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SEÑOR

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Trámite : 002 PATENTES D

1 REGISTRO/ 229 COMPLETEN

E.

S.

D. Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REF:

EXPEDIENTE 00-093-233

TÍTULO SOLICITADO:

"Composiciones Inhibidoras de ciclooxigenasa-2
que tienen rápido acceso de efecto terapéutico"

PUBLICACIÓN:

Gaceta 526 de 31-03-2003, número de publicación
1556

SOLICITANTE:

PHARMACIA CORPORATION

APODERADO:

EMILIO FERRERO

TRÁMITE:

SUSTENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, reconocido apoderado de las sociedades opositoras en el trámite de la referencia, estando dentro de los términos de la prómoga solicitada, por medio del presente escrito, me permito ratificar y sustentar los argumentos del escrito principal de oposición, también radicado dentro del plazo de ley ante esa entidad.

I. RATIFICACIÓN

Reitero a su Despacho la solicitud de negar el beneficio patentario para la totalidad de las reivindicaciones contenidas en el expediente en referencia, por los argumentos que se describen a continuación:

- Antes de la fecha de prioridad se conocían los inhibidores de la ciclooxigenasa-2, sus propiedades y características farmacocinéticas, la posibilidad de su administración por vía oral, los rangos de ingrediente activo en las formulaciones, las dosis unitarias, los excipientes, los usos, y la incidencia directa del tamaño de partícula sobre los parámetros farmacocinéticos de un fármaco.

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- En cuanto a los tamaños de partícula revelados en la presente solicitud de patente -D₉₀ de alrededor de 0.01µm hasta alrededor de 200µm, preferiblemente más pequeñas que 1µm-, se puede afirmar que carecen de nivel inventivo, pues, aún si en gracia de discusión pudiera afirmarse que no existen revelaciones textuales que indiquen que la droga inhibitoria de ciclooxigenasa-2 esté presente en los tamaños de partícula en cuestión, resulta obvio para una persona medianamente versada en la materia técnica respectiva, y teniendo en cuenta lo dicho por esa entidad en la Resolución N° 30887 del 26 de septiembre de 2002, por la cual se niega la patente de invención a la solicitud 98005805 "Tabletas de Oxcarbazepina recubiertas de una película y método para la producción de estas formulaciones", que "no se traduce en ningún avance sobre el estado de la técnica el modificar una propiedad física de un sólido, como es su tamaño de partícula, con el fin de variar su perfil de disolución y determinar la variación de la biodisponibilidad, puesto que este fenómeno es perfectamente conocido y se encuentra al alcance de cualquier persona con mediana formación farmacotécnica". (Subrayado y negrita fuera del texto)
- La eventual biodisponibilidad mejorada de una composición de inhibidores de la COX-2 por obra de la presencia de tal familia de principios activos en los tamaños de partícula revelados, corresponde simplemente a un fenómeno que es conocido, que no traduce ningún avance sobre el estado de la técnica, y que es el resultado de un proceso rutinario de pre-formulación, consistente en realizar ensayos sobre disolución empleando tamaños de partícula diversos.
- Respecto a las composiciones farmacéuticas descritas en las reivindicaciones 14 y 15 de la presente solicitud de patente, es importante resaltar que carecen de especificidad y nivel inventivo, pues en la solicitud US 5,466,823 publicada el 14 de noviembre de 1995, se revela Celecoxib, sus propiedades, e indicación terapéutica y composiciones farmacéuticas que pueden contener el ingrediente activo (entre los que se encuentra Celecoxib) en el rango de alrededor 0.1 a 2000mg. En consecuencia, resulta claro que los rangos propuestos (10mg a 1000mg en la solicitud colombiana 00-093-233) se encuentran totalmente incluidos en los rangos descritos en el documento internacional mencionado anteriormente.
- Es inaceptable a la luz del ordenamiento subregional andino, el pretender obtener exclusiva sobre un método terapéutico para el tratamiento humano o animal, tal como es revelado en las reivindicaciones 16 a 18, pues su

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patentamiento está expresamente prohibido en el artículo 20 (d) de la Decisión 486.

