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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Clarke, Modet & C^o

COLOMBIA

SEÑORES
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

REF: EXPEDIENTE No. 04095478
ELAN PHARMACEUTICALS, INC.
ADMINISTRACIÓN DE AGENTES PARA EL TRATAMIENTO
DE INFLAMACIÓN
FECHA DE LA SOLICITUD: SEPT. 24, 2004

ASUNTO: IMPULSO PROCESAL

DILIA RODRIGUEZ D'ALEMAN, en mi calidad de apoderada de la sociedad solicitante de la patente de la referencia manifiesto a usted lo siguiente:

1. Mediante memorial radicado en ese despacho el 24 de Julio de 2006, el cual no ha sido resuelto aún, solicité que se realizara el examen de patentabilidad.
2. En vista de que ha transcurrido **MAS DE 1 AÑO** sin que se haya atendido dicha solicitud, ruego a usted se sirva dar las instrucciones del caso para que se proceda de inmediato a resolver este asunto.

Cordialmente,

DILIA RODRIGUEZ D'ALEMAN
C.C. 41.654.882 de Bogotá
T.P. 20824

p-578

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 04-095478

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **561** DE

FECHA **28 DE FEBRERO DE 2006** EL TERMINO HABIL EÑALADO POR LA

LEY EXPIRA EL **30 DE MAYO DEL 2006**

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.

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NO__ _X_ _____

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Volume 52(5), 23 March 1999, pp 1072-1074

[About this Journal](#)[Table of Contents](#)[Browse TOC](#)[Find Citing Articles](#)[Email Jumpstart](#)[Save Article Text](#)[Email Article Text](#)[Print Preview](#)**A safety and pharmacokinetic study of intravenous natalizumab in patients with MS**

[Brief Communications]

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Presented at the 50th annual meeting of the American Academy of Neurology; Minneapolis, MN; April 1998.

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Article abstract

A phase 1, randomized, placebo-controlled, five-level dose escalation safety and tolerability and pharmacokinetic study of a single IV dose of natalizumab was performed. Doses of 0.03 to 3.0 mg/kg natalizumab or placebo were studied in 28 stable relapsing-remitting or secondary-progressive MS. All doses were safe and well tolerated in MS. Serum concentrations of natalizumab are detectable for 3 to 8 weeks after a single 1- or 3-mg/kg IV dose and justify controlled efficacy studies.

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Recent History

A safety and pharmacokine...



Clinical relapses in MS are attributed to recurrent inflammatory white matter lesions (plaques) comprised of chronic inflammatory cells, demyelination, and gliosis.¹ MRI may visualize plaques, but new MRI brain lesions occur 5 to 10 times more frequently than clinical exacerbations.²⁻⁵ Gadolinium enhancement of lesions reflects blood-brain barrier (BBB) disruption,^{3,4} which is thought to correlate with the migration of leukocytes into the CNS.⁶

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Leukocyte trafficking across the BBB involves interaction of the cell adhesion molecule [alpha]4[beta]1 integrin (VLA-4), expressed on lymphocytes and monocytes, with its ligand-vascular cell adhesion molecule VCAM-1 on brain endothelial cells.^{6,7} Blockade of this molecular pair should prevent trafficking of leukocytes into the brain and lesion formation. Natalizumab (Antegren, Athena Neurosciences, Inc., South San Francisco, CA) is a humanized, anti-[alpha]4 integrin antibody shown to inhibit trafficking of leukocytes across the BBB and to rapidly reverse experimental allergic encephalomyelitis (EAE).^{8,9} We report a phase 1, randomized, placebo-controlled, five-level dose escalation safety and tolerability study of a single IV dose of natalizumab in MS patients.

Methods. Study patients were stable, clinically definite relapsing-remitting or secondary-progressive MS patients,¹⁰ all of whom were between 19 and 55 years of age and within 15% of their ideal body weight range. Kurtzke's Expanded Disability Status Scale (EDSS) scores were ≤ 5.5 . Excluded were patients with MS exacerbations or infections, and immunomodulatory or any investigational drug recipients. Women of childbearing potential who were pregnant, nursing, or not using adequate birth control were excluded. Regular blood donors, heavy smokers and drinkers, and those with other medical disorders or known drug hypersensitivity were also excluded.

