or more other known therapeutic agents, particularly those commonly utilized in cough/cold preparations, such as, for example, a s bronchodilator such as terbutaline, aminophylline, epinephrine, isoprenaline, metaproterenol, bitoterol, theophylline and albuterol as well as other analgesic agents such as acetaminophen and aspirin. A highly preferred optional component is caffeine. Other optional ingredients well known to the pharmacist's art may also be included in amounts generally known for these ingredients, for example, natural or artificial sweeteners, flavoring agents, colorants and the like to provide a palatable and pleasant looking final product, antioxidants, for example, butylated hydroxy anisole or butylated hydroxy toluene, and preservatives, for example, methyl or propyl paraben or sodium benzoate, to prolong and enhance shelf life.

METHOD OF TREATMENT

The amount of the pharmaceutical composition administered depends upon the percent of active ingredients within its formula, which is a function of the amount of the naphthalene derivative and any optional components such as a decongestant, cough suppressant, expectorant and/or antihistamine required per dose, stability, release characteristics and other pharmaceutical parameters.

Usually from about 1 mg/kg to about 50 mg/kg per day, preferably from about 2 mg/kg to about 30 mg/kg per day and most preferably from about 3 mg/kg per day to about 20 mg/kg per day of the pharmaceutical composition is administered as described herein. This amount can be given in a single dose, or,

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(54) Title: A STABILIZED ANTIHISTAMINE SYRUP CONTAINING AMINOPOLYCARBOXYLIC ACID AS STABILIZER

(57) Abstract

An antihistaminic syrup is stabilized against degradation of the active ingredient, by the addition of and about 0.05 to about 5 mg/mL of an aminopolycarboxylic acid such as a salt of ethylenediaminetetraacetic acid.

It has been found that the addition of small amounts of an aminopolycarboxylic acid, the term specifically including salts of the acids, can stabilize the syrups against degradation. Useful aminopolycarboxylic acids and salts thereof are those which are safe for ingestion and have sufficient solubility in the syrup formulations to make a stable single phase composition. Commercially available compounds which could be used include iminodiacetic acid, methyliminodiacetic acid, nitrilotriacetic acid, ethylenediaminetetraacetic acid ("EDTA"), diethylenetriaminepentaacetic acid, 1,2-diaminocyclohexane-tetraacetic acid, N-hydroxyethylenediaminetriacetic acid and related compounds. Mixtures of two or more of the foregoing are suitable for use. From the aspects of ready availability, safety, efficacy and cost, the alkali metal salts of EDTA are presently preferred, and the remainder of this description will focus on those materials.

An aminopolycarboxylic acid or salt will typically be present in a syrup at about 0.05 mg/mL to about 5 mg/mL. More preferably, the level of aminopolycarboxylic acid will be about 0.1 mg/mL to about 1 mg/mL. As with any additive component in a formulation intended for ingestion, it is desirable to incorporate the minimum level which will yield the desired result. This level can be readily determined by means of an accelerated storage stability test, in which packages of the final product are stored at elevated temperatures above the usual storage temperatures to which the product is expected to be exposed; the present inventors have used temperatures up to 55°C for this purpose, although such temperatures tend to cause a minor discoloration (darkening) of the syrups, probably due to some carmelization of the contained sucrose. It is expected that most drug degradation reactions will be accelerated by the elevated temperature. At predetermined intervals, some of the packages are opened and analyzed to determine the amount of active ingredients and impurities present in the formulation.

Antihistaminic syrup formulations frequently also contain other drugs, for obtaining more than one therapeutic result from a single dose. Typical drug substances included with the antihistamine are sympathomimetic amine decongestants, such as pseudoephedrine or phenylpropanolamine

This syrup is found to exhibit acceptable storage stability.

EXAMPLE 9

A stabilized syrup for pediatric use is formulated according to the previously described general procedure to contain the following ingredients, wherein amounts of all except water are expressed in milligrams.

Ingredient	Amount
Loratadine	0.5
Pseudoephedrine sulfate	3
Acetaminophen	32
Dextromethorphan hydrobromide	1.5
Citric acid	8.78
Flavoring agent	1.5
Glycerin	100
Propylene glycol	100
Sodium benzoate	1
Disodium EDTA	0.25
Coloring agent	1
Sucrose	400
Water	to make 1.0 mL

This syrup is found to exhibit acceptable storage stability.

WHAT IS CLAIMED IS:

1. An antihistaminic syrup formulation containing about 0.05 to about 5 mg/mL of an aminopolycarboxylic acid, including salts thereof.

2. The syrup of claim 1, which contains an antihistaminic ingredient selected from the group consisting of: loratadine; descarboethoxyloratadine; azatadine; and any combination of two or more thereof.

3. The syrup of claim 1, which contains the antihistaminic ingredient loratadine.

4. The syrup of claim 1, which contains the antihistaminic ingredient descarboethoxyloratadine.

5. The syrup of claim 1, which contains the antihistaminic ingredient azatadine.

6. The syrup of claim 1, wherein the aminopolycarboxylic acid is selected from the group consisting of: iminodiacetic acid; methyliminodiacetic acid; nitrilotriacetic acid; ethylenediaminetetraacetic acid; diethylenetriaminepentaacetic acid; 1,2-diaminocyclohexane-tetraacetic acid; N-hydroxyethylenediaminetriacetic acid; and any combination of two or more thereof.

7. The syrup of claim 1, wherein the aminopolycarboxylic acid comprises ethylenediaminetetraacetic acid.

8. The syrup of claim 1, in which the aminopolycarboxylic acid comprises about 0.1 to 1 mg/mL.

9. The syrup of claim 7, in which the aminopolycarboxylic acid comprises about 0.25 to about 0.5 mg/mL.

10. The syrup of claim 1, further containing a therapeutically effective amount of a decongestant, an analgesic, an antitussive, an expectorant, or any combination of two or more thereof.

11. The syrup of claim 1, further containing a decongestant selected from the group consisting of pseudoephedrine and phenylpropanolamine.

12. The syrup of claim 1, further containing the decongestant pseudoephedrine.

13. The syrup of claim 12, which contains the antihistaminic ingredient loratadine.

14. An antihistaminic syrup formulation containing loratadine or descarboethoxyloratadine and about 0.05 to about 5 mg/mL of an aminopolycarboxylic acid or a salt thereof.

15. The syrup of claim 14, wherein the aminopolycarboxylic acid is selected from the group consisting of: iminodiacetic acid; methyliminodiacetic acid; nitrilotriacetic acid; ethylenediaminetetraacetic acid; diethylenetriaminepentaacetic acid; 1,2-diaminocyclohexane-tetraacetic acid; N-hydroxyethylenediaminetriacetic acid; and any combination of two or more thereof.

16. The syrup of claim 14, wherein the aminopolycarboxylic acid comprises ethylenediaminetetraacetic acid.

17. The syrup of claim 14, in which the aminopolycarboxylic acid comprises about 0.1 to 1 mg/mL.