



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

04-32599

21. EXPEDIENTE No.

54. TITULO "NUEVAS FORMAS CRISTALINAS ANHIDRAS DE LA
SABAPENTINA."

51. CLASIFICACION INTERNACIONAL C07C229/20

71. SOLICITANTE WARNER-LAMBERT COMPANY LLC.

DOMICILIO NUEVA JERSEY, ESTADOS UNIDOS DE AMERICA.

74. APODERADO ALVARO CORREA ORDÓÑEZ
TP. 20.281

22. BOGOTA, D.C., ABRIL 6 DE 2004.

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
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SOLICITUD DE :

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Patente de Invención

☐

Patente de Modelo de Utilidad

☐

Capítulo I.

☒

Capítulo II.

②

SOLICITANTE

(71)

Nombre: WARNER-LAMBERT COMPANY LLC

Dirección: 201 Tabor Road, Morris Plains, Nueva Jersey 07950
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Fax:

E-Mail

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Otro

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Cual

Número

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O APODERADO

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Cual

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79,143,366 de

Usaquén

TP 20.281

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Dirección: VER ANEXO

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Título (54)

NUEVAS FORMAS CRISTALINAS ANHIDRAS DE LA GABAPENTINA.

⑦

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C07C 229/28

⑧

Prioridad

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☒

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US

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Octubre 9, 2001

Septiembre 25, 2002

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60/328,375

10/256,155

⑨

Comprobante de pago No. 04-21,101

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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

10

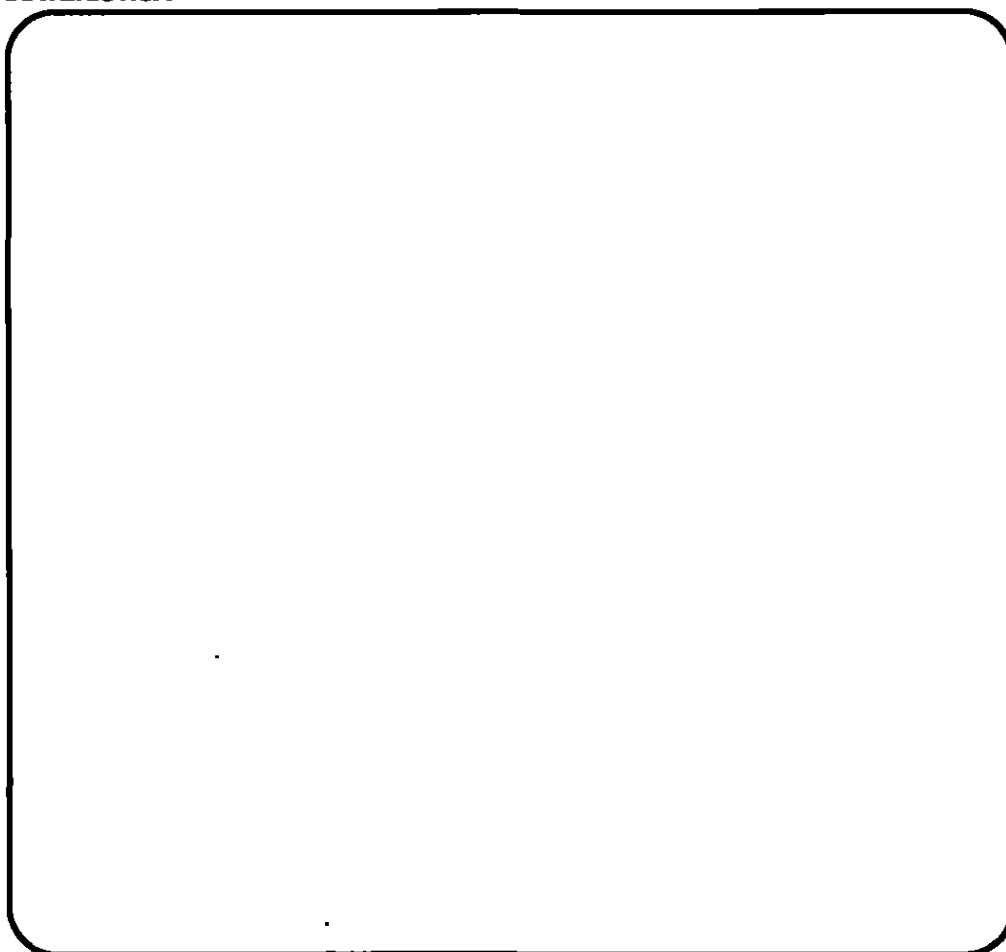
ANEXOS

2

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
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11

FIGURA CARATERISTICA



12

Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de
Usaquén

T.P. 20.281

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3

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Dependencia: 2029 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 21,101
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DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JULIAN ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	030-00110-6	20225347	15/03/2004	68,832,360.00

***** CONCEPTO *****

CANT. CONTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.
	TOTAL :	\$ 422,000.00

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RESPONSABLE : 

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ANEXO - INVENTORES

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Nombre:	<u>CALVITT, Claude Jeffrey</u>
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Nacionalidad ó Domicilio:	<u>ESTADOUNIDENSE</u>

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5

) ss.

I hereby certify that attached hereto is a true and correct copy of the Assignment from Inventors CHEN, BABU, CALVITT and TOBIAS to Warner-Lambert Company of patent rights, in Provisional Patent Application Serial No. 60/328,375, filed October 9, 2001 assigning rights to all corresponding and related applications worldwide, for " NEW ANHYDROUS CRYSTALLINE FORMS OF GABAPENTIN ".



. Dated: March 16, 2004



UNITED STATES
PATENT AND
TRADEMARK OFFICE

--2-30006

6

APRIL 17, 2002

PTAS

Chief Information Officer
Washington, DC 20231
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MERCHANT & GOULD PC
RONALD A. DAIGNAULT
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MINNEAPOLIS, MN 55402-0903



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ASSIGNOR:

CHEN, LINNA R.

DOC DATE: 11/14/2001

ASSIGNOR:

BABU, SURESH R.

DOC DATE: 11/21/2001

ASSIGNOR:

CALVITT, CLAUDE JEFFREY

DOC DATE: 11/30/2001

ASSIGNOR:

TOBIAS, BRIAN

DOC DATE: 12/05/2001

ASSIGNEE:

WARNER-LAMBERT COMPANY
201 TABOR ROAD
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PATENT NUMBER:

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012593/0490 PAGE 2

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ASSIGNMENT DIVISION
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To the Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Linna R. Chen
Suresh R. Babu
Claude Jeffrey Calviit
Brian Tobias

2-8-02

2. Name and address of receiving party(ies):

Warner-Lambert Company
201 Tabor Road
Morris Plains, NJ 07950

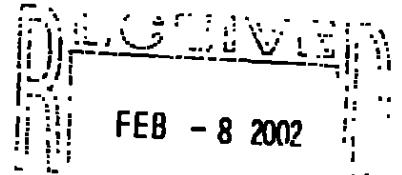
Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

- ☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other:

Execution Date: November 14, 2001, November 21, 2001,
November 30, 2001, December 5, 2001,



4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

B. Patent No.(s)

60/328,375

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Ronald A. Daignault
Address: Merchant & Gould P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903



6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41): \$40.00

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January 21, 2002

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ASSIGNMENT

WHEREAS, we, Linna R. Chen, Suresh R. Babu, Claude Jeffrey Calvitt, and Brian Tobias residing at 3015 Whisperwood Dr. #264, Ann Arbor, MI 48105; 6449 Kings Mill Court, Canton, MI 48187; 6742 Robison Lane, Saline, MI 48176; and 3348 Yellowstone Drive, Ann Arbor, MI 48105, respectively, made certain new and useful inventions and improvements for which we filed a Provisional application in the United States Patent and Trademark Office on October 9, 2001 as application Serial No. 60/328,375 which is entitled NEW ANHYDROUS CRYSTALLINE FORMS OF GABAPENTIN.

AND WHEREAS, Warner-Lambert Company, a corporation organized and existing under and by virtue of the laws of the State of Delaware, and having an office and place of business at 201 Tabor Road, Morris Plains, NJ 07950 (hereinafter "Assignee") is desirous of acquiring the entire right, title and interest in and to said inventions, improvements and application and in and to the Letters Patent to be obtained therefor;

NOW THEREFORE, to all whom it may concern, be it known that for and in consideration of the sum of One Dollar and other good and valuable considerations, the receipt and sufficiency whereof is hereby acknowledged, I/we have sold, assigned, and transferred, and by these presents do sell, assign and transfer unto said Assignee, its successors or assigns, the entire right, title and interest for all countries in and to all inventions and improvements disclosed in the aforesaid application, and in and to said application, all patent applications based upon said Provisional application, all divisions, continuations, or renewals thereof, all Letters Patent which may be granted therefrom, and all reissues or extensions of such patents, and in and to any and all applications which have been or shall be filed in any foreign countries for Letters Patent on the said inventions and improvements, including an assignment of all rights under the provisions of the International Convention, and all Letters Patent of foreign countries which may be granted therefrom; and I/we do hereby authorize and request the Commissioner of Patents and Trademarks to issue any and all United States Letters Patent for the aforesaid inventions and improvements to the said Assignee as the assignee of the entire right, title and interest in and to the same, for the use of the said Assignee, its successors and assigns.