II. COMPLEMENTO DE INFORMACIÓN

El Informe Internacional de Búsqueda practicado por la Oficina Europea de Patentes a la aplicación internacional PCT/WO01/41760, publicada en 14-06-2001, y equivalente a la solicitud en trámite, en tanto invocan la misma prioridad, señala la existencia de dos (2) anterioridades clasificadas como categoría "X, P" que afectan la novedad y el nivel inventivo de dicha solicitud (y por ende los de la solicitud colombiana), las cuales, si bien fueron publicadas después de la fecha de prioridad, lo fueron antes de la fecha de presentación de la solicitud internacional respectiva. Sin perjuicio de reconocer la independencia de cada oficina nacional para evaluar el cumplimiento de los requisitos de patentabilidad, ruego que además de los argumentos y pruebas presentados con el escrito de oposición, se consideren los siguientes:

- a) La Aplicación internacional PCT/WO00/32189 publicada el 8-06-2000 se refiere en su reivindicación 5 a composiciones farmacéuticas que comprenden una o más unidades de dosis de liberación oral que comprende Celecoxib particulado en cantidades entre 10mg y 1000mg, en mezcla íntima con uno o más excipientes farmacéuticamente aceptables, y donde Celecoxib tiene una distribución de tamaño de partícula tal que el D_{90} de esas partículas es menos que 200 μ m, preferiblemente menor que 40 μ m, y más preferiblemente menor que 25 μ m; a su vez, en la reivindicación 6 se describe a Celecoxib particulado en cantidades entre 10mg y 1000mg y donde Celecoxib tiene tamaños de partícula entre 1 μ m y 10 μ m.

Lo anterior permite inferir que tanto las dosis de Celecoxib (10mg a 1000mg) como los tamaños de partícula preferidos en la solicitud colombiana en trámite y consignados en las reivindicaciones 1 a 3 (*D_{90} de alrededor de 0.01 μ m hasta alrededor de 200 μ m, preferiblemente más pequeñas de 1 μ m*), se encontrarían revelados y cobijados con anterioridad en la aplicación PCT WO00/32189, pues en este documento se designan los mismos rangos de dosis y los tamaños de partícula preferidos se encuentran entre 1 μ m y 200 μ m.

- b) La Aplicación internacional PCT/WO00/53149 publicada el 14-09-2000, se refiere en el ejemplo 1 y en la tabla X-1A correspondiente, a la preparación de composiciones de Celecoxib en donde el tamaño de partícula de Celecoxib luego de ser sometido a molienda varía dentro de un rango relativamente

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estrecho y donde por lo menos el 90% de las partículas tienen un tamaño de 30µm o inferior a este (negrita fuera del texto). De esta manera, y en virtud de lo revelado anteriormente, queda demostrado una vez más que los tamaños de partícula consignados en la solicitud CO 00-093-233 carecen de novedad y de nivel inventivo.

III. PRUEBAS

Además de las solicitadas en el escrito de oposición, y de aquellas que oficiosamente considere el despacho, ruego que se tengan como tales las siguientes:

- 2.1. Informe Internacional de Búsqueda practicado por la Oficina Europea de Patentes a la aplicación internacional PCT/WO01/41760.
- 2.2. Apartes de la publicación internacional PCT WO00/32189.
- 2.3. Apartes de la publicación internacional PCT WO00/53149.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P. 44655 del C. S de la J.

(19) World Intellectual Property Organization
International Bureau



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14 June 2001 (14.06.2001)

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(18) International Publication Number
WO 01/41760 A3

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(21) International Application Number: PCT/US00/32434

(22) International Filing Date: 6 December 2000 (06.12.2000)

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(30) Priority Data:
60/169,856 8 December 1999 (08.12.1999) US

(71) Applicant (for all designated States except US): PHARMACIA CORPORATION [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680 (US).

(72) Inventors and

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HAGEMAN, Michael, J. [US/US]; 5262 South 12th Street, Portage, MI 49024 (US). HASKELL, Royal, J. [US/US]; Kalamazoo, MI (US).

(74) Agents: FORBES, James, C. et al.; Pharmacia Corporation, P.O. Box 5110, Chicago, IL 60680 (US).

