



**Industria y Comercio**  
**SUPERINTENDENCIA**

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
**INVENTARIO**

907

Organizacion CSA Ltda

**SOLICITUD**  
**PATENTE DE INVENCION**

03-47109

21. EXPEDIENTE N°

54. TÍTULO

FORMULACION FARMACEUTICA DE GEPIRONA PARA

ADMINISTRACION ORAL

51. CLASIFICACIÓN INTERNACIONAL AGIK 31/506

71. SOLICITANTE AKZO NOBEL N.V.

DOMICILIO Arnheim, Holanda.

74. APODERADO EMILIO FERRERO

Código No. 1092

22. BOGOTÁ, D. C. 04-06-2003

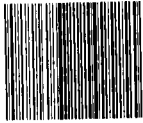
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SUPERINDUSTRIA Y COMERCIO  
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Fecha (AMD): 2003-06-04 16:58:28  
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC  
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE  
PCT  
ENTRADA EN FASE NACIONAL

|                                                           |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                 |                                      |
|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| 1 SOLICITUD DE:                                           |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                 |                                      |
| <input checked="" type="checkbox"/> Patente de Invención. |                                                                                                                                                                                                                                          | <input type="checkbox"/> Patente de Modelo de Utilidad.                                                                                                                                                         |                                      |
| <input type="checkbox"/> Capítulo I.                      |                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> Capítulo II.                                                                                                                                                                |                                      |
| 2 SOLICITANTE (71)                                        | Nombre: AKZO NOBEL N.V.<br>sociedad constituida y existente bajo las leyes de Holanda<br><br>Dirección: Velperweg 76,<br>6824 BM Arnheim.<br>Holanda.<br><br>Domicilio: Arnheim, Holanda.                                                | IDENTIFICACION<br><br>C.C. <input type="checkbox"/> NIT <input type="checkbox"/><br><br>C.E. <input type="checkbox"/> Otro <input type="checkbox"/><br>Cual _____<br><br>Número: _____                          |                                      |
| 3 REPRESENTANTE O APODERADO                               | Nombre: EMILIO FERRERO<br><br>Dirección: Carrera 4ª. No. 72-35<br>Teléfono: 347 36 11<br>Fax:: 217 92 11<br>E-mail: clientes@camyp.com.<br>Domicilio: Bogotá, Colombia.                                                                  | IDENTIFICACION<br><br>C.C. <input checked="" type="checkbox"/> NIT <input type="checkbox"/><br><br>C.E. <input type="checkbox"/> Otro <input type="checkbox"/><br>Cual _____<br><br>Número: 438.019 T.P. 31.929 |                                      |
| 4 INVENTOR (ES) (72)                                      | 1- Johannes, Gerardus, Joseph EGBERINK N.V. Organon,<br>P.O. Box 20<br>5340 BH Oss<br>Holanda.<br><br>1- John, Francis ENGELHART<br>Organon Inc.<br>375 Mt. Pleasant Ave,<br>West Orange, New Jersey 07092.<br>Estados Unidos de América |                                                                                                                                                                                                                 |                                      |
| 5 PCT (86)                                                | Solicitud Internacional No. PCT/EP01/14189<br>Publicación Internacional No. WO 02/45753 A3<br><br>Fecha: 30 de noviembre de 2001<br>Fecha : 13 de junio de 2002                                                                          |                                                                                                                                                                                                                 |                                      |
| 6 Título (54)                                             | FORMULACION FARMACEUTICA DE GEPIRONA PARA ADMINISTRACION ORAL                                                                                                                                                                            |                                                                                                                                                                                                                 |                                      |
| 7                                                         | Clasificación Internacional (51) A61K 31/506                                                                                                                                                                                             |                                                                                                                                                                                                                 |                                      |
| 8                                                         | Prioridad<br><br>SI <input checked="" type="checkbox"/> NO <input type="checkbox"/>                                                                                                                                                      | (33) Pais de Origen<br>EP.                                                                                                                                                                                      | (32) Fecha<br>8 de diciembre de 2000 |
|                                                           |                                                                                                                                                                                                                                          | (31) Número de Solicitud<br>00204388.3                                                                                                                                                                          |                                      |

9

Comprobante de pago No.: 03-36.411

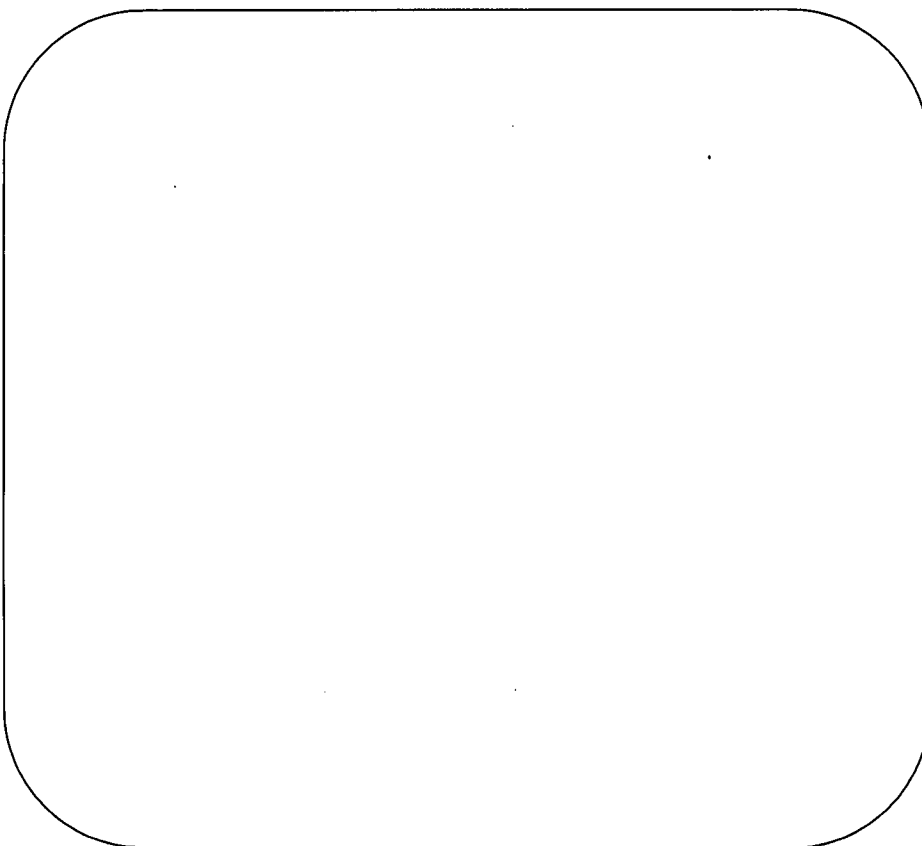
Fecha: 26 de mayo de 2003

10

**Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 400.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11

**FIGURA CARACTERISTICA:**

12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : 

C.C. 438.019 de Usaquén T.P. 31.929



## REPRESENTACION Y PODER

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTATION AND  
POWER OF ATTORNEY

I (we), the undersigned/Yo (nosotros), abajo firmado (s)

AKZO NOBEL N.V.

of/domiciliado (s) en Velperweg 76, 6824

BM Arnhem, THE NETHERLANDS

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin, its renewal, assignment, change of name or domicile, voluntary cancellation or registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or judicial cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute the Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this/Dado y firmado hoy 6 AUG 1998

F.G.M. Hermans

in/en Director Patents Pharma

Signature

AKZO NOBEL N.V.

E.H. Reerink

Deputy Director

Legal Affairs

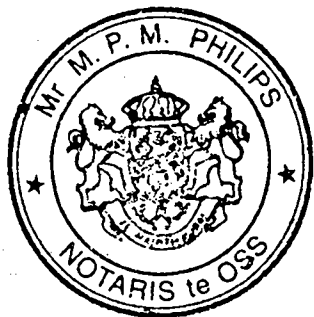
LEGALIZACION

El Señor Cónsul de Colombia debe expedir un *certificado consular* sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a *consular certificate*, on (1) the legal existence of the company, (2) that it is in actual exercise of its Power-of-Attorney, (2) that it is in actual exercise of its company purposes, and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).

Seen for legalization of the signatures of Mr. F.G.M. Hermans and Mr. E.H. Reerink by me, Mr. Martinus Petrus Maria Philips, notary public at Oss, the Netherlands, on this 26th day of August 1998.



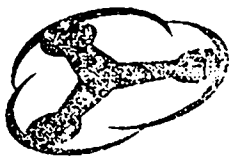
*[Handwritten signature of M. P. M. Philips]*

TRADUCCION No.: 18.11/98  
MARIA ELVIRA MARTELO  
Traductora e Interprete Oficial  
Inglés - Español - Inglés  
Res. No. 2879 Min. Justicia

15499

CHAMBER OF COMMERCE AND INDUSTRY  
FOR GOST-BRABANT (NETHERLAND)

EXCLUSIVE POWER FOR LEGALIZATION OF  
THE ABOVE MENTIONED SIGNATURE(S)



27 AUG 1998

KAMER VAN COOPHANDEL  
GOST-BRABANT  
's-HERTOGENBOSCH

*[Handwritten signature of J. Schellekens]*  
J. Schellekens

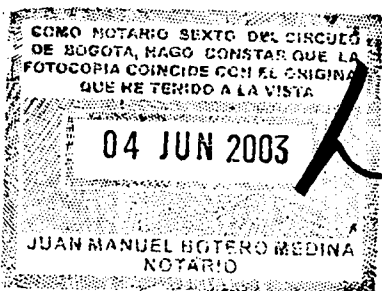
Gezien voor legalisatie van de handtekening van *[Handwritten signature]* Schellekens

's-Gravenhage, 09 SEP 1998



De Minister van  
Buitenlandse Zaken  
voor deze,

Leges f 20,- H.H. van POORTEN



NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.



CONSULADO DE COLOMBIA

COLD 11214-201-001-2

El suscrito Cónsul de Colombia en La Haya, Holanda,  
vistos los documentos presentados por los interesados,

CERTIFICA:

Que el Señor **Martinus Petrus Maria PHILIPS**, quien como Notario Público de Oss, Países Bajos, autenticó las firmas de los signatarios del poder precedente, ejercía en la fecha las funciones indicadas, y su firma corresponde a la registrada en este Consulado.