After providing informed consent, 28 patients were screened sequentially. Seven patients were randomized to placebo and 21 were randomized to active drug treatment (0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg natalizumab). Four were enrolled sequentially for each of the 0.03-, 0.1-, and 0.3-mg/kg groups (three active, one placebo), and eight patients, stratified by sex, were enrolled in the 1.0- and 3.0-mg/kg mg/kg groups (six active, two placebo). Staggered enrollment was used for these two highest dose levels.

Study drug. Natalizumab is derived from a murine monoclonal antibody to human [alpha]4[beta]1 integrin. Murine antibody is humanized by complementarily determining region grafting of the hypervariable region of the gene encoding the murine antibody onto a human immunoglobulin G4 framework. Treatment of guinea pig EAE with either natalizumab or its murine parent of AN100226m results in a striking dose-dependent reversal of both clinical manifestations and CNS leukocytic infiltration.^{8,9} Athena Neurosciences supplied the drug in clear, stoppered individual vials containing 5 mL of 5.0 mg/mL natalizumab or placebo. The calculated dose of study drug was diluted to 100 mL volume with normal saline and was infused IV over 45 minutes.

Safety and tolerability were monitored by physical and neurologic examinations, Kurtzke's EDSS scores, vital signs, laboratory tests (chemistry, hematology, and urinalysis), and EKG. Adverse events were recorded. Brain MRI with and without gadolinium contrast was performed in the 1.0- and 3.0-mg/kg groups at screening, and weeks 1 and 4. Vital signs and pharmacokinetic (PK) samples were obtained at baseline, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 24 hours, as well as at the end of weeks 1, 2, 3, and 4. For the 3.0-mg/kg group, additional samples were collected at the end of weeks of 6 and 8, and for a subset, they were collected at the end of weeks 10, 12, and 14. Total antinatalizumab antibody and anti-idiotypic natalizumab antibody were determined at baseline and termination.

Natalizumab serum concentration. ELISA uses an anti-idiotypic monoclonal antibody (12C4; Athena Neuroscience) specific for natalizumab as the capture antibody. The assay was

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validated for concentrations ranging from 50 to 2,000 pg/mL. Total antinatalizumab antibody ELISA uses natalizumab as both capture and detecting reagent, and 12C4 as the standard. The lower limit for antibody is 5 µg/mL serum. Anti-idiotypic natalizumab antibody ELISA employs a murine antibody (AN100226m) as the capture antibody. The lower limit for this assay is 1.0 µg/mL.

Descriptive statistics were used to summarize all data. Number and percentage of patients in each category summarize qualitative variables. Mean and SD summarize continuous variables.

Results. Demographics. Mean ($\pm$ SD) age was 40.8 ± 9.1 years; weight, 68.1 ± 10.5 kg; and age at onset of MS, 32.3 ± 10.6 years. Fifteen patients (54%) were men and 13 (46%) were women; 20 (71%) had relapsing-remitting MS and eight (29%) had secondary-progressive MS. The mean historic frequency of MS exacerbations for the previous 2 years ranged from 0.7 to 2.3. There were no important differences between placebo and natalizumab groups in demographic or disease characteristics.

Safety and tolerability. Vital signs did not change during study drug infusion nor did any measures detect differences between dose groups. No patient withdrew or reported a serious adverse event. Treatment-emerging signs and symptoms (TESS) occurred in every dose group (23 of 28 patients). All were mild in severity, except for a urinary tract infection on day 9 in the 3-mg/kg group (not study drug related). The most frequently reported TESS was headache. Frequency of patients with one or more TESS was similar in placebo (6 of 7, 86%) and natalizumab (17 of 21, 81%).

Study drug-related adverse events. Three patients reported five study drug-related adverse events, all of which were mild: urticaria (1), 1.0-mg/kg group; and nausea (2), headache (1), and shakiness (1), 3.0-mg/kg group.