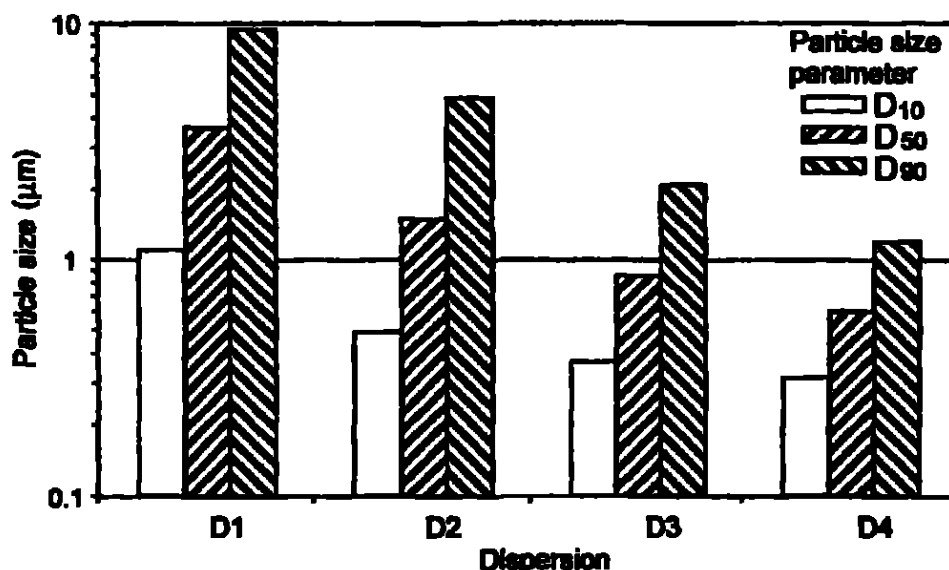
(81) Designated States (national): AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), European patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LJ, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
— with international search report

[Continued on next page]

(54) Title: CYCLOOXYGENASE-2 INHIBITOR COMPOSITIONS HAVING RAPID ONSET OF THERAPEUTIC EFFECT



(57) Abstract: Pharmaceutical compositions are provided comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in the form of solid particles, about 25 % to 100 % by weight of which are smaller than 1 µm. The compositions are useful in treatment or prophylaxis of cyclooxygenase-2 mediated conditions and disorders and have particular advantages where rapid onset of therapeutic effect is desired.

WO 01/41760 A3

INTERNATIONAL SEARCH REPORT

Inventor and Application No.
PCT/US 00/32434

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/42 A61K9/20

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

B. FIELDS SEARCHED

Machinery classification searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than machine documentation to the extent that such documents are reflected in the table searched

Electronic data base consulted during the international search (name of data base used, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 756 529 A (P.C.ISAKSON ET AL.) 26 May 1998 (1998-05-26) claims column 95, line 28 -column 97, line 22	1-18
A	WO 96 25405 A (G.D.SEARLE & CO.) 22 August 1996 (1996-08-22) cited in the application claims page 150, line 24 - line 38	1-18
A	EP 0 863 134 A (MERCK FROSST CANADA) 9 September 1998 (1998-09-09) cited in the application claims page 4, line 10 -page 5, line 15 examples	1-18
	— — — — — -/-	

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

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority (date) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other session
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be distinguished novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document number of the same patent family

Date of the actual completion of the international search

21 May 2001

Date of mailing of the international search report

01/06/2001

Name and mailing address of the ISA

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Authorized officer

Scarponi, U

INTERNATIONAL SEARCH REPORT

Int. Appl. No.
PCT/US 00/32434

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of documents, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00-32189 A (G.D. SEARLE & CO.) 8 June 2000 (2000-06-08) claims examples	1,4,5, 11-18
X,P	WO 00-53149 A (G.D. SEARLE & CO.) 14 September 2000 (2000-09-14) claims 1,4,24,26,28-30,35,37,46,48,57,59,68,70,79 ,81,90 claims 92,101,103,112,114 page 58, line 22 -page 60, line 32 page 41, line 23 -page 45, line 18	1,4,5, 11-18