Que la Compañía **AKZO NOBEL N.V.** es una Sociedad constituida de acuerdo con las leyes de los Países Bajos, cumple su objeto conforme a las mismas y se halla registrada en la Cámara de Comercio y Fábricas de Centraal Gelderland, Arnhem, bajo el número **09007809**;

Que los Señores **Franciscus Guilielmus Maria HERMANS** y **Engbert Harmen REERINK**, signatarios del presente documento, quienes en su carácter de Apoderados de la Empresa **AKZO NOBEL N.V.**, conjuntamente tienen facultad para ello, y cuyas firmas fueron autenticadas ante el Notario Público de Oss, Señor **Martinus Petrus Maria PHILIPS**, son los representantes legales de la citada Empresa en este País.

El Cónsul de Colombia en La Haya, Países Bajos, no asume responsabilidad alguna por el contenido del documento.

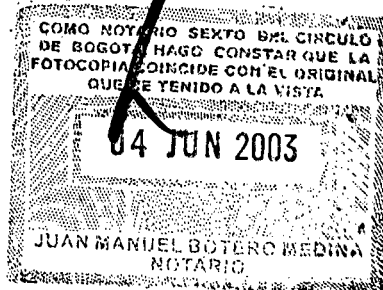
Esta certificación se expide en La Haya, Países Bajos, a los seis (06) días del mes de Noviembre de mil novecientos noventa y ocho (1998).

|                     |       |        |
|---------------------|-------|--------|
| Impuesto de Timbre  | US\$  | 6.00.  |
| Derechos Consulares | US\$. | 100.00 |
| Costo Total Pagado  | US\$. | 106.00 |

Certificación No. 206

  
**JOSE IGNACIO VILLEGAS CORTES**  
CONSUL DE COLOMBIA  
LA HAYA

TRADUCCION No. 18.11/98  
MARIA ELVIRA MARTELO  
Traductora e Interprete Oficial  
Inglés - Español - Inglés  
Res. No. 2879 Min. Justicia



NO SE ASUME  
RESPONSABILIDAD DEL TEXTO

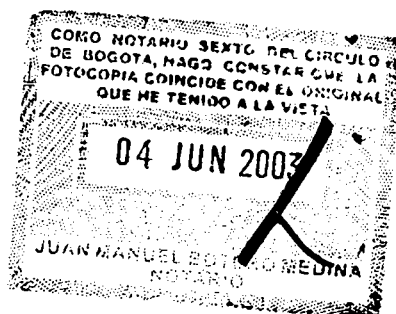
90 NOV 19 11:56

JEFE DE LEGALIZACIONES  
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES  
EXTERIORES

*[Signature]*  
300803

CUYA FIRMA APARECE EN EL  
DOCUMENTO DESEMPEÑA  
LAS FUNCIONES INDICADAS



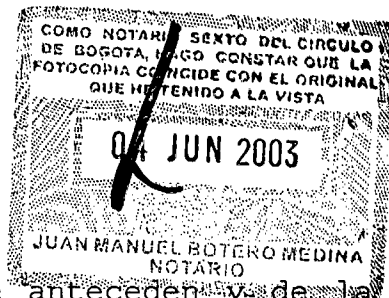
TRADUCCIÓN OFICIAL No. 18.11/98 preparada por María Elvira Martelo, Traductora Oficial debidamente aprobada por el Ministerio de Justicia de Colombia por Resolución 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

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(A continuación se traducen los sellos y legalizaciones de un documento escrito en inglés y español, por el cual AKZO NOBEL N.V. otorga poder a EMILIO FERRERO, GONZALO PERDOMO, LUZ CLEMENCIA DE PAEZ Y GERMAN CAVELIER). Dado y firmado el 6 de agosto de 1998. (Firma ilegible) F.G.M. Hermans, Director de Patentes Farmacéuticas. (Firma ilegible) E.H. Reerink, Subdirector de Asuntos Jurídicos. (Sello Corporativo) AKZO NOBEL N.V.

(Al dorso) Visto por mí, Sr. Martinus Petrus Maria Philips, notario público en Oss, Países Bajos, hoy 26 de agosto de 1998, para legalización de las firmas de F.G.M. Hermans y E.H. Reerink. (Firma ilegible).

(Legalización) CAMARA DE INDUSTRIA Y COMERCIO PARA OOST-BRABANT (PAÍSES BAJOS). Visto exclusivamente para la legalización de la(s) firma(s) que antecede(n). Agosto 27 de 1998. (Firma ilegible) J. Schellenkens.  
(Sello en holandés).



-----  
(En español) Certificación de las firmas que anteceden y de la existencia legal de AKZO NOBEL N.V. expedida por el Consulado de Colombia en La Haya el día 6 de noviembre de 1998, bajo el No.

206. Firmado JOSE IGNACIO VILLEGAS CORTES, Cónsul de Colombia, La Haya. Pagado impuesto de timbre.

(Al dorso) Legalización de la firma que antecede expedida por el MINISTERIO DE RELACIONES EXTERIORES bajo el No. 300803 del 19 de NOVIEMBRE de 1998, firmado por el Jefe de Legalizaciones.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

COLO 11214-801-001-3

Id. 6

Nov. 20/98

*Maria E. Martelo*  
TRADUCCION No. 1811/98  
MARIA ELVIRA MARTELO  
Traductora e Interprete Oficial  
Inglés - Español - Inglés  
Res. No. 2879 Min. Justicia

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR *[Firma]* IDENTIFICADOS CON C.C. No.(s) *[Firma]* ES(SON) AUTENTICA(S)  
SANTAFE DE BOGOTA. 23 NOV. 1998

REPUBLICA DE COLOMBIA  
Notario  
Notario Sexto  
DE BOGOTA

MINISTERIO DE RELACIONES EXTERIORES  
198457  
*[Firma]*  
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPENA LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA  
04 JUN 2005  
JUAN MANUEL BOTERO MEDINA  
NOTARIO

NO SE ASUME RESPONSABILIDAD DEL TEXTO  
98 NOV 24 PM 12:06  
JEFE DE LEGALIZACIONES  
SANTAFE DE BOGOTA D.C.

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
13 June 2002 (13.06.2002)

PCT

(10) International Publication Number  
WO 02/045753 A3

- (51) International Patent Classification<sup>7</sup>: A61K 31/506, 9/22
- (21) International Application Number: PCT/EP01/14189 ✓
- (22) International Filing Date:  
30 November 2001 (30.11.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
00204388.3 8 December 2000 (08.12.2000) EP
- (71) Applicant: AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL).
- (72) Inventors: EGBERINK, Johannes, Gerardus, Joseph; N.V. Organon, Postbus 20, NL-5340-BH Oss (NL). EN-1  
GELHART, John, Francis; Organon Inc., 375 Mt. Pleasant Ave, West Orange, NJ 07092 (US).
- (74) Agent: KRAAK, Hajo; P.O. Box 20, NL-5340 BH Oss (NL).
- (81) Designated States (*national*): AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CQ, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, ZA.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, 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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report
- (88) Date of publication of the international search report:  
29 August 2002
- 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.*

(54) Title: ORAL EXTENDED RELEASE FORMULATION OF GEPIRONE

(57) Abstract: This invention makes a pharmaceutical formulation for oral administration with extended release properties available comprising an amount of gepirone hydrochloride, an amount of a cellulosic polymer matrix and an amount of microcrystalline cellulose characterised in that the amount the pharmaceutically acceptable cellulosic polymer matrix is from 70 to 85 wt%, the amount of carbohydrate binder is from 7 to 10 wt% and the amount of gepirone hydrochloride is from 13 to 21 wt%. The formulation is useful for a treatment for depression or a related central nervous system disorder with gepirone administered in a once-a-day oral formulation for extended release of gepirone.

WO 02/045753 A3

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/14189

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/506 A61K9/22

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 A61K

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, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data, SCISEARCH, INSPEC

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                | Relevant to claim No. |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | EP 0 700 680 A (SQUIBB BRISTOL MYERS CO)<br>13 March 1996 (1996-03-13)<br>cited in the application<br>the whole document<br>claims                                                                                                                                                                | 1-3                   |
| A          | FEIGER A.D.: "A double-blind comparison<br>of gepirone extended release, imipramine,<br>and placebo in the treatment of outpatient<br>major depression."<br>PSYCHOPHARMACOLOGY BULLETIN, (1996) 32/4<br>(659-665).<br>XP001069219<br>the whole document<br>page 660, column 1, paragraph 2<br>-/- | 1-3                   |

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

## \* Special categories of cited documents:

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

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

Date of the actual completion of the international search

7 May 2002

Date of mailing of the international search report

04/06/2002

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Luangkhrot, N

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/14189

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                       | Relevant to claim No. |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A          | <p>WILCOX C.S.: "A double-blind trial of low- and high-dose ranges of gepirone-ER compared with placebo in the treatment of depressed outpatients"</p> <p>PSYCHOPHARMACOLOGY BULLETIN, (1996) 32/3 (335-342).</p> <p>XP001069224</p> <p>the whole document</p> <p>page 336, column 2</p> | 1-3                   |

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/14189

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---|---------------------|----------------------------|---------------------|
| EP 0700680                                | A | 13-03-1996          | US 5478572 A               | 26-12-1995          |
|                                           |   |                     | AT 186462 T                | 15-11-1999          |
|                                           |   |                     | AU 702282 B2               | 18-02-1999          |
|                                           |   |                     | AU 3043895 A               | 21-03-1996          |
|                                           |   |                     | CN 1128142 A               | 07-08-1996          |
|                                           |   |                     | CZ 9502275 A3              | 13-03-1996          |
|                                           |   |                     | DE 69513254 D1             | 16-12-1999          |
|                                           |   |                     | DE 69513254 T2             | 15-06-2000          |
|                                           |   |                     | DK 700680 T3               | 01-05-2000          |
|                                           |   |                     | EP 0700680 A1              | 13-03-1996          |
|                                           |   |                     | ES 2142432 T3              | 16-04-2000          |
|                                           |   |                     | FI 954154 A                | 07-03-1996          |
|                                           |   |                     | GR 3032598 T3              | 31-05-2000          |
|                                           |   |                     | HK 1014666 A1              | 21-07-2000          |
|                                           |   |                     | HU 73182 A2                | 28-06-1996          |
|                                           |   |                     | IL 114984 A                | 28-10-1999          |
|                                           |   |                     | JP 8183736 A               | 16-07-1996          |
|                                           |   |                     | NO 953212 A                | 07-03-1996          |
|                                           |   |                     | NZ 272855 A                | 26-05-1997          |
|                                           |   |                     | PL 310298 A1               | 18-03-1996          |
|                                           |   |                     | RU 2155044 C2              | 27-08-2000          |
|                                           |   |                     | SG 30436 A1                | 01-06-1996          |
|                                           |   |                     | ZA 9507144 A               | 26-03-1996          |

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(NL).