AND, for the consideration aforesaid, I/we do hereby agree that I/we and my/our executors and legal representatives will make, execute and deliver any and all other instruments in writing including any and all further application papers, affidavits, assignments and other

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documents, and will communicate to said Assignee, its successors and representatives all facts known to me/us relating to said improvements and the history thereof and will testify in all legal proceedings and generally do all things which may be necessary or desirable more effectually to secure to and vest in said Assignee, its successors or assigns the entire right, title and interest in and to the said improvements, inventions, applications, Letters Patent, rights, titles, benefits, privileges and advantages hereby sold, assigned and conveyed, or intended so to be.

AND, furthermore I/we covenant and agree with said Assignee, its successors and assigns, that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by me/us and that full right to convey the same as herein expressed is possessed by me/us.

IN TESTIMONY WHEREOF, I have hereunto set my hand this 30th day of November, 2001.

Linna R. Chen
Linna R. Chen

STATE OF Michigan)
COUNTY OF Washtenaw)ss.

On this 30th day of November, 2001 before me personally appeared Linna R. Chen to me known and known to me to be the person described in and who executed the foregoing instrument, and he/she duly acknowledged to me that he/she executed the same for the uses and purposes therein set forth.

[SEAL]

Susan J. Schaefer
Notary Public

SUSAN J. SCHAEFER
NOTARY PUBLIC WASHTENAW CO., MI
MY COMMISSION EXPIRES MAY 13, 2004

IN TESTIMONY WHEREOF, I have hereunto set my hand this 5th day of December, 2001. 11

Suresh R. Babu
Suresh R. Babu

STATE OF Michigan)
COUNTY OF Washtenaw)ss.

On this 5th day of December, 2001 before me personally appeared Suresh R. Babu to me known and known to me to be the person described in and who executed the foregoing instrument, and he/she duly acknowledged to me that he/she executed the same for the uses and purposes therein set forth.

[SEAL]

Susan J. Schaefer
Notary Public

SUSAN J. SCHAEFER
NOTARY PUBLIC WASHTENAW CO., MI
MY COMMISSION EXPIRES Mar 18, 2004

IN TESTIMONY WHEREOF, I have hereunto set my hand this 14 day of November, 2001.

Claude Jeffrey Calvitt
Claude Jeffrey Calvitt

STATE OF Michigan)
COUNTY OF Washtenaw)ss.

On this 14th day of November, 2001 before me personally appeared Claude Jeffrey Calvitt to me known and known to me to be the person described in and who executed the foregoing instrument, and he/she duly acknowledged to me that he/she executed the same for the uses and purposes therein set forth.

[SEAL]

Gus J. Schaefer
Notary Public

GUS J. SCHAEFER
GUS J. SCHAEFER & COMPANY, P.C.
NOTARY PUBLIC - MICHIGAN
COMMISSION EXPIRES MAR 13, 2004

IN TESTIMONY WHEREOF, I have hereunto set my hand this 21 day of November, 2001.

Brian Tobias
Brian Tobias

STATE OF Michigan)
COUNTY OF Washtenaw)ss.

On this 21st day of November, 2001 before me personally appeared Brian Tobias, to me known and known to me to be the person described in and who executed the foregoing instrument, and he/she duly acknowledged to me that he/she executed the same for the uses and purposes therein set forth.

[SEAL]

Lucinda M. Malocha
Notary Public

LUCINDA M. MALOCHA
NOTARY PUBLIC WASHTENAW CO., MI
MY COMMISSION EXPIRES Sep 21, 2004

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(21) International Application Number: PCT/US02/31706

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GH, GM,
HN, 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, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(71) Applicant (for all designated States except US):
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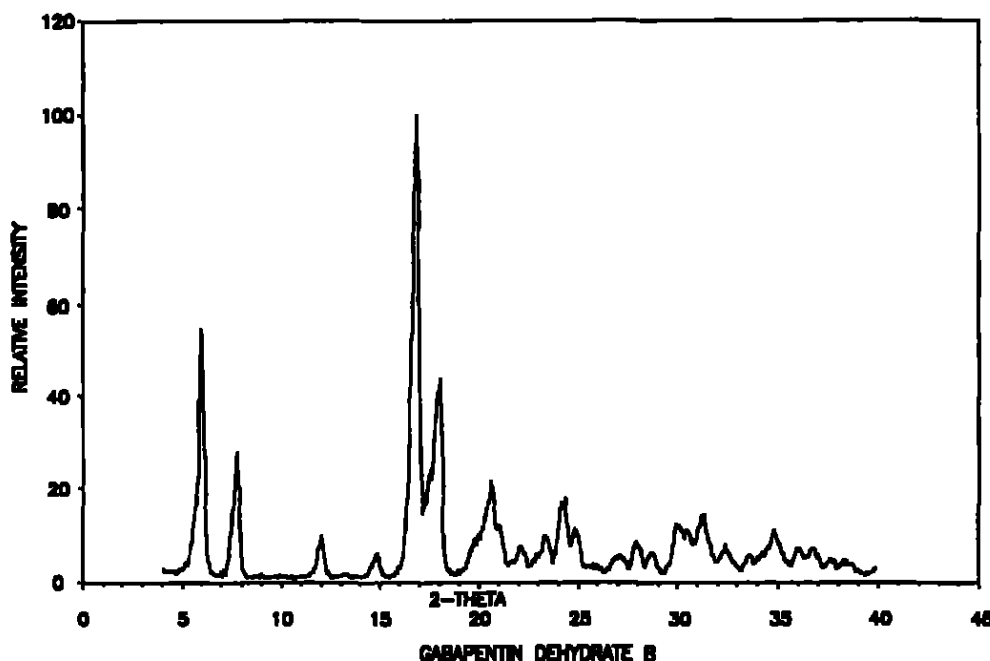
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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

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6742 Robison Lane, Saline, MI 48176 (US). TOBIAS,

Published:
— with international search report

[Continued on next page]

(54) Title: NEW ANHYDROUS CRYSTALLINE FORMS OF GABAPENTIN



(57) Abstract: Described are new crystalline anhydrous forms of gabapentin formed from gabapentin monohydrate. The new crystalline forms provide advantages in the manufacture of the therapeutic agent.

WO 03/031391 A1

WO 03/031391 A1



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

The present invention provides further process improvements to provide pure crystalline forms of the therapeutic agent, gabapentin. The present process eliminates the need of using organic solvents such as methanol described earlier in methods of producing gabapentin and its monohydrate. The present
5 process offers faster manufacturing processing, better safety, less solvent disposal and less loss of yield upon recrystallization.

Brief Description of the Drawings

Fig. 1 shows the ^{13}C -ssNMR spectra for the four crystalline forms of gabapentin.

10 Fig. 2 shows the X-ray powder diffractogram for crystalline gabapentin anhydrate.

Fig. 3 shows the X-ray powder diffractogram for crystalline gabapentin monohydrate.

15 Fig. 4 shows the X-ray powder diffractogram for crystalline gabapentin dehydrate A.

Fig. 5 shows the X-ray powder diffractogram for crystalline gabapentin dehydrate B.

Detailed Description of the Preferred Embodiment

The present invention provides novel crystalline forms of gabapentin,
20 the dehydrate Form A and dehydrate Form B. The present invention also includes improvements in the preparation of gabapentin monohydrate, the precursor to the new crystalline dehydrate of the present invention. Initially, gabapentin monohydrate was reported in U.S. Patent 4,894,476 as a new crystalline form for therapeutic purposes and also as a means of purifying commercial gabapentin, an
25 anhydrous form, by reconversion of the monohydrate to gabapentin.

The present invention is based on a discovery that the known anhydrous form of gabapentin can only be crystallized from solvents or solvent mixtures with a water activity of less than about 0.8 to about 0.9 and gabapentin monohydrate can only be crystallized from water or solvent mixtures with a water
30 activity of greater than about 0.8 to about 0.9. Gabapentin monohydrate can be prepared by suspending gabapentin in a solvent or solvent mixture having a water activity of at least about 0.8 to about 0.9, crystallizing the resulting monohydrate and

collecting the product on a suction filter. Solvent mixtures include solvents that are miscible with water such as alcohol, preferably a lower alkanol such as methanol or ethanol.

5 Gabapentin dehydrate A can be produced from the monohydrate when the immediate environment surrounding the monohydrate has a water activity of less than approximately 0.85; i.e. less than between about 0.8 to about 0.9. (In the vapor phase this means that the relative humidity is less than 85%). This can be achieved by applying a vacuum, a desiccant, and/or applying heat.

10 For example, dehydrate A can be produced from the monohydrate at subambient temperatures provided the relative humidity is less than about 85% (water activity less than 0.85).