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61K 31/415	A1	(11) International Publication Number: WO 00/32189 (43) International Publication Date: 8 June 2000 (08.06.00)
(21) International Application Number: PCT/US99/28411 (22) International Filing Date: 30 November 1999 (30.11.99) (30) Priority Data: '60/110,333 30 November 1998 (30.11.98) US (71) Applicant (for all designated States except US): G. D. SEARLE & CO. (US/US); 5200 Old Orchard Road, Skokie, IL 60077 (US). (72) Inventors; and (73) Inventors/Applicants (for US only): GAO, Daichen (CN/US); 1446 S. Paulina Avenue, Chicago, IL 60605 (US). HLINAK, Anthony, J. (US/US); 1803 Longmeadow Drive, Lindenhurst, IL 60046 (US). MAZHARY, Ahmad, M. (US/US); 1461 Lancaster Lane, Algonquin, IL 60102 (US). TRUBLOVE, James, E. (US/US); 1006 Regency Lane, Libertyville, IL 60048 (US). VAUGHN, Margaret, B., Woodhull (US/US); 764 Rosewood, Winnetka, IL 60093 (US). (74) Agent: STREIT, Richard, J.; Ladas & Perry, 224 S. Michigan Avenue, Chicago, IL 60604 (US).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW. ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Russian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, NG, TD, TG). Published With international search report.	
(54) Title: CYCLOOXYGENASE COMPOSITIONS (57) Abstract Pharmaceutical compositions are provided comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients. The compositions are useful in treatment or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.		

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to :
about 1000 mg in intimate mixture with one or more pharmaceutically.
5 acceptable excipients, wherein a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib characterized by at least one of
 - (a) a time to reach 100 ng/ml not greater than about 0.5 h after
administration;
 - 10 (b) a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration;
 - (c) a duration of time wherein concentration remains above 100 ng/ml not less than about 12 h;
 - (d) a terminal half-life ($T_{1/2}$) not less than about 10 h; and
 - 15 (e) a maximum concentration (C_{max}) not less than about 200 ng/ml.
2. A composition of Claim 1 wherein the time course of blood serum concentration of celecoxib is characterized by a T_{max} not greater than about 3 h, preferably not greater than about 2 h, and more preferably not greater than about 1.7 h, after administration.
- 20 3. A composition of Claim 1 wherein the C_{max} is not less than about 200 ng/ml, preferably not less than about 400 ng/ml.
4. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically
25 acceptable excipients, and having relative bioavailability not less than about 50%, preferably not less than about 70%, by comparison with an orally delivered solution containing an equivalent amount of celecoxib.
5. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to
30 about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having a distribution of celecoxib particle sizes

such that D_{90} of the particles is less than 200 μm , preferably less than 100 μm , more preferably less than 40 μm , and most preferably less than 25 μm , in the longest dimension of said particles.

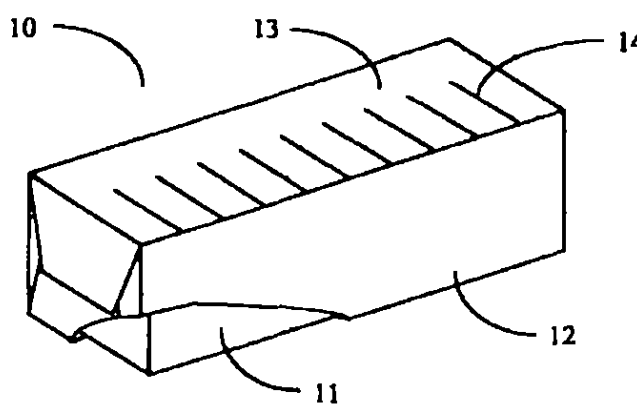
- 5 6. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having a mean celecoxib particle size of about 1 μm to about 10 μm .
- 10 7. A composition of any of Claims 1 to 6 wherein the amount of celecoxib in each dose unit is about 50 mg to about 800 mg, preferably about 75 mg to about 400 mg, and more preferably about 100 mg to about 200 mg.
8. A composition of any of Claims 1 to 7 that is suitable, by oral administration to a subject of a dose unit once or twice a day, for providing therapeutically or prophylactically effective inhibition of cyclooxygenase-2.
- 15 9. A composition of any of Claims 1 to 7 that is suitable, by oral administration to a subject of a dose unit once or twice a day, for treatment or prophylaxis of a cyclooxygenase-2 mediated condition or disorder.
10. A composition of any of Claims 1 to 9 wherein said dose units are in a form of discrete solid articles.
- 20 11. A composition of Claim 10 wherein said articles are tablets, pills, hard or soft capsules, lozenges, sachets or pastilles.
12. A composition of Claim 10 in the form of unit dosage capsules or tablets.
13. A composition of Claim 12 wherein said excipients are selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents and lubricants.
- 25 14. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable diluents in a total amount of about 5% to about 99% by weight, preferably about 10% to about 85% by weight, of the composition.