(81) Designated States (*national*): AE, AG, AL, AU, BA, BB,  
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European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent  
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*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: PHARMACEUTICAL FORMULATION OF GEPIRONE FOR ORAL ADMINISTRATION

(57) Abstract: This invention makes a pharmaceutical formulation for oral administration with extended release properties available comprising an amount of gepirone hydrochloride, an amount of a cellulosic polymer matrix and an amount of microcrystalline cellulose characterised in that the amount the pharmaceutically acceptable cellulosic polymer matrix is from 70 to 85 wt%, the amount of carbohydrate binder is from 7 to 10 wt% and the amount of gepirone hydrochloride is from 13 to 21 wt%. The formulation is useful for a treatment for depression or a related central nervous system disorder with gepirone administered in a once-a-day oral formulation for extended release of gepirone.

WO 02/45753 A2

## PHARMACEUTICAL FORMULATION OF GEPIRONE FOR ORAL ADMINISTRATION

The invention relates to a pharmaceutical formulation for oral

- 5 administration with extended release properties comprising an amount of gepirone hydrochloride, an amount of a cellulosic polymer matrix and an amount of microcrystalline cellulose.

- Such pharmaceutical formulations are described in EP 700 680 for use in  
10 the treatment of CNS disorders such as anxiety, depression and panic disorders. Gepirone is a drug which induces undesirable effects when high peak levels are reached. An even distribution of drug levels in blood is desirable to have a suitably tolerated therapeutic dose level. It was reported that optimal treatment of major depressive disorder was obtained  
15 with daily doses of up to 100 mg gepirone HCl (Wilcox et al; Psychopharmacology Bulletin). The administration of the total daily amount of gepirone was spread over the day by providing 20 mg gepirone HCl extended release tablets at intervals during the day. This was done not only because it was indicated in the prior art (EP 700 680) that  
20 extended release formulations can reliably be produced and have slow release properties when the content is at most 12% gepirone HCl of the total content, with a preferred maximum of 11 wt %, and the content of microcrystalline cellulose at least 10% with a preferred minimum of 11 wt %, but also because it could be expected that once-a-day high doses will  
25 be badly tolerated even when given as an extended release formulation.

- Contrary to what is to be expected it was found that suitable higher strengths extended release tablets can be prepared and are well tolerated in a once a day dosage form in those patients already habituated to lower  
30 dosages.

Clearly, it is more accommodating for such patients to have a once-a-day formulation available.

- 35 This invention makes a pharmaceutical formulation according to the opening paragraph available in which the amount of the pharmaceutically acceptable cellulosic polymer matrix is from 70 to 85 wt %, the amount of carbohydrate binder is from 7 to 10 wt % and the amount of gepirone

hydrochloride is from 13 to 21 wt %. The formulation may optionally contain further pharmaceutically acceptable additives, such as glidants, lubricants and colorants.

- 5 The invention makes a once per day medical treatment available with gepirone HCl in a pharmaceutical formulation for oral administration having the above-defined composition. This treatment is useful and well-tolerated by those patients treated for depression or a related central nervous system disorder, who are started on a treatment regime beginning  
10 with doses of about 20 mg gepirone HCl per day, and which is gradually built up to 60-100 mg gepirone HCl per day.

- A pharmaceutical formulation for oral administration is usually a tablet or a capsule. Contrary to what would have been the weight of an 80 mg  
15 tablet according to EP 700 680, tablets according to the present invention can have a total weight of at most 450 mg. Despite the high relative amount of gepirone HCl over the cellulosic polymer matrix material and also over the carbohydrate binder, oral formulations, in particular tablets, could still be made with acceptable dissolution properties of gepirone and  
20 sufficient stability during production and handling.

- A pharmaceutically acceptable cellulosic polymer matrix has the function of retaining gepirone HCl so that an extended release effect is obtained. Suitable matrixes include hydroxyalkylsubstituted alkylcelluloses having a  
25 viscosity of 15,000 cps to 100,000 cps. Hydroxymethyl propylcellulose (HPMC) of grades K15M and K100M is preferred and grade K100M, Premium (Methocel) is in particular preferred. The amounts of components in the pharmaceutical formulation of the invention are expressed as weight percentage (wt %) of the total weight of the  
30 formulation, which is usually a tablet. The term alkyl as used here means a branched or unbranched saturated unsubstituted carbon chain. In view of the required viscosities, the alkyl groups referred to in this paragraph do not comprise more than 6 carbon atoms.

- 35 The term pharmaceutically acceptable for suitable additives for use in carrying out the invention refers to requirements set for pharmaceutical auxiliaries in general. These requirements with regard to safety and non-interference with the active principle in pharmaceutical formulations are

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generally known to the skilled person. A standard compilation of pharmaceutically acceptable carriers and excipients can be found in the Handbook of Pharmaceutical excipients (2<sup>nd</sup> edition edited by A. Wade and P.J. Weller; Published by the American Pharmaceutical Association,

5 Washington and The Pharmaceutical Press, London in 1994). Additives to a pharmaceutical formulation, such as carriers, binders, glidants, lubricants and colorants are used for example in order to obtain certain cohesiveness, coloration and flowability of the tablets. In a preferred embodiment of this invention magnesium stearate, colloidal silicon dioxide  
10 and iron oxide pigments are used.

Glidants and lubricants are agents reducing the adhesiveness of the powder mixture or tablets during production. Methods of use of such additives are known in the art of making pharmaceutical compositions as for example described in chapter 19 of Remington's Pharmaceutical  
15 Sciences (18th edition Editor A.R. Gennaro; Mack Publishing Comp; Easton, Pennsylvania).

Binders are agents used to impart cohesive properties to a pharmaceutical composition resulting in minimal loss from the pharmaceutical composition during production and handling. Carbohydrate binders are  
20 for example cellulose, methylcellulose, ethylcellulose, hydroxypropylcellulose, sugars, starches, amylopectin, dextrin, maltodextrin, gums and alginates. Microcrystalline cellulose, and in particular Avicel pH 101, is a preferred binder for use in this invention.

25 The term pharmaceutical formulation for oral administration with extended release properties is used in this description to refer to the characteristics of extended release of gepirone according to the disclosure in EP 700 680. Specifically, a formulation according to the invention has a release rate of gepirone from the formulation such that about 18 to 24  
30 hours are required to attain from about 90 to about 95% absorption of gepirone.

Oral pharmaceutical formulations according to the present invention can be prepared by methods known in the art, e.g. as described in the  
35 standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture). Some caution in

handling the compressed high strength formulations of this invention is advisable in order to avoid breaking and cracks in tablets.

Gepirone may be prepared by any method known in the art. Typically the  
5 compound is prepared by the methods described in US patent No. 4,423,049. Pharmaceutical extended release compositions containing gepirone are disclosed in EP 700 680. The contents of these documents are incorporated herein by reference.

10 The following examples will serve to illustrate how to perform the invention.

Example 1

15 Manufacturing procedure of batches of 160,000 tablets

**Composition of tablets** (Numbers in the table are amounts in mg)

| Ingredients                                             | 40 mg | 60 mg | 80 mg | Function                         |
|---------------------------------------------------------|-------|-------|-------|----------------------------------|
| Gepirone HCl                                            | 40.0  | 60.0  | 80.0  | Active principle                 |
| Hydroxypropyl Methylcellulose (Methocel K100M, Premium) | 290.0 | 290.0 | 290.0 | Drug release controlling polymer |
| Microcrystalline Cellulose (Avicel pH 101)              | 52.12 | 31.0  | 33.7  | Diluent                          |
| Euroxide yellow or red (E7055, E7056 or E7016)          | 0.08  | 1.2   | 3.5   | Colorant                         |
| Colloidal silicon dioxide (cab-o-sil M5)                | 1.6   | 1.6   | 1.6   | Glidant                          |
| Magnesium stearate NF                                   | 1.2   | 1.2   | 1.2   | Lubricant                        |

Active pre-mixture:

20 Transfer the colloidal silicon dioxide, NF, colorant (40 mg: Euroxide Yellow E 7056; 60 mg: Euroxide Yellow E 7055; 80 mg: Euroxide yellow E 7055 and Euroxide Red E 7016), gepirone HCl powder and 20% of hydroxypropyl methylcellulose USP in 2 cu. Ft. planetary mixer (Hobart mixer). Mix ingredients for 15 minutes in a planetary mixer (Hobart  
25 Mixer). Label as 'Active Pre-Mix'.

Blend for slugging

Mill the Active Pre-Mix in a Fitzmill using a perforated plate No. 0020 at high speed, impact forward to deagglomerate lumps, if any.

5

Transfer the Active Pre-Mix in a 10 cu. Ft. "V"-blender without an I-bar, while passing through #12 mesh screen and transfer the balance of 80% HPMC, microcrystalline cellulose, NF and 50% of magnesium stearate, NF in the V-blender without an I-bar. Blend ingredients in the V-blender

10 without an I bar for 24 minutes and label as "Blend for Slugging".

Slugging

Compress the blend into slugs using 7/8" round flat face bevelled edge (40) bevelled plain (60, 80) tooling using a rotary Kikusui-Hercules

15 compression machine.

In process controls:

|                     |         |
|---------------------|---------|
| Weight:             | 2250 mg |
| Hardness:           | 7 kp    |
| Targeted thickness: | 0.255"  |

Final Blend

20 Mill the slugs in an S.S. Fitzmill with screw feeder using a perforated plate No. 0093 at medium speed, knives forward and screw feeder setting of  $3.5 \pm 0.5$ . Transfer the milled mass into a 10 cu. Ft. S.S. V-blender without I-bar. Screen the balance of 50% magnesium stearate, NF through #18 mesh and transfer also into the V-blender. Blend for 6 minutes.