Typically, once the monohydrate is formed, drying the monohydrate at a temperature of about 50-175°C or below the melting point of gabapentin will form dehydrate Form A. The heating process may take place until a constant weight
15 of dehydrate Form A is obtained. Typically, heating may be carried out between about 70 and 100°C and, for example, at about 80°C for about three hours.

Gabapentin dehydrate Form A has been found to convert to a more stable crystalline form, dehydrate Form B on standing at ambient temperatures. The material may be allowed to stand, for example in an inert atmosphere or in a sealed
20 container. The rate of conversion from dehydrate A to B is directly related to the purity of starting gabapentin dehydrate A.

Water content of the reported forms is less than 0.5% by weight whereas gabapentin monohydrate contains about 9% water by weight.

25 The novel crystalline forms have been characterized by their unique X-ray powder diffraction patterns and their characteristic chemical shifts in their respective solid state ¹³C NMR spectra.

Tables 1-4 below compare the two novel crystalline forms of gabapentin, dehydrate A and dehydrate B, to the known anhydrous crystalline form of gabapentin, and gabapentin monohydrate.

30

2-Theta	d(Å)	Intensity
6.1	14.5	100
12.2	7.3	50
18.3	4.8	23
24.4	3.6	10

2-Theta	d(A)	Intensity
6.0	14.8	53
7.7	11.4	27
16.8	5.3	100
18.0	4.9	40
20.6	4.3	17
24.3	3.65	13

Tables 5-8 compare the chemical shifts in parts per million (ppm) for the various crystalline forms of gabapentin including the novel crystalline forms of the present invention, dehydrate Form A and dehydrate Form B.

Table 5.	Table 6.	Table 7.	Table 8
Chemical Shifts(ppm) of Gabapentin	Chemical Shifts(ppm) of Gabapentin Monohydrate	Chemical Shifts(ppm) of Gabapentin Dehydrate A	Chemical Shifts (ppm) of Gabapentin Dehydrate B
22.4	22.7	22.1	23.3
28.2	27.4	27.0	28.5
29.8	35.7	33.7	35.0
34.8	36.4	36.2	36.2
35.5	44.1	37.6	37.1
36.3	47.3	41.0	42.3
39.6	178.5	51.0	48.2
40.1		177.4	178.3
47.7			
179.6			

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All ¹³C-ssNMR spectra were acquired with a Varian 400MHz NMR spectrometer utilizing high power proton decoupling and cross-polarization with magic angle spinning at approximately 6 kHz. Chemical shifts were referenced to external hexamethylbenzene (methyl signal at 17.3ppm). Each specimen was prepared by packing a sample into a 7mm canister-design silicon nitride rotor using a packing tool and sealing the rotor with a cap. Spectra were acquired under ambient conditions. ¹³C-ssNMR spectra for the four Forms are shown in Figure 1.

10

Example

Example 1 - Preparation of gabapentin monohydrate

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Gabapentin anhydrate, 100 grams, was suspended in 480 mL of water and stirred for one hour with seeds of crystalline monohydrate added. Following crystallization, the gabapentin monohydrate was isolated by suction filtration.

Example 2 - Crystalline gabapentin dehydrate Form A and B

20

Form A: Two batches of gabapentin monohydrate, 200 mg and 100 grams were heated at from 70-80°C for three hours to provide gabapentin dehydrate Form A.

Density of the new dehydrate, Form A, was determined to be 1.156 grams/mL by hexane displacement method. Samples of the gabapentin dehydrate Form A were analyzed by Karl Fischer for water and by HPLC for gabapentin.

The dehydrate crystalline Forms A and B meet the water
5 specification ($\leq 0.5\%w/w$) and the assay specification (98.5%-101.5%w/w on an anhydrous basis).

Elemental analysis and 1H NMR confirmed the chemical composition of gabapentin dehydrate Form A.

Vapor sorption analysis showed that gabapentin dehydrate Form A
10 does not pick up significant amount of moisture ($<0.5\%$) at $25^\circ C$ at relative humidity $<85\%$.

Form B: The two batches of dehydrate Form A obtained above were allowed to stand. Within one month, Form A was found to convert to gabapentin dehydrate Form B by 20%. Within one year, complete conversion to dehydrate
15 Form B was found. Samples of the batches were monitored by ^{13}C -ssNMR until conversion was complete as evidenced by the disappearance of dehydrate Form A.

Both crystalline forms were characterized by their respective solid state NMR spectra and X-ray powder diffractograms.

The above specification, examples and data provide a complete
20 description of the manufacture and use of the composition of the invention. Since many embodiments of the invention can be made without departing from the spirit and scope of the invention, the invention resides in the claims hereinafter appended.

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WE CLAIM:

1. A process for the preparation of crystalline gabapentin dehydrate Form B comprising:
 - (a) dehydrating gabapentin monohydrate to form crystalline gabapentin dehydrate Form A, and
 - (b) allowing dehydrate A to stand at ambient temperatures to form crystalline gabapentin dehydrate Form B.
2. The process of claim 1, where the dehydrating step (a) is carried out by applying a vacuum, a desiccant or heat.
3. The process of claim 1, wherein the gabapentin monohydrate is dehydrated in an environment in which water activity is maintained below about 0.8 and about 0.9.
4. The process of claim 2, wherein heat is applied at a temperature between about 50 to about 175°C.
5. The process of claim 1, wherein dehydrate Form A is allowed to stand in an inert atmosphere or sealed container.
6. The process of claim 2, wherein gabapentin monohydrate is prepared from the following steps which comprise:
 - (a) suspending gabapentin in a solvent or solvent mixture having a water activity value of greater than about 0.8 to about 0.9;
 - (b) crystallizing and collecting gabapentin monohydrate on a filter.
7. The process of claim 6, wherein the solvent is water.
8. A crystalline gabapentin dehydrate Form A having an X-ray powder diffraction containing at least one of the following 2-theta values measured using CuK α radiation: 18.8 or 25.1.

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9. A crystalline gabapentin dehydrate Form A having an X-ray powder diffraction containing the following 2-theta values measured using CuK α radiation: 18.8, 25.1 and 26.1.

10. A crystalline gabapentin dehydrate Form A having an X-ray powder diffraction containing the following 2-theta values measured using CuK α radiation: 6.2, 12.5, 16.1, 18.8, 19.2, 25.1 and 26.1.

11. A crystalline gabapentin dehydrate Form A characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million referenced to an external methyl signal at 17.3 ppm for hexamethylbenzene: 22.1, 27.0, 33.7, 36.2, 37.6, 41.0, 51.0 and 177.4.

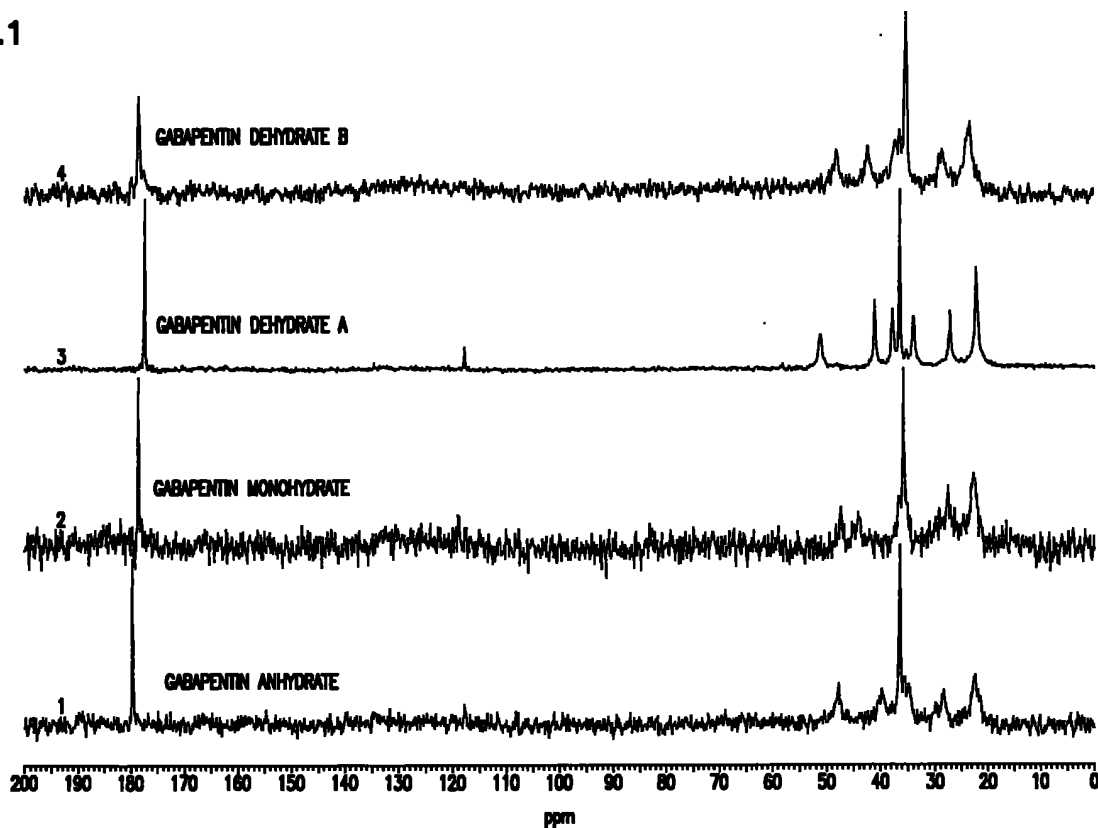
12. A crystalline gabapentin dehydrate Form B having an X-ray powder diffraction containing at least one of the following 2-theta values measured using CuK α radiation: 6.0 or 16.8.