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50. A composition of Claim 12 comprising unit dosage capsules each containing
- (a) about 100 mg of celecoxib;
 - (b) about 149.75 mg of lactose monohydrate;
 - (c) about 2.7 mg of croscarmellose sodium;
 - 5 (d) about 6.75 mg of polyvinylpyrrolidone;
 - (e) about 8.1 mg of sodium lauryl sulfate; and
 - (f) about 2.7 mg of magnesium stearate.
51. A composition of Claim 12 comprising unit dosage capsules each containing
- (a) about 200 mg of celecoxib;
 - 10 (b) about 49.75 mg of lactose monohydrate;
 - (c) about 2.7 mg of croscarmellose sodium;
 - (d) about 6.75 mg of polyvinylpyrrolidone;
 - (e) about 8.1 mg of sodium lauryl sulfate; and
 - (f) about 2.7 mg of magnesium stearate.
- 15 51. A composition of Claim 12 comprising unit dosage tablets each containing
- (a) about 100 mg of celecoxib;
 - (b) about 101.88 mg of lactose monohydrate;
 - (c) about 7.5 mg of croscarmellose sodium;
 - (d) about 6.25 mg of polyvinylpyrrolidone;
 - 20 (e) about 25 mg of microcrystalline cellulose;
 - (f) about 7.5 mg of sodium lauryl sulfate; and
 - (g) about 1.88 mg of magnesium stearate.
52. A composition of Claim 12 comprising unit dosage tablets each containing
- (a) about 200 mg of celecoxib;
 - 25 (b) about 203.8 mg of lactose monohydrate;
 - (c) about 15 mg of croscarmellose sodium;
 - (d) about 12.5 mg of polyvinylpyrrolidone;
 - (e) about 50 mg of microcrystalline cellulose;
 - (f) about 15 mg of sodium lauryl sulfate; and
 - 30 (g) about 3.75 mg of magnesium stearate.
53. A composition of Claim 12 comprising unit dosage capsules or tablets each providing a 100 mg or 200 mg dose of celecoxib.

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77. A method of Claim 76 wherein the condition or disorder is rheumatoid arthritis.
78. A method of Claim 76 wherein the condition or disorder is osteoarthritis.
79. A method of Claim 76 wherein the condition or disorder, or a symptom of the condition or disorder, is pain.
80. A method of preparing a composition of Claim 12 comprising
- (a) wet granulating celecoxib together with one or more excipients to form a wet granulated mixture;
 - (b) drying the wet granulated mixture; and
 - (c) encapsulating the dried granulated mixture or compressing the dried granular mixture into tablets.
81. A method of Claim 80 wherein, prior to the wet granulating step, the celecoxib is milled such that D_{90} of the resulting particles is less than 200 μm , preferably less than 100 μm , more preferably less than 40 μm , and most preferably less than 25 μm , in the longest dimension of said particles.
82. A method of Claim 81 wherein said milling is performed with a pin mill to provide celecoxib particles of D_{90} less than 25 μm , in the longest dimension of said particles.
83. A method of Claim 82 wherein said milling results in a mean celecoxib particle size of about 1 μm to about 10 μm , preferably about 5 μm to about 7 μm .