25 Compress tablets with a rotary Kikusui-Libra compression machine using 0.338" X 0.405" Ovoid rectangular dies.

In process controls:

|                   |                |                |
|-------------------|----------------|----------------|
| Strength, mg      | 40 & 60        | 80             |
| Run Weight, mg    | $385 \pm 27$   | $410 \pm 29$   |
| Hardness, kp      | $18 \pm 4$     | $20 \pm 8$     |
| Thickness, inches | 0.230 to 0.260 | 0.235 to 0.265 |

Store in tight containers untill further use or testing.

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**Gepirone release pattern of tablets** (Numbers in the table represent the percentage dissolution of the theoretical content of the tablets)

| Released after: → | 1 hr | 5 hr | 12 hr | 20 hr | recovery |
|-------------------|------|------|-------|-------|----------|
| 20 mg tablets     | 19   | 49   | 77    | 93    | 102      |
| 40 mg tablets     | 21   | 50   | 77    | 93    | 100      |
| 60 mg tablets     | 21   | 51   | 81    | 97    | 102      |
| 80 mg tablets     | 22   | 52   | 80    | 96    | 101      |

#### Example 2

5

For upscaling the manufacturing for batches of 800,000 tablets certain adaptations were applied:

Thus, procedures are according to the methods described in example 1, but the active pre-mix is blended in a 340 qt. AZMF Glen mixer for 28 minutes, the size of the V-blender used is 30 cu. Ft. and final blending is done for 7 minutes. Tablets had similar properties as measured in example 1. Special attention is given to the problem of friability of the 80 mg strength tablets. It is preferred to compress 80 mg tablets at a speed of the compression machine of 20 rotations per minute, i.e. in general at a speed of less than 30 rpm, set at the tablet compression machine in order to reduce the number of tablets with cracks.

## Claims

1. A pharmaceutical formulation for oral administration with extended  
release properties comprising an amount of gepirone hydrochloride, an  
5 amount of a cellulosic polymer matrix and an amount of  
microcrystalline cellulose characterised in that the amount the  
pharmaceutically acceptable cellulosic polymer matrix is from 70 to 85  
wt %, the amount of carbohydrate binder is from 7 to 10 wt % and the  
amount of gepirone hydrochloride is from 13 to 21 wt %.
- 10 2. The pharmaceutical formulation according to claim 1, characterised in  
that the cellulosic polymer matrix is a hydroxymethyl propylcellulose  
having a viscosity of 15,000 cps to 100,000 cps.
- 15 3. The pharmaceutical formulation according to claim 1, characterised in  
that the microcrystalline cellulose is Avicel pH 101.
4. A treatment for depression or a related central nervous system disorder  
with gepirone administered in a once-a-day oral formulation for  
20 extended release of gepirone, characterised in that the formulation is  
according to claim 1.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|                                                      |                                                                                                                                                         |                                                         |
|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Applicant's or agent's file reference<br>2000.602 W0 | <b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |                                                         |
| International application No.<br>PCT/EP 01/14189     | International filing date (day/month/year)<br>30/11/2001                                                                                                | (Earliest) Priority Date (day/month/year)<br>08/12/2000 |
| Applicant<br>AKZO NOBEL N.V.                         |                                                                                                                                                         |                                                         |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

**4. With regard to the title,**

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

ORAL EXTENDED RELEASE FORMULATION OF GEPIRONE

**5. With regard to the abstract,**

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/14189

18

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K31/506 A61K9/22

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 A61K

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, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data, SCISEARCH, INSPEC

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                 | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | EP 0 700 680 A (SQUIBB BRISTOL MYERS CO)<br>13 March 1996 (1996-03-13)<br>cited in the application<br>the whole document<br>claims                                                                                                                                                                 | 1-3                   |
| A          | FEIGER A.D.: "A double-blind comparison<br>of gepirone extended release, imipramine,<br>and placebo in the treatment of outpatient<br>major depression."<br>PSYCHOPHARMACOLOGY BULLETIN, (1996) 32/4<br>(659-665).<br>XP001069219<br>the whole document<br>page 660, column 1, paragraph 2<br>-/-- | 1-3                   |

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

## ° Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

7 May 2002

Date of mailing of the international search report

04/06/2002

Name and mailing address of the ISA

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Authorized officer

Luangkhot, N

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 01/14189

19

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                         |                       |
|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category °                                           | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                      | Relevant to claim No. |
| A                                                    | <p>WILCOX C.S.: "A double-blind trial of low- and high-dose ranges of gepirone-ER compared with placebo in the treatment of depressed outpatients"</p> <p>PSYCHOPHARMACOLOGY BULLETIN, (1996) 32/3 (335-342). ,</p> <p>XP001069224</p> <p>the whole document</p> <p>page 336, column 2</p> <p>-----</p> | 1-3                   |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 01/14189

RD

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 4  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/14189

21

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---|---------------------|----------------------------|---------------------|
| EP 0700680                                | A | 13-03-1996          | US 5478572 A               | 26-12-1995          |
|                                           |   |                     | AT 186462 T                | 15-11-1999          |
|                                           |   |                     | AU 702282 B2               | 18-02-1999          |
|                                           |   |                     | AU 3043895 A               | 21-03-1996          |
|                                           |   |                     | CN 1128142 A               | 07-08-1996          |
|                                           |   |                     | CZ 9502275 A3              | 13-03-1996          |
|                                           |   |                     | DE 69513254 D1             | 16-12-1999          |
|                                           |   |                     | DE 69513254 T2             | 15-06-2000          |
|                                           |   |                     | DK 700680 T3               | 01-05-2000          |
|                                           |   |                     | EP 0700680 A1              | 13-03-1996          |
|                                           |   |                     | ES 2142432 T3              | 16-04-2000          |
|                                           |   |                     | FI 954154 A                | 07-03-1996          |
|                                           |   |                     | GR 3032598 T3              | 31-05-2000          |
|                                           |   |                     | HK 1014666 A1              | 21-07-2000          |
|                                           |   |                     | HU 73182 A2                | 28-06-1996          |
|                                           |   |                     | IL 114984 A                | 28-10-1999          |
|                                           |   |                     | JP 8183736 A               | 16-07-1996          |
|                                           |   |                     | NO 953212 A                | 07-03-1996          |
|                                           |   |                     | NZ 272855 A                | 26-05-1997          |
|                                           |   |                     | PL 310298 A1               | 18-03-1996          |
|                                           |   |                     | RU 2155044 C2              | 27-08-2000          |
|                                           |   |                     | SG 30436 A1                | 01-06-1996          |
|                                           |   |                     | ZA 9507144 A               | 26-03-1996          |

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From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

## PCT

### NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                                    |                |     |                 |    |              |  |     |  |              |  |          |  |
|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|-----|-----------------|----|--------------|--|-----|--|--------------|--|----------|--|
| To:<br><br>KRAAK, H.<br>P.O. Box 20<br>NL-5340 BH Oss<br>PAYS-BAS | <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Behandeld door</td> <td style="width: 50%;">CBR</td> </tr> <tr> <td>Beoordeeld door</td> <td>AL</td> </tr> <tr> <td>Besluit d.d.</td> <td></td> </tr> <tr> <td>aan</td> <td></td> </tr> <tr> <td>Besluit d.d.</td> <td></td> </tr> <tr> <td>Aflegger</td> <td></td> </tr> </table> | Behandeld door | CBR | Beoordeeld door | AL | Besluit d.d. |  | aan |  | Besluit d.d. |  | Aflegger |  |
| Behandeld door                                                    | CBR                                                                                                                                                                                                                                                                                                                                                                                |                |     |                 |    |              |  |     |  |              |  |          |  |
| Beoordeeld door                                                   | AL                                                                                                                                                                                                                                                                                                                                                                                 |                |     |                 |    |              |  |     |  |              |  |          |  |
| Besluit d.d.                                                      |                                                                                                                                                                                                                                                                                                                                                                                    |                |     |                 |    |              |  |     |  |              |  |          |  |
| aan                                                               |                                                                                                                                                                                                                                                                                                                                                                                    |                |     |                 |    |              |  |     |  |              |  |          |  |
| Besluit d.d.                                                      |                                                                                                                                                                                                                                                                                                                                                                                    |                |     |                 |    |              |  |     |  |              |  |          |  |
| Aflegger                                                          |                                                                                                                                                                                                                                                                                                                                                                                    |                |     |                 |    |              |  |     |  |              |  |          |  |

|                                     |            |
|-------------------------------------|------------|
| Date of mailing<br>(day/month/year) | 13.03.2003 |
|-------------------------------------|------------|

|                                                      |                               |
|------------------------------------------------------|-------------------------------|
| Applicant's or agent's file reference<br>2000.602 WO | <b>IMPORTANT NOTIFICATION</b> |
|------------------------------------------------------|-------------------------------|

|                                                 |                                                          |                                              |
|-------------------------------------------------|----------------------------------------------------------|----------------------------------------------|
| International application No.<br>PCT/EP01/14189 | International filing date (day/month/year)<br>30/11/2001 | Priority date (day/month/year)<br>08/12/2000 |
|-------------------------------------------------|----------------------------------------------------------|----------------------------------------------|

|                                     |
|-------------------------------------|
| Applicant<br>AKZO NOBEL N.V. 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.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

|                                                                                                                                                                                                                                                                                         |                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Name and mailing address of the IPEA/<br><br><div style="text-align: center;">  </div> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br><br>Senkel, H<br><br>Tel.+49 89 2399-8071 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|



## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                       |                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Applicant's or agent's file reference<br>2000.602 WO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)                                         |                                              |
| International application No.<br>PCT/EP01/14189                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | International filing date (day/month/year)<br>30/11/2001                                                                                                              | Priority date (day/month/year)<br>08/12/2000 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K31/506                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                       |                                              |
| Applicant<br>AKZO NOBEL N.V. et al.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                       |                                              |
| <p>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.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> 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).</p> <p>These annexes consist of a total of sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"><li>I <input checked="" type="checkbox"/> Basis of the report</li><li>II <input type="checkbox"/> Priority</li><li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li><li>IV <input type="checkbox"/> Lack of unity of invention</li><li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li><li>VI <input type="checkbox"/> Certain documents cited</li><li>VII <input type="checkbox"/> Certain defects in the international application</li><li>VIII <input type="checkbox"/> Certain observations on the international application</li></ul> |                                                                                                                                                                       |                                              |
| Date of submission of the demand<br><br>03/06/2002                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Date of completion of this report<br><br>13.03.2003                                                                                                                   |                                              |
| Name and mailing address of the international preliminary examining authority:<br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Authorized officer<br><br>Luangkhot, N<br><br>Telephone No. +49 89 2399 7857<br> |                                              |

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP01/14189

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
- Description, pages:

1-7 as originally filed

Claims, No.:

1-4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP01/14189

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 4 regarding industrial applicability.

because:

- ☒ the said international application, or the said claims Nos. 4 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

|                               |      |            |
|-------------------------------|------|------------|
| Novelty (N)                   | Yes: | Claims 1-4 |
|                               | No:  | Claims     |
| Inventive step (IS)           | Yes: | Claims     |
|                               | No:  | Claims 1-4 |
| Industrial applicability (IA) | Yes: | Claims 1-3 |

INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

International application No. PCT/EP01/14189

No: Claims

2. Citations and explanations  
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 4 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) The documents cited in the International Search Report (ISR) were numbered respectively from D1-D3; this numbering results from the citation order in the ISR and will be used for the procedure. Unless not specified, the cited passages of each document in the ISR will be considered.