13. A crystalline gabapentin dehydrate Form B having an X-ray powder diffraction containing the following 2-theta values measured using CuK α radiation: 6.0, 16.8 and 18.0.

14. A crystalline gabapentin dehydrate Form B having an X-ray powder diffraction containing the following 2-theta values measured using CuK α radiation: 6.0, 7.7, 16.8, 18.0, 20.6 and 24.3.

15. A crystalline gabapentin dehydrate Form B characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million referenced to an external methyl signal at 17.3 ppm for hexamethylbenzene: 23.3, 28.5, 35.0, 36.2, 37.1, 42.3, 48.2 and 178.3.

FIG. 1



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FIG.2

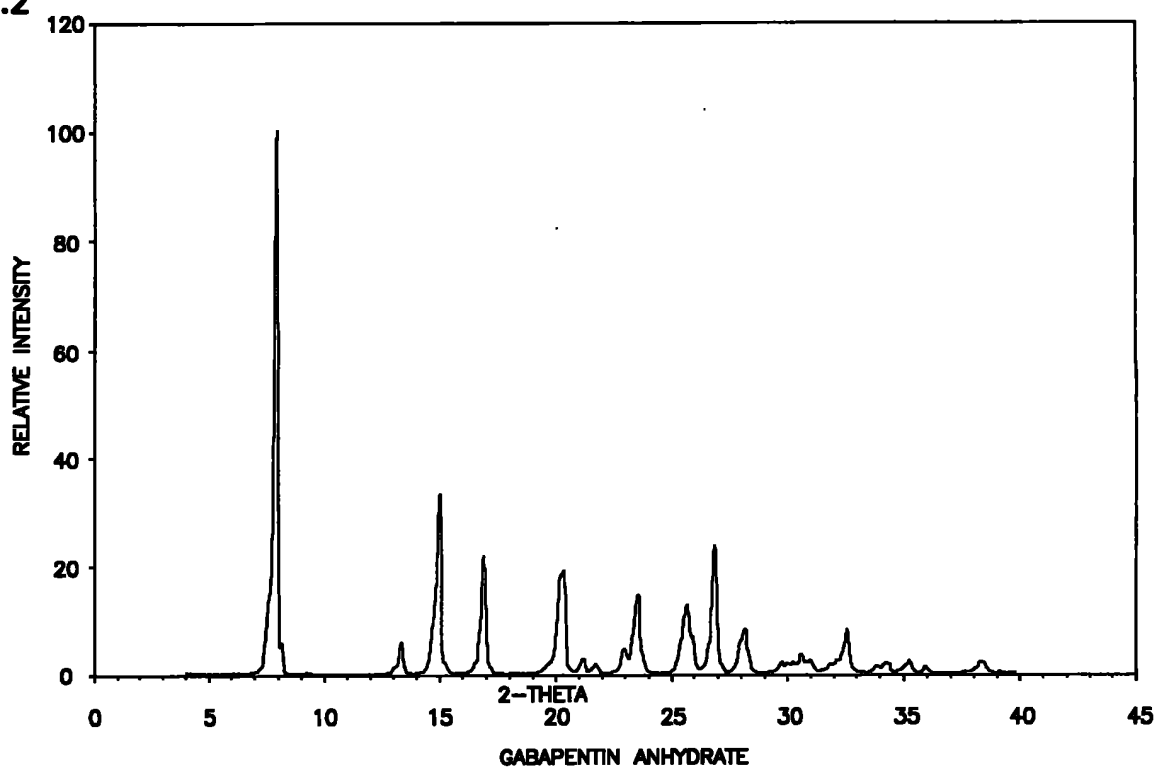
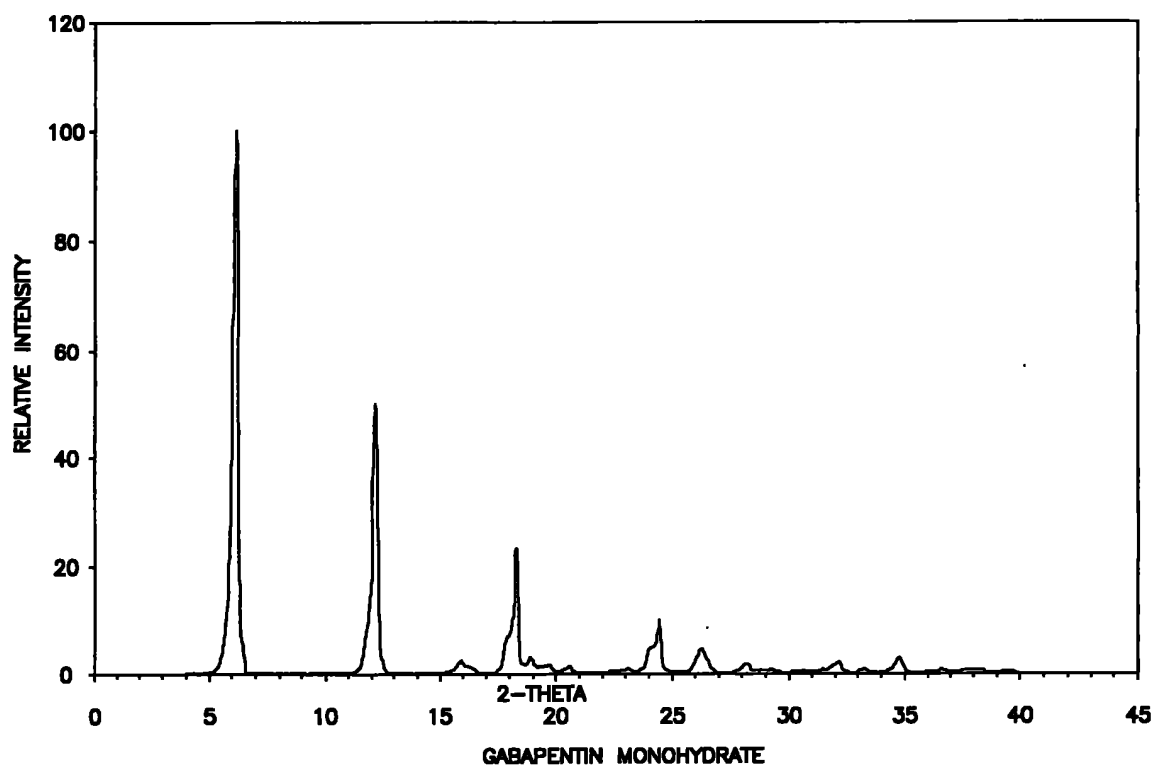


FIG.3



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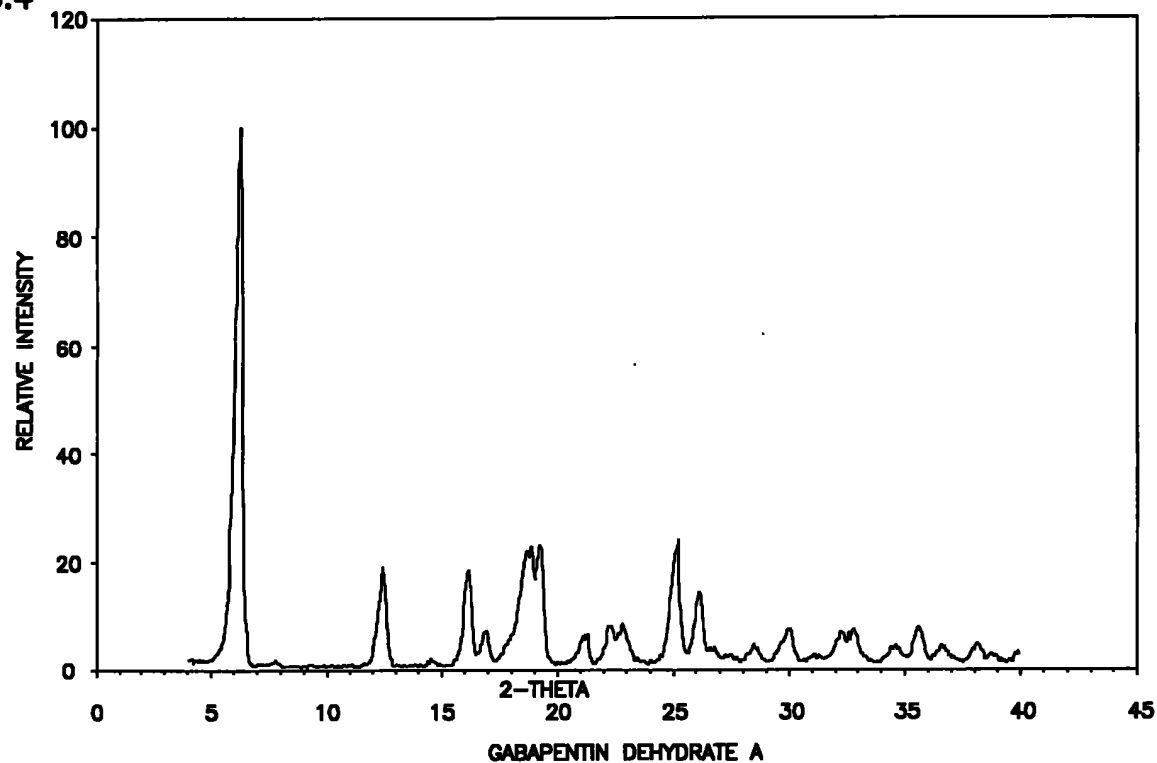
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FIG.4