Laboratory. Only two patients had a liver function test that exhibited results two times the normal value. One placebo recipient exhibited a single aspartate transaminase elevation at week 3, and one 0.3-mg/kg patient had a single alanine transaminase elevation at week 2. Minor decreases in red blood cell, white cell, and platelet indices were noted randomly.

MRI in the 1- and 3-mg/kg groups revealed no trends in the number of lesions related to treatment group.

Pharmacokinetics. Mean PK measurements by dose group are summarized in the table. Serum natalizumab concentrations for the 0.03- and 0.1-mg/kg groups fell rapidly to below detectable limits after drug infusion. Those in the 0.3-mg/kg group had detectable serum natalizumab concentrations for 1 week, whereas those in the 1.0- and 3.0-mg/kg group had detectable concentrations for 3 to 8 weeks (figure). Serum concentrations exhibited a biexponential decline, with a relatively rapid distribution phase followed by a prolonged terminal phase.

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Parameter	1.0 mg/kg	3.0 mg/kg	10.0 mg/kg	30.0 mg/kg	100.0 mg/kg
Mean $\pm$ SD	1.0 $\pm$ 0.2	3.0 $\pm$ 0.5	10.0 $\pm$ 1.0	30.0 $\pm$ 2.0	100.0 $\pm$ 5.0
CV, %	20.0	16.7	10.0	6.7	5.0
Mean $\pm$ SD	1.0 $\pm$ 0.2	3.0 $\pm$ 0.5	10.0 $\pm$ 1.0	30.0 $\pm$ 2.0	100.0 $\pm$ 5.0
CV, %	20.0	16.7	10.0	6.7	5.0
Mean $\pm$ SD	1.0 $\pm$ 0.2	3.0 $\pm$ 0.5	10.0 $\pm$ 1.0	30.0 $\pm$ 2.0	100.0 $\pm$ 5.0
CV, %	20.0	16.7	10.0	6.7	5.0
Mean $\pm$ SD	1.0 $\pm$ 0.2	3.0 $\pm$ 0.5	10.0 $\pm$ 1.0	30.0 $\pm$ 2.0	100.0 $\pm$ 5.0
CV, %	20.0	16.7	10.0	6.7	5.0

Table Pharmacokinetic measurements by dose group

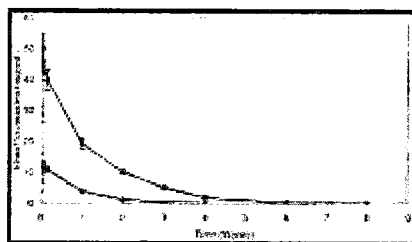
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Figure. Comparison of serum concentrations of natalizumab determined for 9 weeks after single IV infusions of 1 mg/kg ([black four pointed star]) compared with 3 mg/kg ([black circle]).

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Antibody assays. Total natalizumab or anti-idiotypic antibody were not detected in the 0.03-, 0.1-, 0.3-, and 1.0-mg/kg groups, but were detected in three patients in the 3.0-mg/kg group. Two patients had low levels of antibody from week 8 until the end of the study and one patient had a barely detectable response at weeks 8 and 11, but not later.

Discussion. Natalizumab was safe and well tolerated in a study of 28 MS patients. TESS reported by three or more active drug or placebo patients in our study were minor and self-limiting. Three patients reported five TESS deemed study related: headache, nausea,² shakiness, and urticaria. Minor liver function test changes noted were not associated with natalizumab treatment. There were no in-study exacerbations nor was increased disease activity detected by MRI. Three patients in the 3.0-mg/kg group developed both total and anti-idiotypic antibodies. The importance of the appearance of anti-idiotypic antibodies remains to be determined.

Our PK studies reveal that a 1.0- and 3.0-mg/kg IV dose of natalizumab results in a sustained serum level for 3 to 8 weeks. This suggests that the use of a single IV dose of natalizumab may limit acute MS relapses. Further study of natalizumab in double-blind, controlled studies is warranted.