2) Novelty (Art. 33(2) PCT)

None of the cited documents describes a composition containing 13-21wt% of gepirone (G), 70-85wt% of a cellulosic polymer matrix (CPM) and 7-10wt% of microcrystalline cellulose (MicroC).

Therefore, claims 1-4 are novel.

3) Inventive step (Art. 33(3) PCT)

Claims 1-4 do not involve an inventive step for this following reason:

D1, cited as the closest prior art, is directed to an extended release oral composition containing at most 12wt% of G, 70-85wt% of CPM and 10-20% of MicroC (see claims 1 and 4).

The difference consists in that the gepirone is in an amount of at least 13wt% in the present application, whereas in D1 at most 12wt%.

The effect achieved by D1 and the **subject-matter of the present claims** is an

INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET

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International application No. PCT/EP01/14189

extended release of the active substance.

The problem that the subject-matter of the **present claims underlies** can be seen as to provide as asserted in the letter of 17.09.2002 an improvement on the pharmaceutical formulation for a higher dose gepirone treatment regimen.

The solution proposed in the present application, which consists in **increasing slightly** the amount of gepirone to 13wt%, is not inventive because the claimed starting range which amounts 13wt% **is too close from the upper range of D1 (12 wt%)**. The skilled man, willing to improve the formulation with higher dose of gepirone, will try a slightly higher concentration of drug i.e. herein 13.0 wt% (and decrease consequently the concentration of diluent) and arrive at the subject-matter of the claims.

As long as no surprising effect of a composition of 13wt% gepirone over a composition of 12wt% gepirone is shown, inventive step can not be acknowledged.

The examining division **does not consider** that present claims are drafted in such a manner that a protection is given for a **once-a-day high doses gepirone tablet** as it seems to be suggested with the letters of 26.06.2002 and 17.09.2002. Herewith applicant should bear in mind that D3 (see conclusion) already teaches that a once-daily dosing gepirone regimen achieves beneficial effects such as good tolerableness, efficacy, compliance... Therefore as the benefits of a once-daily-dosing gepirone regimen is already known from D3, a **single tablet** containing a high dose (**not concentration**) of gepirone (instead of taking the same dose of drug with 3 or 5 different tablets simulataneously or distributed over the day) will not be inventive over D3 because it is a matter of routine for the skilled man to formulate a tablet with higher dose of gepirone.

4)For the assessment of the present claim 4 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5)The term "Avicel pH101" employed in claim 3 and appearing to be a registered trade mark has no precise meaning as it is not internationally accepted as a standard de-

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP01/14189

scriptive term, thereby rendering the definition of the subject-matter of this claim 3 unclear (Article 6 PCT).

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPFA/

CHAPTER II

PCT

These documents represent confirmation of an application filed by facsimile.

DEMAND

Date of facsimile: 3-6-2002

under Article 31 of the Patent Cooperation Treaty:  
ned requests that the international application specified below be the subject of  
onal preliminary examination according to the Patent Cooperation Treaty.

Name of authority with which facsimile was filed: E.p.o. München

For International Preliminary Examining Authority use only

Date of receipt of DEMAND

|                                                                                                                                                                                                                                                                                   |                                                          |                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------|
| Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION                                                                                                                                                                                                                         |                                                          | Applicant's or agent's file reference<br>2000.602 WO    |
| International application No.<br>PCT/EP01/14189                                                                                                                                                                                                                                   | International filing date (day/month/year)<br>30-11-2001 | (Earliest) Priority date (day/month/year)<br>08-12-2000 |
| Title of invention<br>"Pharmaceutical formulation of Gepirone for oral administration"                                                                                                                                                                                            |                                                          |                                                         |
| Box No. II APPLICANT(S)                                                                                                                                                                                                                                                           |                                                          |                                                         |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)<br><br>Akzo Nobel N.V.<br>Velperweg 76<br>6824 BM ARNHEM<br>The Netherlands                                      |                                                          | Telephone No.:<br>0412-666380                           |
|                                                                                                                                                                                                                                                                                   |                                                          | Facsimile No.:<br>0412-650592                           |
|                                                                                                                                                                                                                                                                                   |                                                          | Teleprinter No.:                                        |
| State (i.e. country) of nationality: NL                                                                                                                                                                                                                                           |                                                          | State (i.e. country) of residence: NL                   |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)<br><br>EGBERINK, Johannes, Gerardus, Joseph<br>N.V. Organon<br>P.O. Box 20<br>5340 BH Oss<br>The Netherlands     |                                                          |                                                         |
| State (i.e. country) of nationality: NL                                                                                                                                                                                                                                           |                                                          | State (i.e. country) of residence: NL                   |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)<br><br>ENGELHART, John, Francis<br>Organon Inc.<br>375 Mt. Pleasant Ave<br>NJ 07092 West Orange<br>United States |                                                          |                                                         |
| State (i.e. country) of nationality: US                                                                                                                                                                                                                                           |                                                          | State (i.e. country) of residence: US                   |
| <input type="checkbox"/> Further applicants are indicated on a continuation sheet.                                                                                                                                                                                                |                                                          |                                                         |

## Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative  
and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.  
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.  
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: (Family name followed by given name; for a legal entity, full official designation.  
The address must include postal code and name of country.)

H. Kraak  
P.O. Box 20  
5340 BH Oss  
The Netherlands

Telephone No.:

0412-666382

Facsimile No.:

0412-650592

Teleprinter No.:

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

## Box No. IV. STATEMENT CONCERNING AMENDMENTS

The applicant wishes the international Preliminary Examining Authority\*

- (i) ☒ to start the international preliminary examination on the basis of the international application as originally filed.
- (ii) ☐ to take into account the amendments under Article 34 of  
☐ the description (amendments attached).  
☐ the claims (amendments attached).  
☐ the drawings (amendments attached).
- (iii) ☐ to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).
- (iv) ☐ to disregard any amendments of the claims made under Article 19 and to consider them as reversed.
- (v) ☐ to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

## Box No. V ELECTION OF STATES

☒ The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT) except  
.....  
.....  
.....  
(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

## Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

## 1. amendments under Article 34

|             |   |        |
|-------------|---|--------|
| description | : | sheets |
| claims      | : | sheets |
| drawings    | : | sheets |

## 2. letter accompanying amendments under Article 34

: sheets

## 3. copy of amendments under Article 19

: sheets

## 4. copy of statement under Article 19

: sheets

## 5. other (specify):

: sheets

For International Preliminary  
Examining Authority use only

received

not received

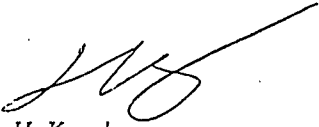
☐☐☐☐☐☐☐☐☐☐☐☐☐☐

The demand is also accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney4. ☒ fee calculation sheet2. ☐ copy of general power of attorney5. ☐ other (specify):3. ☐ statement explaining lack of signature

## Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

  
H. Kraak

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.☐ The applicant has been informed accordingly.4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

## FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

|                                       |                |
|---------------------------------------|----------------|
| International application No.         | PCT/EP01/14189 |
| Applicant's or agent's file reference | 2000.602 WO    |

For International Preliminary Examining Authority use only

COPY

Date stamp of the IPEA

Applicant Akzo Nobel N.V.

## Calculation of prescribed fees

- |                                                                                                                                                                                                                                     |            |                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|---------------------------------------|
| 1. Preliminary examination fee.....                                                                                                                                                                                                 | EUR 1530,= | <input checked="" type="checkbox"/> P |
| 2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)..... | EUR 159,=  | <input checked="" type="checkbox"/> H |
| 3. Total of prescribed fees<br>Add the amounts entered at P and H<br>and enter total in the TOTAL box .....                                                                                                                         | EUR 1689,= |                                       |
|                                                                                                                                                                                                                                     | TOTAL      |                                       |

## Mode of Payment

- |                                                                                                       |                                           |
|-------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below) | <input type="checkbox"/> cash             |
| <input type="checkbox"/> cheque                                                                       | <input type="checkbox"/> revenue stamps   |
| <input type="checkbox"/> postal money order                                                           | <input type="checkbox"/> coupons          |
| <input type="checkbox"/> bank draft                                                                   | <input type="checkbox"/> other (specify): |

## Deposit Account Authorization (this mode of payment may not be available at all IPEAs)

The IPEA / EPO ☒ is hereby authorized to charge the total fees indicated above to my deposit account.☒ (this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

2809.0012

03-06-2002

Deposit Account Number

Date (day/month/year)

H. Kraak

Signature

Form PCT/IPEA/401 (Annex) (January 1996)

See Notes to the fee calculation sheet

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. # 1564

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum) 2000.602 WO

Box No. I TITLE OF INVENTION

"PHARMACEUTICAL FORMULATION OF GEPIRONE FOR ORAL ADMINISTRATION"

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

Akzo Nobel N.V.

Velperweg 76

4 BM ARNHEM

The Netherlands

☐ This person is also inventor

Telephone No.  
0412-666219

Facsimile No.  
0412-650592

Teleprinter No.