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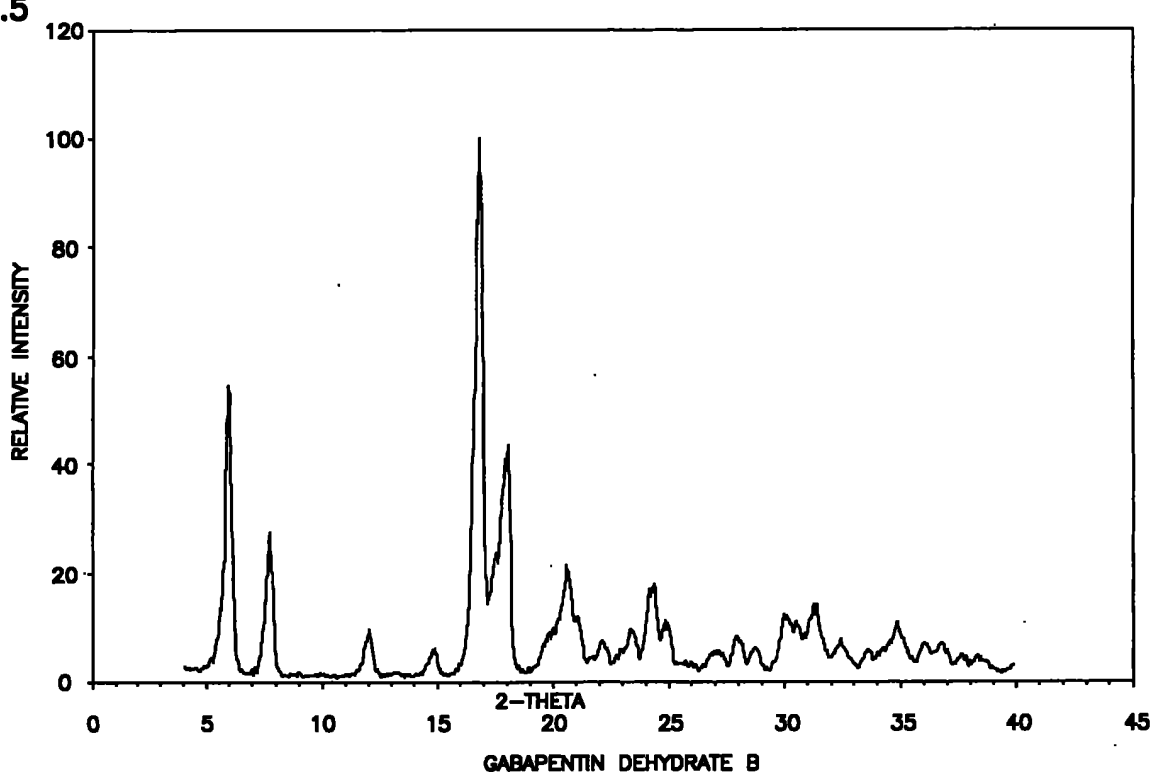
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410028

FIG.5



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/31706

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C229/28 C07C227/40

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 240 677 A (AISIN SEIKI) 14 October 1987 (1987-10-14) *example 3*	1-15
A	WO 98 28255 A (PESACHOVICH MICHAEL ; SINGER CLAUDE (IL); TEVA PHARMA (IL); PILARSK) 2 July 1998 (1998-07-02) *abstract; page 7, lines 26-34; page 8 and page 11*	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

16 December 2002

Date of mailing of the international search report

30/12/2002

Name and mailing address of the ISA

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4-000038
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/31706

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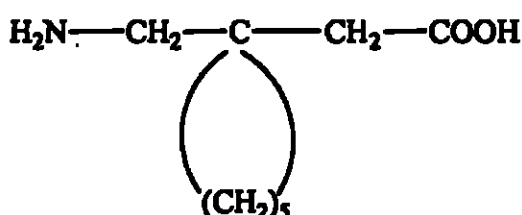
NUEVAS FORMAS CRISTALINAS ANHIDRAS DE LA GABAPENTINA

Campo de la Invención

La presente invención se relaciona con nuevas formas cristalinas anhidras de la gabapentina preparadas a partir de gabapentina monohidratada.

Antecedentes de la Invención

Gabapentina es un nombre genérico utilizado para identificar al compuesto químico ácido (1-aminometil)-1-ciclohexanacético



Sirve para el tratamiento terapéutico de ciertos trastornos cerebrales tales como ciertas formas de epilepsia, desvanecimientos, hipoquinesia y traumas craneanos. Las patentes de los Estados Unidos Nos. 4.024.175 y 4.087.544 cubren el compuesto y sus usos. También describen una sal ácida, es decir el clorhidrato de gabapentina hidratado en una relación de 4:4:1 y una sal sódica de gabapentina hidratada en una relación de 2:1. La patente de los Estados Unidos No. 4.894.476 describe la gabapentina monohidrato y un proceso para su producción. Estas patentes se incorporan a la presente como referencia.

Síntesis de la Invención

La presente invención presenta nuevas formas cristalinas de gabapentina, Forma A deshidratada y Forma B deshidratada. Estas nuevas formas cristalinas se preparan a partir de la gabapentina monohidrato. El gabapentina monohidrato es deshidratado en un ambiente en el cual la

actividad hídrica se mantiene por debajo de aproximadamente 0,8 a aproximadamente 0,9, o se lo calienta a una temperatura de aproximadamente 50-175°C para formar la Forma A de gabapentina deshidratada. Esta forma cristalina se convierte luego, al reposar a temperatura ambiente, en una forma cristalina más estable de gabapentina, la Forma B deshidratada.

La presente invención presenta otras mejoras al proceso para producir formas cristalinas puras del agente terapéutico gabapentina. El presente proceso elimina la necesidad de utilizar solventes orgánicos tales como metanol, antes descriptos en los métodos para producir gabapentina y su monohidrato. El presente proceso ofrece un procesamiento de elaboración más rápido, mayor seguridad, menos desechos de solvente y menor pérdida de rendimiento con la recrystalización.

Breve Descripción de los Dibujos

La Figura 1 ilustra los espectros de RMN de ^{13}C -ss de las cuatro formas cristalinas de gabapentina

La Figura 2 ilustra el difractograma de rayos X en polvo para la gabapentina cristalina, anhidrato

La Figura 3 el difractograma de rayos X en polvo para la gabapentina cristalina, monohidrato.

La Figura 4 el difractograma de rayos X en polvo para la gabapentina cristalina deshidratada A.

La Figura 5 el difractograma de rayos X en polvo para la gabapentina cristalina deshidratada B.

Descripción Detallada de la Realización Preferida

La presente invención presenta novedosas formas cristalinas de gabapentina, la Forma deshidratada A y la Forma deshidratada B. La presente invención incluye asimismo mejoras en la preparación de la gabapentina monohidrato, el precursor de la nueva forma deshidratada cristalina de acuerdo con la presente invención. En un principio, la gabapentina monohidrato fue dada a conocer en la patente de los Estados Unidos No. 4.894.476 como nueva forma cristalina para usos terapéuticos y también como medio para la purificación de la gabapentina comercial, una forma anhidra, mediante reconversión del monohidrato a gabapentina.

La presente invención se basa en un hallazgo con respecto a que la forma anhidra conocida de gabapentina sólo puede cristalizar de solventes o mezclas de solventes con una actividad hídrica inferior a aproximadamente 0,8 a aproximadamente 0,9 y el gabapentina monohidrato sólo puede cristalizar de agua o mezclas de solventes con una actividad hídrica superior a aproximadamente 0,8 a aproximadamente 0,9. La gabapentina monohidrato se puede preparar suspendiendo gabapentina en un solvente o mezcla de solventes con una actividad hídrica de por lo menos aproximadamente 0,8 a aproximadamente 0,9, cristalizando el monohidrato obtenido y recogiendo el producto en un filtro por aspiración. Las mezclas de solventes incluyen solventes que son miscibles con agua tales como alcohol, preferentemente un alcohól inferior tal como metanol o etanol.