Disclosure [↑](#)

Drs. Willmer-Hulme and Koller are employees of Athena Neuroscience, and Dr. Koller owns shares, but none own important equity in the company.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 5/078, A61K 38/05	A1	(11) International Publication Number: WO 99/06437 (43) International Publication Date: 11 February 1999 (11.02.99)
(21) International Application Number: PCT/US98/16070 (22) International Filing Date: 31 July 1998 (31.07.98) (30) Priority Data: 08/904,423 31 July 1997 (31.07.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/904,423 (CIP) Filed on 31 July 1997 (31.07.97) (71) Applicants (for all designated States except US): ATHENA NEUROSCIENCES, INC. [US/US]; 800 Gateway Boulevard, South San Francisco, CA 94080 (US). AMERICAN HOME PRODUCTS CORPORATION [US/US]; 5 Giraldi Farms, Madison, NJ 07940 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): THORSETT, Eugene, D. [US/US]; 571 Buena Vista, Moss Beach, CA 94038 (US). SEMKO, Christopher, M. [CA/US]; 2361 Carpenter Court, Fremont, CA 94539 (US). PLEISS, Michael, A. [US/US]; 848 Stella Court, Sunnyvale, CA 94087 (US). KREFT, Anthony [US/US]; 43 Barley Court, Langhorne, PA 19047		(US). KONRADI, Andrei, W. [US/US]; 95 Cervantes #105, San Francisco, CA 94123 (US). GRANT, Francine, S. [FR/US]; 3735 Sacramento Street, San Francisco, CA 94118 (US). BAUDY, Reinhardt, Bernhard [DE/US]; 5281 Harrington Court, Doylestown, PA 18901 (US). SARANTAKIS, Dimitrios [US/US]; 262 Sentinel Avenue, Newtown, PA 18940 (US). (74) Agents: SWISS, Gerald, F. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, 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, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, 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 <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: SULFONYLATED DIPEPTIDE COMPOUNDS WHICH INHIBIT LEUKOCYTE ADHESION MEDIATED BY VLA-4

(57) Abstract

Disclosed are compounds which bind VLA-4. Certain of these compounds also inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4. Such compounds are useful in the treatment of inflammatory diseases in a mammalian patient, e.g., human, such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. The compounds can also be administered for the treatment of inflammatory brain diseases such as multiple sclerosis.

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13. A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of Claims 1 or 2 under conditions wherein said compound binds to VLA-4.

5 → 14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more compounds of Claim 1 or 2.

10 15. A method for treating an inflammatory disease in a mammalian patient which disease is mediated by VLA-4 which method comprises administering to said patient a therapeutically effective amount of the pharmaceutical composition of Claim 14.

15 16. The method according to Claim 15 wherein said inflammatory disease is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other
20 cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

25 17. The method of claim 14 wherein R¹ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl.

30 18. The method of claim 14 wherein R¹ is selected from the group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-

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DILIA RODRIGUEZ D' ALEMAN

Radicación	04-95478
Trámite	002
Evento	001
Actuación	430
Oficio	16553
Folios	11

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25-02-2003

1. Documentos estudiados

1.4. Prioridad: Folios: 1
Fecha: 25-02-2002, País y número: US60/360,134.
Fecha: 23-04-2002, País y número: US60/374,501.

Título de la solicitud: "ADMINISTRACIÓN DE AGENTES PARA EL TRATAMIENTO DE INFLAMACIÓN".

El objeto de la presente solicitud de patente de invención consiste en agentes que se unen específicamente e inhiben un receptor de integrina que comprende una subunidad alfa-4 y los usos terapéuticos de los mismos.

Reivindicaciones 1- 29 y 34: Un método para tratar una enfermedad.

Reivindicaciones 30—33 y 35-37: Una composición.

Reivindicaciones 38-41: Una terapia.

Reivindicaciones 42-58: El uso del inhibidor de integrina.

El problema planteado en esta solicitud es la necesidad de reducir crónicamente la inflamación patológica.