State (i.e. country) of nationality: The Netherlands

State (i.e. country) of residence: The Netherlands

This person is applicant ☒ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

Egberink, Johannes, Gerardus, Joseph

N.V.Organon

Postbus 20

5340 BH Oss

The Netherlands

This person is:

☐ applicant only

☐ applicant and inventor

☒ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality: NL

State (i.e. country) of residence: NL

This person is applicant ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Kraak, Hajo

P.O. Box 20

5340 BH Oss

The Netherlands

Telephone No.  
0412-666382

Facsimile No.  
0412-650592

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

| Continuation of Box No. III <b>FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS</b>                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>If none of the following sub-boxes is used, this sheet is not to be included in the request.</i>                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                           |
| <p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)</small></p> <p><b>Engelhart, John, Francis</b><br/> <b>Organon Inc.</b><br/> <b>375 Mt. Pleasant Ave</b><br/> <b>NJ 07092 West Orange</b><br/> <b>United States</b></p> | <p><small>This person is:</small></p> <p><input type="checkbox"/> applicant only</p> <p><input type="checkbox"/> applicant and inventor</p> <p><input checked="" type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p> |
| <p><small>State (i.e. country) of nationality:</small> <b>US</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p><small>State (i.e. country) of residence:</small> <b>US</b></p>                                                                                                                                                                                        |
| <p><small>This person is applicant for the purposes of</small></p> <p> <input type="checkbox"/> all designated States                  <input type="checkbox"/> all designated States except the United States of America                  <input type="checkbox"/> the United States of America only                  <input type="checkbox"/> the States indicated in the Supplemental Box         </p>                                                                                            |                                                                                                                                                                                                                                                           |
| <p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)</small></p>                                                                                                                                                             | <p><small>This person is:</small></p> <p>applicant only</p> <p>applicant and inventor</p> <p>inventor only (If this check-box is marked, do not fill in below.)</p>                                                                                       |
| <p><small>State (i.e. country) of nationality:</small></p>                                                                                                                                                                                                                                                                                                                                                                                                                                           | <p><small>State (i.e. country) of residence:</small></p>                                                                                                                                                                                                  |
| <p><small>This person is applicant for the purposes of</small></p> <p> <input type="checkbox"/> all designated States                  <input type="checkbox"/> all designated States except the United States of America                  <input type="checkbox"/> the United States of America only                  <input type="checkbox"/> the States indicated in the Supplemental Box         </p>                                                                                            |                                                                                                                                                                                                                                                           |
| <p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)</small></p>                                                                                                                                                             | <p><small>This person is:</small></p> <p><input type="checkbox"/> applicant only</p> <p><input type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>            |
| <p><small>ate (i.e. country) of nationality:</small></p>                                                                                                                                                                                                                                                                                                                                                                                                                                             | <p><small>State (i.e. country) of residence:</small></p>                                                                                                                                                                                                  |
| <p><small>This person is applicant for the purposes of</small></p> <p> <input type="checkbox"/> all designated States                  <input type="checkbox"/> all designated States except the United States of America                  <input type="checkbox"/> the United States of America only                  <input type="checkbox"/> the States indicated in the Supplemental Box         </p>                                                                                            |                                                                                                                                                                                                                                                           |
| <p><input type="checkbox"/> Further applicants and/or (further) inventors are indicated on another continuation sheet.</p>                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                           |

## Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

## Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line) .....

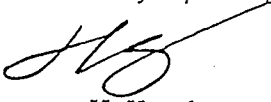
## National Patent (if other kind of protection or treatment desired, specify on dotted line):

- |                                                                |                                                                                  |                                                            |
|----------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------|
| <input checked="" type="checkbox"/> AE United Arab Emirates    | <input type="checkbox"/> GH Ghana                                                | <input checked="" type="checkbox"/> MX Mexico              |
| <input checked="" type="checkbox"/> AG Antigua and Barbuda     | <input type="checkbox"/> GM Gambia                                               | <input checked="" type="checkbox"/> MZ Mozambique          |
| <input checked="" type="checkbox"/> AL Albania                 | <input checked="" type="checkbox"/> HR Croatia                                   | <input checked="" type="checkbox"/> NO Norway              |
| <input type="checkbox"/> AM Armenia                            | <input checked="" type="checkbox"/> HU Hungary                                   | <input checked="" type="checkbox"/> NZ New Zealand         |
| <input type="checkbox"/> AT Austria                            | <input checked="" type="checkbox"/> ID Indonesia                                 | <input checked="" type="checkbox"/> PL Poland              |
| <input checked="" type="checkbox"/> AU Australia               | <input checked="" type="checkbox"/> IL Israel                                    | <input type="checkbox"/> PT Portugal                       |
| <input type="checkbox"/> AZ Azerbaijan                         | <input checked="" type="checkbox"/> IN India                                     | <input checked="" type="checkbox"/> RO Romania             |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina  | <input checked="" type="checkbox"/> IS Iceland                                   | <input checked="" type="checkbox"/> RU Russian Federation  |
| <input checked="" type="checkbox"/> BB Barbados                | <input checked="" type="checkbox"/> JP Japan                                     |                                                            |
| <input checked="" type="checkbox"/> BG Bulgaria                | <input type="checkbox"/> KE Kenya                                                | <input type="checkbox"/> SD Sudan                          |
| <input checked="" type="checkbox"/> BR Brazil                  | <input type="checkbox"/> KG Kyrgyzstan                                           | <input type="checkbox"/> SE Sweden                         |
| <input type="checkbox"/> BY Belarus                            | <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea     | <input checked="" type="checkbox"/> SG Singapore           |
| <input checked="" type="checkbox"/> BZ Belize                  | <input checked="" type="checkbox"/> KR Republic of Korea                         | <input checked="" type="checkbox"/> SI Slovenia            |
| <input checked="" type="checkbox"/> CA Canada                  | <input type="checkbox"/> KZ Kazakhstan                                           | <input checked="" type="checkbox"/> SK Slovakia            |
| <input type="checkbox"/> CH & LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> LC Saint Lucia                               | <input checked="" type="checkbox"/> SL Sierra Leone        |
| <input checked="" type="checkbox"/> CN China                   | <input checked="" type="checkbox"/> LK Sri Lanka                                 | <input type="checkbox"/> TJ Tajikistan                     |
| <input checked="" type="checkbox"/> CO Colombia                | <input checked="" type="checkbox"/> LR Liberia                                   | <input type="checkbox"/> TM Turkmenistan                   |
| <input checked="" type="checkbox"/> CR Costa Rica              | <input type="checkbox"/> LS Lesotho                                              | <input checked="" type="checkbox"/> TR Turkey              |
| <input checked="" type="checkbox"/> CU Cuba                    | <input checked="" type="checkbox"/> LT Lithuania                                 | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> CZ Czech Republic          | <input type="checkbox"/> LU Luxembourg                                           |                                                            |
| <input type="checkbox"/> DE Germany                            | <input checked="" type="checkbox"/> LV Latvia                                    | <input type="checkbox"/> TZ United Republic of Tanzania    |
| <input type="checkbox"/> DK Denmark                            | <input checked="" type="checkbox"/> MA Morocco                                   | <input checked="" type="checkbox"/> UA Ukraine             |
| <input checked="" type="checkbox"/> DM Dominica                | <input type="checkbox"/> MD Republic of Moldova                                  | <input type="checkbox"/> UG Uganda                         |
| <input checked="" type="checkbox"/> DZ Algeria                 |                                                                                  | <input type="checkbox"/> US United States of America       |
| <input checked="" type="checkbox"/> EC Ecuador                 | <input checked="" type="checkbox"/> MG Madagascar                                |                                                            |
| <input checked="" type="checkbox"/> EE Estonia                 | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia | <input checked="" type="checkbox"/> UZ Uzbekistan          |
| <input type="checkbox"/> ES Spain                              | <input checked="" type="checkbox"/> MN Mongolia                                  | <input checked="" type="checkbox"/> VN Viet Nam            |
| <input type="checkbox"/> FI Finland                            | <input type="checkbox"/> MW Malawi                                               | <input checked="" type="checkbox"/> YU Yugoslavia          |
| <input type="checkbox"/> GB United Kingdom                     |                                                                                  | <input checked="" type="checkbox"/> ZA South Africa        |
| <input checked="" type="checkbox"/> GD Grenada                 |                                                                                  | <input type="checkbox"/> ZW Zimbabwe                       |
| <input checked="" type="checkbox"/> GE Georgia                 |                                                                                  |                                                            |

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- ☒ PH...Philippines
- ☐ .....
- ☐ .....

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| <b>Box No. VI PRIORITY CLAIM</b>                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                        | Further priority claims are indicated in the Supplemental Box <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                 |
| The priority of the following earlier application(s) is hereby claimed:                                                                                                                                                                                                                                                                                                                                                                                            |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| Country<br><i>(in which, or for which, the<br/>application was filed)</i>                                                                                                                                                                                                                                                                                                                                                                                          | Filing Date<br><i>(day/month/year)</i> | Application No.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Office of filing<br><i>(only for regional or<br/>international application)</i> |
| item (1)<br>NL                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 08-12-2000                             | 00204388.3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | EPO                                                                             |
| item (2)                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| item (3)                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| <i>Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):</i>                                                                                                                                                                                                                                |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| <input checked="" type="checkbox"/> The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): <span style="float: right;">1</span>                                                                                                                                                                                                                  |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| <b>Box No. VII INTERNATIONAL SEARCHING AUTHORITY</b>                                                                                                                                                                                                                                                                                                                                                                                                               |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| Choice of International Searching Authority (ISA) <i>(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):</i> ISA <u>EPO</u>                                                                                                                                                                                                                  |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| Earlier search <i>Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request</i> |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| Country (or regional Office):                                                                                                                                                                                                                                                                                                                                                                                                                                      | Date (day/month/year)                  | Number:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                 |
| EP                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 08-12-2000                             | 00204388.3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                 |
| <b>Box No. VIII CHECK LIST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| This international application contains the following number of sheets:<br><br>1. request: 4 sheets<br>2. description: 7 sheets<br>3. claims: 1 sheets<br>4. abstract: 1 sheets<br>5. drawings: sheets<br>6 Sequence listing: sheets<br><br>Total: 13 sheets                                                                                                                                                                                                       |                                        | This international application is accompanied by the item(s) marked below:<br><br>1. <input type="checkbox"/> separate signed power of attorney<br>2. <input checked="" type="checkbox"/> copy of general power of attorney<br>3. <input type="checkbox"/> statement explaining lack of signature<br>4. <input type="checkbox"/> priority document(s) identified in Box No VI as item(s):<br><br>5. <input checked="" type="checkbox"/> fee calculation sheet<br>6. <input type="checkbox"/> separate indications concerning deposited microorganisms<br>7. <input type="checkbox"/> nucleotide and/or amino acid sequence listing (diskette)<br>8. <input type="checkbox"/> other (specify): |                                                                                 |
| Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.                                                                                                                                                                                                                                                                                                                                                                      |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| <b>Box No. IX SIGNATURE OF APPLICANT OR AGENT</b>                                                                                                                                                                                                                                                                                                                                                                                                                  |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| <i>to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading request)</i>                                                                                                                                                                                                                                                                                                |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| <br>H. Kraak                                                                                                                                                                                                                                                                                                                                                                    |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                 |

|                                                                                                                                             |                                                                                                 |  |
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| For receiving Office use only                                                                                                               |                                                                                                 |  |
| 1. Date of actual receipt of the purported international application:                                                                       | 2. Drawings:<br><input type="checkbox"/> received<br><br><input type="checkbox"/> not received: |  |
| 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: |                                                                                                 |  |
| 4. Date of timely receipt of the required corrections under PCT Article 11(2):                                                              |                                                                                                 |  |
| 5. International Searching Authority specified by the applicant: ISA/                                                                       | 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid         |  |

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# PCT

## FEE CALCULATION SHEET

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Annex to the Request

International application No.