Se puede producir gabapentina deshidratada A a partir del monohidrato cuando el medio inmediato que rodea al monohidrato tiene una actividad hídrica inferior a aproximadamente 0,85, es decir, inferior a un valor de aproximadamente 0,9 a aproximadamente 0,9. (en la fase de vapor, esto significa que la humedad relativa es inferior a 85 %). Esto se puede obtener mediante la aplicación de vacío, un desecante, y/o la aplicación de calor.

Por ejemplo, se puede producir la forma deshidratada a partir del monohidrato a temperaturas subambientales siempre que la humedad relativa sea inferior a aproximadamente 85 % (actividad hídrica inferior a 0,85).

Típicamente, una vez que se forma el monohidrato, el secado del monohidrato a una temperatura de aproximadamente 50-175°C o inferior al punto de fusión de la gabapentina da origen a la Forma deshidratada A. El proceso de calentamiento puede tener lugar hasta obtener un peso constante de la forma deshidratada A. Típicamente, el calentamiento se puede llevar a cabo a una temperatura de 70 a 100°C y, por ejemplo, a aproximadamente 80°C por espacio de tres horas.

Se ha descubierto que la forma deshidratada A de Gabapentina se convierte en una forma cristalina más estable, la Forma deshidratada B al reposar a temperaturas ambientales. Se puede dejar que el material repose, por ejemplo en atmósfera inerte o un recipiente herméticamente cerrado. La tasa de conversión de la forma deshidratada A a la B está directamente relacionada con la pureza de la forma deshidratada A de gabapentina de partida.

El contenido de agua de las formas dadas a conocer es inferior a 0,5 % en peso, en tanto que la gabapentina monohidrato contiene aproximadamente 9 % en peso de agua.

Las novedosas formas cristalinas han sido caracterizadas por sus singulares patrones de difracción de rayos X en polvo y sus desplazamientos químicos característicos en sus respectivos espectros de RMN de ^{13}C en estado sólido.

Las siguientes Tablas 1-4 comparan las dos novedosas formas cristalinas de gabapentina, la forma deshidratada A y la forma deshidratada

B, con la forma cristalina anhidra conocida de gabapentina y la gabapentina monohidrato.

Tabla 1. Datos de PXRD de la Gabapentina		
2-Theta	d(Å)	Intensidad
7,9	11,1	100
15,0	5,9	33
16,9	5,2	22
20,4	4,4	18
23,6	3,8	15
25,7	3,5	13
27,0	3,3	23

Tabla 2. Datos de PXRD de la Gabapentina Monohidrato		
2-Theta	d(Å)	Intensidad
6,1	14,5	100
12,2	7,3	50
18,3	4,8	23
24,4	3,6	10

Tabla 3. Datos de PXRD de la Gabapentina Deshidratada A		
2-Theta	d(Å)	Intensidad
6,2	14,2	100
12,5	7,1	18
18,8	4,7	21
19,2	4,6	22
25,1	3,5	21
26,1	3,4	11

Tabla 4. Datos de PXRD de la Gabapentina Deshidratada B		
2-Theta	d(Å)	Intensidad
6,0	14,8	53
7,7	11,4	27
16,8	5,3	100
18,0	4,9	40
20,6	4,3	17
24,3	3,65	13

Se adquirieron los datos de difracción de Rayos X (PXRD) con un Difractómetro de Rayos X en Polvo Rigaku Ultima+ equipado con un objetivo de cobre funcionando a 40 kV/40 mA y produciendo rayos X de una longitud de onda de 1,542 Angstroms. Se ajustó tanto la hendidura de divergencia como la hendidura de difusión a 1°. La hendidura de recepción fue ajustada a 0,3 mm. El difractómetro estaba equipado con un cambiador de muestras Rigaku ASC-6°. La preparación de las muestras consistió en la introducción de una cantidad suficiente de la muestra para llenar una placa de muestreo y en el alisado de la superficie raspando con suavidad y aplanando sin compactar la muestra. En condiciones ambiente, las muestras fueron exploradas en forma continua de 4° a 40° 2-Theta a una velocidad de 5°/minuto. Los datos de PXRD de las cuatro Formas están consignados en las Tablas 1 a 4 antes expuestas. Los números son correspondientes a los picos de por lo menos 10 % del pico más intenso y han sido redondeados a partir de los datos brutos, lo que representa una precisión de aproximadamente ± 0,2 con respecto a los valores 2-theta y d(Å) dado el error experimental de rutina. En las Figuras 2-5 se exponen los difractogramas de PXRD de las cuatro Formas.

Las Tablas 5-8 comparan los desplazamientos químicos en partes por millón (ppm) para las diversas formas cristalinas de gabapentina, incluyendo las novedosas formas cristalinas de acuerdo con la presente invención, la Forma deshidratada A y la Forma deshidratada B.

Tabla 5 Desplazamientos químicos (ppm) de la Gabapentina	Tabla 6 Desplazamientos químicos (ppm) de la Gabapentina Monohidrato	Tabla 6 Desplazamientos químicos (ppm) de la Forma Deshidratada de Gabapentina A	Tabla 6 Desplazamientos químicos (ppm) de la Forma Deshidratada de Gabapentina B
22,4 28,2 29,8 34,8 35,5 36,3 39,6 40,1 47,7 179,6	22,7 27,4 35,7 36,4 44,1 47,3 178,5	22,1 27,0 33,7 36,2 37,6 41,0 51,0 177,4	23,3 28,5 35,0 36,2 37,1 42,3 48,2 178,3

Todos los espectros de RMN ^{13}C -ss fueron adquiridos en un espectrómetro de RMN Varian a 400 MHz, utilizando desacoplamiento protónico de alta potencia y polarización cruzada con ángulo mágico, con una rotación de aproximadamente 6 kHz. Los desplazamientos químicos fueron tomados como referencia el hexametilbenceno (señal de metilo a 17,3 ppm). Se preparó cada muestra empacando una muestra en un rotor de nitrato de silicio de diseño en tubo de 7 mm utilizando una herramienta empacadora y sellando el rotor con una tapa. Se adquirieron los espectros en condiciones ambiente. En la Figura 1 se ilustran los espectros de RMN ^{13}C -ss para las cuatro Formas.

Ejemplo

Ejemplo 1 – Preparación de Gabapentina monohidrato

Se suspendió gabapentina, 100 gramos, en 480 ml de agua y se lo agitó por espacio de 1 hora con la adición de siembra de monohidrato cristalino. Después de la cristalización, se aisló gabapentina monohidrato por filtración por aspiración.

Ejemplo 2 – Gabapentina cristalina deshidratada Formas A y B

Forma A: Se calentaron dos lotes de gabapentina monohidrato, de 200 mg y 100 gramos a una temperatura de 70-80°C por espacio de tres horas para producir la Forma deshidratada A de gabapentina.

Se determinó que la densidad de la nueva forma deshidratada A era de 1,156 gramos/ml mediante el método de desplazamiento en hexano. Las muestras de la Forma A deshidratada de gabapentina fueron analizadas según Karl Fischer para determinar el contenido de agua y por HPLC para medir la gabapentina.

Las formas cristalinas deshidratadas A y B cumplen con las especificaciones con respecto al agua ($\leq 0,5$ p/p) y la especificación con respecto al análisis (98,5 %-101,5 % p/p tomando la forma anhidra como base).

En análisis elemental y de RMN de ^1H confirmó la composición química de la Forma deshidratada A de gabapentina.

El análisis de sorción de vapor demostró que la Forma A deshidratada de gabapentina no absorbe una cantidad significativa de humedad ($< 0,5$ %) a una humedad relativa de < 85 %.

Forma B: Se dejó que los dos lotes de la Forma deshidratada A antes obtenidos reposaran. En el término de un mes, se encontró que la forma A se convertía en la Forma B deshidratada de gabapentina en un 20 %. En un plazo de un año, se encontró la conversión completa a la Forma deshidratada B. Las muestras de los lotes fueron monitoreadas por RMN de ^{13}C -ss hasta la conversión completa, según lo evidenciado por la desaparición de la Forma deshidratada A.

Ambas formas cristalinas fueron caracterizadas por sus respectivos espectros de RMN en estado sólido y difractogramas de rayos X en polvo.

La memoria descriptiva que antecede, junto con los ejemplos y datos presentan una descripción completa de la elaboración y uso de la composición de la presente invención. Dado que se pueden efectuar numerosas realizaciones de la presente invención sin apartarse del espíritu y alcance de la misma, la invención se basa en las reivindicaciones adjuntas a continuación.

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma como la misma debe ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo.