Para solucionar este problema técnico la solicitud en estudio proporciona métodos para reducir la inflamación, vía la administración crónica de un agente que se une selectivamente a la integrina alfa-4.

La invención se catalogó según la Clasificación Internacional de Patentes (IPC.) como: A61P 29/00.

3. De la solicitud de Patente (según el caso)

3.1. Reivindicaciones (artículo 30 D 486)

La reivindicación 30 utiliza la frase "comprende un agente en una cantidad suficiente", esta frase no permite establecer cuál o cuales son los posibles agentes que contiene la composición y tampoco se está delimitando en forma clara y concisa la materia que se desea proteger. Adicionalmente el solicitante caracteriza el agente por su utilidad para aliviar los síntomas de la inflamación, el solicitante debe ser más específico al establecer cuál es la composición que desea proteger. Una composición debe caracterizarse por los componentes o sustancias que la componen y la proporción de las mismas, lo cual constituye las características técnicas esenciales de la misma.

Las reivindicaciones 31 y 35 a 37 caracterizan una composición, por la actividad de un agente o por la fuente de la inflamación, por lo tanto estas reivindicaciones no son claras ni concisas ya que el solicitante no establece las características técnicas esenciales de la misma.

La reivindicación 34 establece una falsa dependencia con la reivindicación 33, debido a que la reivindicación 34 habla de un método y la reivindicación 33 establece una composición.

Las reivindicaciones anteriores no cumplen con el requisito de definición, claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. Excepción a la patentabilidad (artículo 20 D486 literal d)

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Las reivindicaciones 1 a 29, 34 y 38 a 41, establecen un método para tratar la inflamación y una terapia de combinación para el tratamiento crónico de la inflamación. Por lo tanto, estas reivindicaciones no son objeto de patente

5. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Las reivindicaciones 42 a 58 establecen el uso del inhibidor de integrina alfa-4 para la preparación de un medicamento y el tratamiento de una condición patológica. Por lo anterior a estas reivindicaciones no se les puede otorgar patente.

6. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 25-02-2002

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación
D1	Neurology Vol. 52(5), 23 march 1999, pp 1072-1074	A safety and pharmacokinetic study of intravenous natalizumab in patients with MS	03-1999
D2	WO9906437	Sulfonilated dipeptide compounds which inhibit leukocyte adhesión mediated by VLA-4	11-02-1999

7. Análisis de patentabilidad (según requisito) (artículo 14 D486)

7.1 Novedad (artículo 16 D486)

La reivindicación 30 habla de una composición para tratamiento crónico de inflamación que comprende un agente en una cantidad suficiente para aliviar los síntomas de la inflamación. El documento D1 da a conocer un estudio que establece la farmacocinética del natalizumab como agente útil para tratar la inflamación el cual se encuentra en una composición contenida en viales individuales de 5ml de 5.0 mg/mL de natalizumab (folios 339 y 340), el estudio demuestra que la infusión de esta composición en solución salina normal es seguro y bien tolerado (folio 342). El documento D2 discute compuestos que inhiben la adhesión de leucocitos mediada por VLA-4 mediante compuestos dipeptídicos sulfonilados que poseen acción antiinflamatoria (folio 344), este documento presenta una composición farmacéutica que comprende un vehículo farmacéuticamente aceptable y una cantidad terapéuticamente efectiva de uno o mas de estos compuestos. Por lo tanto, el elemento característico de la composición reivindicada que consiste en contener un agente en una cantidad

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suficiente para aliviar la inflamación, ya era conocido en D1y D2; por lo cual las composiciones de la reivindicación 30 y sus dependientes 32 a 33 y 35 a 37 no pueden considerarse nuevas.

8. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	Neurology Vol. 52(5), 23 march 1999, pp 1072-1074	30 a 33 y 35-37	Novedad
D2	WO9906437	30 a 33 y 35-37	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 notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 21 DIC. 2007

CONCEPTO TÉCNICO No. 2306	EXAMINADOR TÉCNICO Código No. 202073
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