Applicant's or agent's  
file reference **2000.602 WO**

Date stamp of the receiving Office

Applicant  
**Akzo Nobel N.V.**

## CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE ..... **EUR. 102,=** **T**2. SEARCH FEE ..... **EUR 945,=** **S**International search to be carried out by **EPO**  
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains **13** sheets,  
first 30 sheets ..... **EUR 409,=** **b<sub>1</sub>****X****EUR 9,=****b<sub>2</sub>**

remaining sheets

additional amount

Add amounts entered at b<sub>1</sub> and b<sub>2</sub> and enter total at B ..... **EUR 409,=** **B**

Designation Fees

The international application contains **62** designationsnumber of designation fees ..... amount of designation fee **EUR 528,=** **D**  
payable (maximum 6)Add amounts entered at B and D and enter total at I ..... **EUR 937,=** **I**  
(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)4. FEE FOR PRIORITY DOCUMENT ..... **EUR. 30,=** **P**

5. TOTAL FEES PAYABLE

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and enter total in the TOTAL box ..... **EUR 2014,=**

TOTAL

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## MODE OF PAYMENT

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2809 0012

30 November 2001

Deposit Account Number

Date (day/month/year)

Signature **H. Kraak**

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59 (rev.)

Ich (Wir) / I (We) / Je (Nous)

Akzo Nobel N.V.  
Velperweg 76  
6824 BM Arnhem  
The Netherlands

bevollmächtigte(n) hiermit / do hereby authorise / autorise (autorisons) par la présente

Schalkwijk, Pieter Cornelis  
Van Deursen, Petrus Hubertus  
Quelle-Fontijn, Monique  
Hesselink, Dinah E.  
Zonneveld, Hendrik Jan  
De Vries, Adriaan Jacobus  
Alferink, Petrus Johannes Theodorus  
Van den Broek, Ludovicus, A.G.M.

Address of place of business:  
Akzo Nobel N.V.  
Intellectual Property Department (Dept. AIP)  
P.O. Box 9300  
6800 SB Arnhem  
The Netherlands

mich (uns) in den durch das Europäische Patentübereinkommen geschaffenen Verfahren in allen meinen (unseren) Patentangelegenheiten zu vertreten, alle Handlungen für mich (Uns) vorzunehmen und Zahlungen für mich (Uns) in Empfang zu nehmen.

to represent me (us) in all proceedings established by the European Patent Convention and to act for me (us) in all patent transactions and to receive payments on my (our) behalf.

à me (nous) représenter pour ce qui concerne toutes mes (nos) affaires de brevet dans toute procédure instituée par la Convention sur le brevet européen et, à ce titre, à agir en mon (notre) nom et à recevoir des paiements pour mon (notre) compte.

☒ Die Vollmacht gilt auch für Verfahren nach dem Vertrag über die internationale Zusammenarbeit auf dem Gebiet des Patentwesens. This authorisation shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty. Ce pouvoir s'applique également à toute procédure instituée par le Traité de coopération en matière de brevets.

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Ort/Place/Lieu Arnhem, the Netherlands

Datum / Date November 22, 2001

Unterschrift(en) / Signature(s)

P.C. Schalkwijk  
(Holder of Proxy)

P.H. van Deursen  
(Holder of Proxy)

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Le formulaire doit être signé de la propre main du (des) mandant(s) (dans le cas de personnes morales, de la personne ayant qualité pour signer). Veuillez ajouter à la machine, après la signature, le (les) nom(s) du (des) signataire(s) en mentionnant, dans le cas de personnes morales, ses (leurs) fonctions au sein de la société.

SUPPLEMENTARY SHEET

|                        |                                     |
|------------------------|-------------------------------------|
| This sheet is part of: | EPA/EPO/OEB Form 1004. 1 04.92      |
| concerning:            | General Authorisation No. 59 (rev.) |
| signed in the name of: | Akzo Nobel N.V.                     |
| dated:                 | November 22, 2001                   |

Additional representatives:

Address of place of business:

KRAAK, Hajo  
HOGENBIRK, Marijke  
DE WEERD, Petrus Gerardus  
Wilhelmus  
VAN WEZENBEEK, Petrus Maria  
Gerardus Franciscus  
HERMANS, Franciscus G.M.

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VAN GENT, Marieke  
KEUS, Jacobus Albertus Ronald

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## FORMULACIÓN FARMACÉUTICA DE GEPIRONA PARA ADMINISTRACIÓN ORAL

La invención está relacionada con una formulación farmacéutica para administración oral con propiedades de liberación extendida que comprende una cantidad de clorhidrato de gepirona, una cantidad de matriz de polímero celulósico y una cantidad de celulosa microcristalina.

Dichas formulaciones farmacéuticas están descritas en EP 700 680 para ser utilizadas en trastornos del sistema nervioso central como ansiedad, depresión y trastornos de pánico. La gepirona es un fármaco que induce efectos indeseables cuando se alcanzan altos niveles pico. Es deseable alcanzar una distribución pareja de los niveles del fármaco en la sangre a fin de obtener un nivel de dosis terapéutica apropiado. Se informó que el tratamiento óptimo de un trastorno depresivo mayor se obtuvo con dosis diarias de hasta 100 mg de gepirona HCl (Wilcox et al; Psychopharmacology Bulletin). La administración de la cantidad total diaria de gepirona se distribuyó en el curso del día dando 20 mg de gepirona HCl en tabletas de liberación prolongada a intervalos durante el día. Esto se hizo no sólo porque estaba indicado en el estado de la técnica (EP 700 680) que es posible producir de manera fiable presentaciones de liberación prolongada para que tengan propiedades de liberación lenta cuando el contenido de gepirona HCl es de no más de 12% del contenido total, con un contenido máximo preferido de 11% en peso y el contenido de celulosa microcristalina es de no menos de 10%, con un mínimo preferido de 11% en peso, sino también porque es de esperar que las dosis altas dadas una sola vez al día sean mal toleradas incluso cuando se administran en una presentación de liberación prolongada.

Contrario a lo que era dable esperar, se encontró que es posible preparar tabletas de liberación prolongada con dosis más altas, que son apropiadas y bien toleradas en una

forma de dosificación de una sola vez al día en aquellos pacientes que ya están habituados a dosis más bajas.

Está claro que resulta más cómodo para estos pacientes tener a su disposición una presentación de una sola vez al día.

Esta invención representa una formulación farmacéutica conforme al párrafo introductor disponible de manera que la cantidad de la matriz de polímero celulósico farmacéuticamente aceptable corresponda a entre 70 a 85% en peso, la cantidad de carbohidrato fijador es de 7 a 10% en peso y la cantidad de clorhidrato de gepirona es de 13 a 21% en peso. La formulación opcionalmente puede contener otros aditivos farmacéuticamente aceptables, como deslizantes, lubricantes y colorantes.

La invención hace que el tratamiento médico una vez al día con clorhidrato de gepirona esté disponible en una formulación farmacéutica para administración oral que tenga la composición arriba definida. Este tratamiento es útil y bien tolerado por los pacientes que están en tratamiento de depresión o un trastorno relacionado del sistema nervioso central, quienes comienzan un régimen de tratamiento que se inicia con dosis de cerca de 20 mg de gepirona HCl al día y que gradualmente se les aumenta hasta llegar a 60 a 100 mg de gepirona HCL al día.

Una formulación farmacéutica para administración oral suele ser una tableta o una cápsula. Contrario a lo que habría sido el peso de una tableta de 80 mg según EO 700 680, las tabletas de la presente invención pueden tener un peso total de al menos 450 mg. Pese a la elevada cantidad relativa de gepirona HCl en relación con el material de la matriz de polímero celulósico y también en relación con el carbohidrato fijador, las formulaciones

orales, en especial las tabletas, se podrían hacer de todas maneras con propiedades aceptables de gepirona y estabilidad aceptable durante la producción y el manejo.

Una matriz de polímero celulósico farmacéuticamente aceptable tiene la función de retener la gepirona HCl de tal manera que se pueda obtener un efecto de liberación prolongada. Las matrices propicias para este fin incluyen alquilcelulosas hidroxialquilo-sustituídas que tengan una viscosidad de 15000 cps a 100.000 cps. La hidroximetil propilcelulosa (HPMC) de grados K15M y K100M es la preferida y la de grado K100M Premium (Methocel) es la que más se prefiere. Las cantidades de los componentes de la formulación farmacéutica de la invención se expresan como porcentaje en peso (%p) del peso total de la formulación que suele ser una tableta. El término alquilo tal como se usa en el presente documento significa una cadena de átomos de carbono no sustituida saturada ramificada o no ramificada. En vista de las viscosidades requeridas, los grupos alquilo a que se refiere el presente párrafo no comprenden más de 6 átomos de carbono.