1. Un proceso para la preparación de la Forma B cristalina deshidratada de gabapentina que comprende:

- (a) deshidratar de gabapentina monohidrato para formar la Forma A cristalina deshidratada de gabapentina y
- (b) dejar que la forma A deshidratada repose a temperatura ambiente para formar la Forma B cristalina deshidratada de gabapentina.

2. El proceso de acuerdo con la reivindicación 1, en el cual el paso de deshidratación (a) se lleva a cabo aplicando un vacío, un desecante o calor.

3. El proceso de acuerdo con la reivindicación 1, en el cual se deshidrata la gabapentina monohidrato en un ambiente en el cual la actividad hídrica se mantiene por debajo de aproximadamente 0,8 a aproximadamente 0,9.

4. El proceso de acuerdo con la reivindicación 2, en el cual se aplica calor a una temperatura ambiente de entre aproximadamente 50 y aproximadamente 175°C.

5. El proceso de acuerdo con la reivindicación 1, en el cual se deja que la forma A deshidratada repose en atmósfera inerte o en un envase sellado.

6. El proceso de acuerdo con la reivindicación 2, en el cual se prepara gabapentina monohidrato mediante los siguientes pasos, que comprenden

(a) suspender gabapentina en un solvente o mezcla de solventes con una actividad hídrica de más de aproximadamente 0,8 a aproximadamente 0,9;

(b) cristalizar y recoger gabapentina monohidrato en un filtro.

7. El proceso de acuerdo con la reivindicación 6, en el cual el solvente es agua.

8. Una Forma A de gabapentina deshidratada cristalina que tiene una difracción de rayos X en polvo que contiene por lo menos uno de los siguientes valores 2-theta medidos utilizando radiación CuK α : 18,8 o 25,1.

9. Una Forma A de gabapentina deshidratada cristalina que tiene una difracción de rayos X en polvo que contiene por lo menos uno de los siguientes valores 2-theta medidos utilizando radiación CuK α : 18,8, 25,1 y 26,1.

10. Una Forma A de gabapentina deshidratada cristalina que tiene una difracción de rayos X en polvo que contiene por lo menos uno de los siguientes valores 2-theta medidos utilizando radiación CuK α : 6,2, 12,5, 16,1, 18,8, 19,2, 25,1 y 26,1.

11. Una Forma A de gabapentina deshidratada cristalina que se caracteriza por tener una resonancia magnética nuclear de ^{13}C en estado sólido que tiene los siguientes desplazamientos químicos expresados en partes por millón con referencia a una señal de metilo externa a razón de 17,3 ppm para el hexametilbenceno: 22,1, 27,0, 33,7, 36,2, 37,6, 41,0, 51,0 y 177,4.

12. Una Forma B de gabapentina deshidratada cristalina que tiene una difracción de rayos X en polvo que contiene por lo menos uno de los siguientes valores 2-theta medidos utilizando radiación CuK α : 6,0 o 16,8.

13. Una Forma B de gabapentina deshidratada cristalina que tiene una difracción de rayos X en polvo que contiene por lo menos uno de los siguientes valores 2-theta medidos utilizando radiación CuK α : 6,0, 16,9 y 18,0.

14. Una Forma B de gabapentina deshidratada cristalina que tiene una difracción de rayos X en polvo que contiene por lo menos uno de los siguientes valores 2-theta medidos utilizando radiación CuK α : 6,0, 7,7, 16,8, 18,0, 20,6 y 24,3.

15. Una Forma B de gabapentina deshidratada cristalina que se caracteriza por tener una resonancia magnética nuclear de ^{13}C en estado

sólido que tiene los siguientes desplazamientos químicos expresados en partes por millón con referencia a una señal de metilo externa a razón de 17,3 ppm para el hexametilbenceno: 23,3, 28,5, 35,0, 36,2, 37,1, 42,3, 48,2 y 178,3.

p. WARNER-LAMBERT COMPANY

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Resumen

Se describen nuevas formas anhidras cristalinas de gabapentina formadas a partir de gabapentina monohidrato. Las nuevas formas cristalinas ofrecen ventajas para la elaboración del agente terapéutico.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Daignault, Ronald A.
MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-2903
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

14-07-2003

Applicant's or agent's file reference
4105.90WOU1

IMPORTANT NOTIFICATION

International application No.

PCT/US 02/ 31706

International filing date (day/month/year)

03/10/2002

Priority date (day/month/year)

09/10/2001

Applicant

WARNER-LAMBERT COMPANY LLC et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for International preliminary examination of the international application:

07/05/2003

2. This date of receipt is:



the actual date of receipt of the demand by this Authority (Rule 61.1(b)).



the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).



the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IBPA/404), received the required corrections.

- 3.

☐ ATTENTION: That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the PCT Applicant's Guide, Volume II.



(If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPBA/

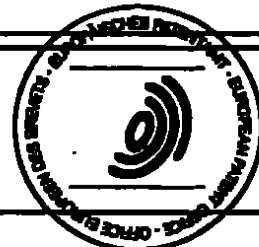


European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

KENNEDY M B

Tel. (+49-89) 2399-2976



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Daignault, Ronald A.
MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-2903
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

29/08/2003

Applicant's or agent's file reference
4105.90WOU1

IMPORTANT NOTIFICATION

International application No.

PCT/US 02/ 31706

International filing date (day/month/year)

03/10/2002

Priority date (day/month/year)

09/10/2001

Applicant

WARNER-LAMBERT COMPANY LLC et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

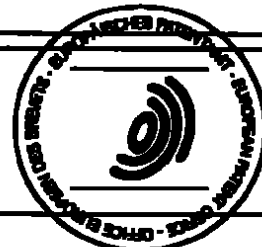
Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

KENNEDY M B
Tel. (+49-89) 2399 2828



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 4105.90WOU1	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US 02/ 31706	International filing date (day/month/year) 03/10/2002	Priority date (day/month/year) 09/10/2001
International Patent Classification (IPC) or national classification and IPC G07C229/28		
Applicant WARNER-LAMBERT COMPANY LLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 2 sheets, including this cover sheet.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:
I ☒ Basis of the report
II ☐ Priority
III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV ☐ Lack of unity of invention
V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI ☐ Certain documents cited
VII ☐ Certain defects in the international application
VIII ☐ Certain observations on the international application

Date of submission of the demand 07/05/2003	Date of completion of this report 26/08/2003
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer JONES M H Tel. (+49-89) 2399 2828



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US 02/31706

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I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

PATENT C OPERATION TREATY

48 KCW
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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Daignault, Ronald A.
MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-2903
ETATS-UNIS D'AMERIQUE

WRITTEN OPINION

(PCT Rule 66)

ATY RESP W.O. - July 23, 2003

Applicant's or agent's file reference 4105.90WOU1✓		Date of mailing (day/month/year) 23/06/2003
International application No. PCT/US 02/ 31706		REPLY DUE within 1 / 00 months/days from the above date of mailing
International filing date (day/month/year) 03/10/2002	Priority date (day/month/year) 09/10/2001	
International Patent Classification (IPC) or both national classification and IPC C07C229/28		
Applicant WARNER-LAMBERT COMPANY LLC et al.		

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.8.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 09/12/2004

Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Examiner Formalities officer (incl. extension of time limits) Tel. (+49-89) 2399 2828
---	--

Form PCT/IPEA/408 (cover sheet) (march 2002)



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WRITTEN OPINION

International application No. PCT/US 02/ 31706

I. Basis of the opinion

1. The basis of this written opinion is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

1. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claims references).
2. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

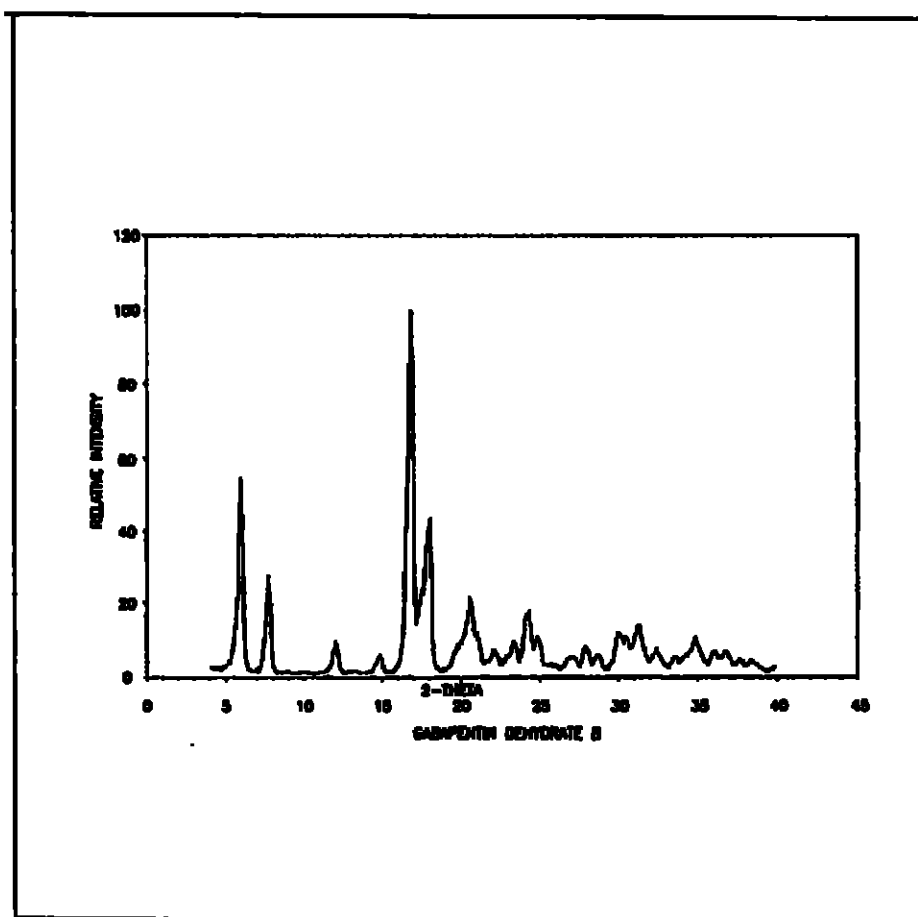
NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

WO 03/031391

PCT/US02/31706

ARTE FINAL 12 x 12

TITULO: NUEVAS FORMAS CRISTALINAS ANHIDRAS DE LA GABAPENTINA.