(51) International Patent Classification: A61K	A2	(11) International Publication Number: WO 00/53149 (43) International Publication Date: 14 September 2000 (14.09.00)
(21) International Application Number: PCT/US00/06097 (22) International Filing Date: 9 March 2000 (09.03.00) (30) Priority Data: <u>60/123,644</u> 10 March 1999 (10.03.99) US (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; P.O. Box 5110, Skokie, IL 60077 (US). (72) Inventors and (73) Inventors/Applicants (for US only): KEANE, J., Timothy [US/US]; 66 Broadview Drive, Clayton, MO 63105 (US). SCHUH, Joseph, R. [US/US]; 2055 Rutline Drive, St. Louis, MO 63146 (US). SCRIVNER, Alan, R. [US/US]; 744 Lakeshore Manor Court, Wildwood, MO 63038 (US). (74) Agents: WILLIAMS, Scott, A. et al.; Seindger, Powers, Leavitt & Roedel, 16th floor, One Metropolitan Square, St. Louis, MO 63102 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GR, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.
(54) Title: METHOD AND COMPOSITION FOR ADMINISTERING A CYCLOOXYGENASE-2 INHIBITOR (57) Abstract Food compositions comprising at least one cyclooxygenase-2 inhibitor, methods for the treatment or prophylaxis of a condition or disorder in a non-human where administration of a cyclooxygenase-2 inhibitor is indicated comprising feeding such food compositions to the non-human, articles of manufacture comprising such food compositions, and methods for the preparation of food compositions comprising a cyclooxygenase-2 inhibitor. 		

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containing a metered dose of the cyclooxygenase-2 inhibitor.

In another embodiment, an article of manufacture 30 of the present invention is illustratively shown in Fig. 4. The article comprises a slab of brittle food material 31, illustratively a baked material such as a biscuit or cracker, wherein is substantially homogeneously distributed a cyclooxygenase-2 inhibitor. The article is readily breakable, for example by hand, along linear grooves 32 to provide substantially even-sized portions 33 each containing a metered dose of the cyclooxygenase-2 inhibitor. If desired the grooves can be replaced by equivalent means for creating linear zones of reduced mechanical strength, such as linearly aligned perforations or indentations.

Distinct versions of each article of manufacture can be prepared to provide, for example, a low, medium or high dose amount of cyclooxygenase-2 inhibitor per unit volume of food material. Depending upon the animal treated, the severity of the condition treated, and other relevant factors, the animal owner can select a version of the article of manufacture containing the most convenient and appropriate unit dose amount of the cyclooxygenase-2 inhibitor.

EXAMPLES

The following examples illustrate aspects of the present invention but should not be construed as limitations. The symbols and conventions used in these examples are consistent with those used in the contemporary animal food composition and veterinary literature. Unless otherwise stated, all percentages recited in these examples are weight percents based on total composition weight.

Example 1: Preparation of Celecoxib Compositions

Three separate Celecoxib compositions having the compositions set forth in Table X-1A are prepared for use in the preparation of the animal food compositions of the succeeding examples:

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TABLE X-1A

INGREDIENT	WEIGHT FRACTION (%)		
	Composition 1A-1	Composition 1A-2	Composition 1A-3
Celecoxib	37.04	74.07	40
Lactose Monohydrate (NF, Ph Eur)	55.46	18.43	40.75
Sodium Lauryl Sulfate (NF, Ph Eur)	3	3	3
Povidone (K29-32 USP)	2.5	2.5	2.5
Croscarmellose Sodium (NF, Ph Eur)	1	1	3
Magnesium Stearate (NF, Ph Eur)	1	1	0.75
Microcrystalline Cellulose (Avicel PH-102 NF)	0	0	10
Total	100	100	100

Lactose monohydrate is commercially available from Formost Farms, Baraboo, Wisconsin. The Ac-Di-Sol brand of croscarmellose sodium is commercially available from FMC Corporation, Chicago, Illinois. Sodium lauryl sulfate is commercially available from Henkel Corporation, Cincinnati, Ohio. The Povidone brand of polyvinylpyrrolidone is commercially available from International Specialty Products. Magnesium stearate is commercially available from Mallinckrodt Inc., St. Louis, Missouri. The Avicel brand of microcrystalline cellulose is commercially available from FMC Corporation, Philadelphia, Pennsylvania.

- 10 An illustrative process for the preparation of composition 1A-1 is described below. Compositions 1A-2 and 1A-3 are prepared in a similar manner.

Milling: The Celecoxib was milled in an impact-type pin mill with counter rotating disks. At mill speeds ranging from about 8960 rpm/5600 rpm to about 11200 rpm/5600 rpm (rotating rpm/counter rotating rpm) particle size varied within relatively narrow ranges (at least 90% of the particles were 30-microns or less in size) suggesting that mill speed is not narrowly critical to the bulk drug micronization process.

Dry Mixing: The Celecoxib, lactose, Povidone and croscarmellose sodium

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were transferred to a 120 L Niro Fielder PMA-120 high speed granulator and mixed for about 3 minutes at fast chopper and impeller speeds. This dry mixing time provided adequate mixing of Celecoxib with the carrier materials prior to the start of the wet granulation step.

5 Wet Granulation: Sodium lauryl sulfate (8.1 kg) was dissolved in purified USP water (23.7 kg). This solution was progressively added to the granulator at a rate of about 14 kg/minute. Total granulation time was about 6.5 minutes. During this granulation, the main blade and chopper blade of the granulator were placed on the fast speed setting. The wet granulated mixture was about 8.1% water by weight.

10 Drying: The wet granulation was delumped using a Quadro Comil Model 198 S screening mill equipped with rotating impeller and a coarse screen. Wet milling was used to eliminate large material lumps that formed as a by-product of the wet granulation operation. If not removed, these lumps would have prolonged the subsequent fluidized bed drying operation and increased the variation with respect to
15 moisture control. The delumped granulation was transferred to an Aeromatic Fluid Bed Dryer T-8. The inlet air temperature and flow rate were adjusted to about 60°C and about 5000 to 6000 ft³/minute. The granulation was dried in the fluidized bed dryer to reduce the moisture content to between 0.5% to 2.5%. Moisture content was monitored using a Computrac Moisture Analyzer. Drying continued until the loss on
20 drying of the granulation was not more than 1.0%. It may be desirable to combine two or more granulation sections for this drying step and subsequent processing steps.

 Dry Milling: The dry granules were passed through a Fluid Air Mill Model 007 impact mill (conventional hammer) equipped with a 0.028 inch to 0.063 inch screen, knives forward, and 2400 rpm speed. Dry milling was used in combination
25 with the wet granulation step to control the final size distribution of the granules.

 Blending and Lubrication: The milled granules were then placed in a PK Cross-Flow Blender 75 Cubic Foot diffusion mixer/V- blender. The magnesium stearate was added and the mixture blended for about 5 minutes. The blending time provided blended material that was uniform with respect to the concentration of
30 Celecoxib. Blender rotational speed was 10.6 revolutions per minute. The final blend was used to combine materials from multiple granulation sections into a single uniform mixture and to evenly distribute lubricant into the material.

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- alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-alkylamino, N-alkyl-N-alkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl and N-alkyl-N-phenylaminosulfonyl; and
- 25 wherein R⁴ is hydrido or fluoro;
 or a pharmaceutically-acceptable salt thereof.
4. A method of claim 1 wherein said cyclooxygenase-2 inhibitor is selected from Celecoxib, Deracoxib, Rofecoxib and Valdecoxib.
5. A method of claim 1 wherein said cyclooxygenase-2 inhibitor is Deracoxib.
6. A method of claim 1 wherein said animal has a weight greater than about 1 kg.
7. A method of claim 1 wherein said animal has a weight within the range of about 2 kg to about 70 kg.
8. A method of claim 1 wherein said animal has a weight within the range of about 50 kg to about 1500 kg.
9. A method of claim 1 wherein said animal is a dog.
10. A method of claim 1 wherein said animal is a horse.
11. A method of claim 1 wherein said metered amount of said food composition contains an amount of said selective cyclooxygenase-2 inhibitor that is between about 0.1 mg/kg animal body weight to about 15 mg/kg animal body weight.
12. A method of claim 1 wherein said metered amount of said food composition

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Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°: **08389**

ASUNTO:	Radicación N°	00-93233
	Trámite	002
	Evento	001
	Actuación	430
	Folios	046

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., y Laboratorio Franco Colombiano Lafranco S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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


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

09 OCT. 2003

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

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Let's go
Muel
29-10-2023

Obs.