PATENT COOPERATION TREATY

-f)!!()151

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PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

DAIGNAULT, Ronald, A.
Merchant & Gould P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
United States of America

Date of mailing (day/month/year)

05 June 2003 (05.06.03)

Applicant's or agent's file reference

4105.90WOU1

International application No.

PCT/US02/31706

International filing date (day/month/year)

03 October 2002 (03.10.02)

IMPORTANT NOTIFICATION

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

WARNER-LAMBERT COMPANY
201 Tabor Road
Morris Plains, NJ 07950
United States of America

State of Nationality

US

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

WARNER-LAMBERT COMPANY LLC
201 Tabor Road
Morris Plains, NJ 07950
United States of America

State of Nationality

US

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.20

Authorized officer

El Mostafa MOUSSAID (Fax 338-87 20)

Telephone No. (41-22) 338 9242

PATENT COOPERATION TREATY

PCT/US02/31706

.. 25/09/03 52

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PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

DAIGNAULT, Ronald, A.
Merchant & Gould P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
United States of America

Date of mailing (day/month/year) 08 May 2003 (08.05.03)	
Applicant's or agent's file reference 4105.90WOU1	IMPORTANT NOTIFICATION
International application No. PCT/US02/31706	International filing date (day/month/year) 03 October 2002 (03.10.02)
International publication date (day/month/year) 17 April 2003 (17.04.03)	Priority date (day/month/year) 09 October 2001 (09.10.01)
Applicant WARNER-LAMBERT COMPANY et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
09 Octo 2001 (09.10.01)	60/328,375	US	23 Octo 2002 (23.10.02)
25 Sept 2002 (25.09.02)	10/256,155	US	08 May 2003 (08.05.03)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Sylvaine DESCLOUX (Fax 338-87-20)
Facsimile No. (41-22) 338.87.20	Telephone No. (41-22) 338 8437

PATENT COOPERATION TREATY

53

From the RECEIVING OFFICE

PCT

NOTIFICATION RELATING
TO PRIORITY CLAIM(PCT Rules 26bis.1 and 26bis.2 and
Administrative Instructions, Sections 302 and 314)

To: RONALD A. DAIGNAULT MERCHANT & GOULD P.C. P.O. BOX 2903 MINNEAPOLIS, MINNESOTA 55402-0903		Date of mailing (day/month/year) 02 MAY 2003
Applicant's or agent's file reference 4105.90WOU1		IMPORTANT NOTIFICATION
International application No. PCT/US02/31708	International filing date (day/month/year) 03 Oct 2002	
Applicant WARNER- LAMBERT COMPANY		

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application.

1. ☒ Correction of priority claim. In accordance with the applicant's notice received on : 18 JANUARY 2003
the following priority claim has been corrected to read as follows:
US 25 SEPTEMBER 2003 10/256,155
☒ even though the indication of the number of the earlier application is missing.
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
2. ☐ Addition of priority claim. In accordance with the applicant's notice received on :
the following priority claim has been added:
☐ even though the indication of the number of the earlier application is missing.
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
3. ☐ As a result of the correction and/or addition of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:
4. ☐ The priority claim (see also item 3, below, if applicable) is considered not to have been made because:
☐ the applicant failed to respond to the invitation under Rule 26bis.2(a) (Form PCT/RO/110) within the prescribed time limit.
☐ the applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).
☐ the applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.
The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(1B).
5. ☒ In case where multiple priorities have been claimed, the above item(s) relate to the following priority claim(s):
ITEM 2
6. A copy of this notification has been sent to the International Bureau and
☒ to the International Searching Authority

Name and mailing address of the receiving Office Assistant Commissioner for Patent, Box PCT Washington, D.C. 20231 Attn:RO/US	Authorized officer Virginia Irby VI
Facsimile No. 703-305-3230	Telephone No. 703-305-3748

Form PCT/RO/111 (July 1998)

. ATENT COOPERATION TRE. iY

. 0001154

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PCT

From the INTERNATIONAL BUREAU

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and
Administrative Instructions, Sections 402 and 409)

To:

DAIGNAULT, Ronald, A.
Merchant & Gould P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
United States of AmericaDate of mailing (day/month/year)
22 January 2003 (22.01.03)Applicant's or agent's file reference
4105.90WOU1

IMPORTANT NOTIFICATION

International application No.
PCT/US02/31706International filing date (day/month/year)
03 October 2002 (03.10.02)

Applicant

WARNER-LAMBERT COMPANY et al

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application.

1. ☒ Correction of priority claim. In accordance with the applicant's notice received on: 16 January 2003 (16.01.03), the following priority claim has been corrected to read as follows:
US 25 September 2002 (25.09.02) 10/258,155
- ☐ even though the indication of the number of the earlier application is missing.
- ☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
2. ☐ Addition of priority claim. In accordance with the applicant's notice received on: , the following priority claim has been added:
- ☐ even though the indication of the number of the earlier application is missing.
- ☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
3. ☐ As a result of the correction and/or addition of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:
4. ☐ Priority claim considered not to have been made.
- ☐ The applicant failed to respond to the invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.
- ☐ The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).
- ☐ The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.
- The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(18).
5. ☐ In case where multiple priorities have been claimed, the above item(s) relate to the following priority claim(s):
6. A copy of this notification has been sent to the receiving Office and
- ☐ to the International Searching Authority (where the international search report has not yet been issued).
- ☒ the designated Offices (which have already been notified of the receipt of the record copy).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Catherine MASSETTI (Fax 338-87-20)

Telephone No. (41-22) 338.83.38

55

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION (X) MODELO DE UTILIDAD	()	()
Indicacion de que se solicita la concesion de una patente	(X)	()
Datos de Identificacion del solicitante o de la persona que presenta la solicitud	(X)	()
- Descripcion de la invencion	(X)	()
Dibujos de ser estos pertinentes	(X)	()
Comprobante de Pago de las tasas establecidas (X)		

COMPLETA () INCOMPLETA ()

DISEÑO INDUSTRIAL ()

- Indicacion de que se solicita el registro de Diseño Industrial	()	()
- Datos de Identificación del solicitante o de la persona que presenta la solicitud	()	()
- Representacion gráfica y fotografica del Diseño Industrial o muestra del Material que incorpora el diseño	()	()
Comprobante de pago de las tasas establecidas	()	()

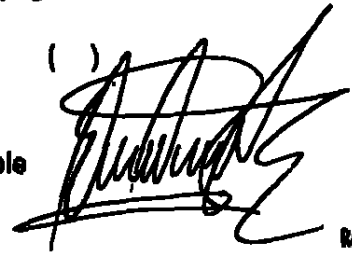
COMPLETA () INCOMPLETA ()

ESQUEMA DE TRAZADO ()

- Indicacion de que solicita el registro de un Esquema de trazado	()	()
- Datos de Identificación del solicitante o de la persona que presenta la solicitud	()	()
Representacion gráfica del esquema de trazado	()	()
Comprobante de pago de las tasas establecidas	()	()

COMPLETA () INCOMPLETA ()

Firma Responsable



Fecha Abril 6 de 2004.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04032579 00000000 Folios: 54
Fecha (AMD): 2004-04-06 17:29:43
Trámite : 011 PCT-PATENT 379 FASE INCI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES



2020
Bogotá, D.C.,

Doctor:
ALVARO CORREA ORDOÑEZ

Oficio N° 04229

ASUNTO:	Solicitante	WARNER-LAMBERT COMPANY LLC
	Radicación N°	04-32599
	Solicitud internacional	PCT/US02/31706
	Fecha inicio fase nacional	09/05/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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.

El anterior requerimiento fue notificado por fijación en lista de fecha, 12 de Mayo 2004.

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