El término aditivos farmacéuticamente aceptables o apropiados que pueden ser empleados para realizar la invención hace referencia a los requisitos establecidos para los auxiliares farmacéuticos en general. Estos requisitos con respecto a la seguridad y la no interferencia con el principio activo de las formulaciones farmacéuticas son generalmente conocidas para el técnico versado en la materia. Se puede encontrar una recopilación estándar de vehículos y excipientes farmacéuticamente aceptables en el Handbook of Pharmaceutical Excipients (Wade y P.J. Weller, 2ª edición publicada por la American Pharmaceutical Association), Washington y The Pharmaceutical Press, Londres, 1994). Los aditivos a una formulación farmacéutica, como vehículos, fijadores, deslizantes, lubricantes y colorantes se usan por ejemplo con el fin de obtener cierta cohesión, coloración y fluidez de las tabletas. En una versión preferida de esta invención, se usan estearato de magnesio, bióxido de silicio coloidal y pigmentos de óxido de hierro.

Los deslizantes y lubricantes son agentes que reducen la adhesividad de la mezcla del polvo o las tabletas durante la producción. Los métodos de uso de dichos aditivos son conocidos en el arte de hacer composiciones farmacéuticas como por ejemplo lo describe el capítulo 19 del texto Remington's Pharmaceutical Sciences (18ª edición, AR. Gennaro, Mack Publishing Co.; Easton, Pensilvania).

Los fijadores son agentes que se usan para impartirles propiedades cohesivas a una composición farmacéutica que den lugar a una mínima pérdida de la composición farmacéutica durante la producción y la manipulación. Los carbohidratos fijadores son, por ejemplo, celulosa, metilcelulosa, etilcelulosa, hidroxipropilcelulosa, azúcares, almidones, amilopectina, dextrina, maltodextrina, gomas y alginatos. La celulosa microcristalina, y en particular el Avicel pH 101, es un fijador preferido para usar en esta invención.

El término formulación farmacéutica para administración oral con propiedades de liberación prolongada se emplea en esta descripción para hacer referencia a las características de liberación prolongada de la gepirona conforme a las enseñanzas de EP 700 680. De modo específico, una formulación conforme a la invención tiene una tasa de liberación de gepirona a partir de la formulación tal que se necesitan de 18 a 24 horas para lograr una absorción de entre 90 y 95% de la gepirona.

Las formulaciones farmacéuticas conforme a la presente invención pueden prepararse por medio de métodos conocidos en la técnica; por ejemplo, los descritos en la referencia estándar, Gennaro et al., Remington's Pharmaceutical Sciences (18ª edición, Mack Publishing Co.; 1990, en particular la Parte 8: Pharmaceutical Preparations and Their Manufactura). Es aconsejable tener ciertos cuidados en la manipulación de las formulaciones comprimidas de alta potencia de esta invención con el fin de evitar la ruptura y agrietamiento de las tabletas.

La gepirona se puede preparar mediante cualquier método conocido en la técnica. La preparación más usual es a través de los métodos descritos en la patente estadounidense No. 4.423.049. Las composiciones de liberación prolongada que contienen gepirona se enseñan en EP 700 680. El contenido de estos documentos se incorpora al presente por medio de referencia.

Los siguientes ejemplos sirven para ilustrar cómo llevar a cabo la invención.

Ejemplo 1

Proceso de manufactura de lotes de 160.000 tabletas

Composición de las tabletas (Los números de la tabla corresponden a cantidades en mg)

| Ingredientes                                             | 40 mg | 60 mg | 80 mg | Función                                         |
|----------------------------------------------------------|-------|-------|-------|-------------------------------------------------|
| Gepirona HCl                                             | 40,0  | 60,0  | 80,0  | Principio activo                                |
| Hidroxipropil metilcelulosa<br>(Methocel K100M, Premium) | 290,0 | 290,0 | 290,0 | Polímero que controla la liberación del fármaco |
| Celulosa microcristalina<br>(Avicel pH 101)              | 52,12 | 31,0  | 33,7  | Diluyente                                       |
| Euróxido amarillo o rojo<br>(E7055, E7056 o E7016)       | 0,08  | 1,2   | 3,5   | Colorante                                       |
| Bióxido de sílice coloidal<br>(cab-o-sil M5)             | 1,6   | 1,6   | 1,6   | Deslizante                                      |
| Estearato de magnesio NF                                 | 1,2   | 1,2   | 1,2   | Lubricante                                      |

Premezcla activa:

Transfiera el bióxido de sílice coloidal, NF, colorante (40 mg: Euróxido Amarillo E7056; 60 mg: Euróxido Amarillo E7055; 80 mg: Euróxido Amarillo E7055 y Euróxido Rojo

E7016); gepirona HcL en polvo y 20% de hidroxipropil metilcelulosa USP en el mezclador planetario de 56,6 litros (mezclador Hobart). Mezcle los ingredientes durante 15 minutos en un mezclador planetario (mezclador Hobart). Marque como “Premezcla activa”.

Mezcle.

Molture la premezcla activa en un Fitzmill usando una placa perforada No. 0020 a alta velocidad, impacte hacia delante para desaglomerar los grumos que queden.

Transfiera la premezcla activa a una mezcladora en V de 293,1 litros sin barra en I, mientras que pasa a través de una criba de malla #12 y transfiera el 80% de HPMC pendiente, celulosa microcristalina, NF y 50% de estearato de magnesio, NF al mezclador en V sin barra I. Mezcle los ingredientes en el mezclador en V sin barra I durante 24 minutos y marque “Mezcla para barritas”.

Barritas

Comprima la mezcla para formar barritas usando un labrador (60, 80) de plano biselado (40) borde biselado faz plana redonda 7/8” usando una máquina compresora Kikusui-Hercules.

Controles durante el proceso:

|                 |         |
|-----------------|---------|
| Peso:           | 2250 mg |
| Dureza:         | 7 kp    |
| Grosor deseado: | 0,64 cm |

Mezcla final:

Molture las barritas en un molino SS Fitzmill con alimentador de tornillo usando una placa perforada No. 0093 a velocidad media, con los cuchillos hacia delante y el parámetro del alimentador de tornillo en  $3,5 \pm 0,5$ . Transfiera la masa molida a un mezclador en V de

289.6 litros sin barra en I. Criebe el 50% pendiente del estearato de magnesio, NF a través de una malla #18 y transféralo también al mezclador en V. Mezcle durante 6 minutos.

Comprima las tabletas con una máquina compresora Kikusui-Libra usando troqueles ovoides de 0,859 cm X 1,029 cm.

Controles durante el proceso

|                 |              |               |
|-----------------|--------------|---------------|
| Potencia, mg    | 40 & 60      | 80            |
| Peso fluido, mg | 385 ± 27     | 410 ± 29      |
| Dureza, kp      | 18 ± 4       | 20 ± 8        |
| Espesor, cm     | 0,584 a 0,66 | 0,597 a 0,673 |

Almacene en recipiente hermético hasta el uso o las pruebas posteriores.

Perfil de liberación del fármaco de las tabletas preparadas como se acaba de describir en el ejemplo anterior. Las tabletas adicionales de 20 mg fueron hechas conforme al procedimiento descrito en EP 700 680 para comparación del perfil de liberación del fármaco de las tabletas de 60 y 80 mg conforme a la presente invención, :

**Patrón de liberación de gepirona de las tabletas** (Los números que aparecen en la tabla representan el porcentaje de disolución del contenido teórico de las tabletas).

|                        |        |         |          |          |              |
|------------------------|--------|---------|----------|----------|--------------|
| Liberado después de: → | 1 hora | 5 horas | 12 horas | 20 horas | recuperación |
| Tabletas de 20 mg      | 19     | 49      | 77       | 93       | 102          |
| Tabletas de 40 mg      | 21     | 50      | 77       | 93       | 100          |
| Tabletas de 60 mg      | 21     | 51      | 81       | 97       | 102          |
| Tabletas de 80 mg      | 22     | 52      | 80       | 96       | 101          |

Ejemplo 2

Para escalar hacia arriba la manufactura con el propósito de obtener lotes de 800.000 tabletas se aplicaron ciertas adaptaciones:

Así las cosas, los procedimientos concuerdan con los métodos descritos en el ejemplo 1, pero la premezcla activa es mezclada en una mezcladora AZMF Glen de 321,76 litros durante 28 minutos, el tamaño de la mezcladora en V es de 849,5 litros y la mezcla final se hace durante 7 minutos. Las tabletas tenían propiedades similares a las medidas en el ejemplo 1. Se prestó especial atención al problema de friabilidad de las tabletas de 80 mg. Se prefiere comprimir las tabletas de 80 mg a una velocidad de 20 rotaciones por minuto en la máquina compresora, es decir, en general a una velocidad de menos de 30 rpm como parámetro de la máquina compresora de tabletas con el fin de reducir el número de tabletas que presentan grietas.

### Reivindicaciones

1. Una formulación farmacéutica para administración oral con propiedades de liberación prolongada que comprende una cantidad de clorhidrato de gepirona, una cantidad de matriz de polímero celulósico y una cantidad de celulosa microcristalina caracterizada porque la cantidad de matriz de polímero de celulosa farmacéuticamente aceptable es de 70 a 85% en peso, la cantidad de carbohidrato fijador de es de 7 a 10% en peso y la cantidad de clorhidrato de gepirona es de 13 a 21% en peso.
2. La formulación farmacéutica conforme a la reivindicación 1, caracterizada porque la matriz de polímero celulósico es una hidroximetil propilcelulosa que tiene una viscosidad de 15.000 cps a 100.000 cps.
3. La formulación farmacéutica conforme a la reivindicación 1, caracterizada porque la celulosa microcristalina es Avicel pH 101.
4. Un tratamiento para la depresión o un trastorno relacionado del sistema nervioso central con gepirona administrada en una formulación oral una vez al día para liberación prolongada de la gepirona, caracterizada porque la formulación es conforme a la reivindicación 1.

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 Fecha (AND): 2003-06-04 16:58:28  
 Folios: 50  
 Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC  
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 36,411  
 FECHA : MAYO 26 DE 2003

\*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE       | TIPO PAGO    | BANCO         | CUENTA      | No. PAGO | FECHA PGO  | Vr. PAGO      |
|-------------------|--------------|---------------|-------------|----------|------------|---------------|
| CAVELIER ABOGADOS | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 15534380 | 26/05/2003 | 28,695,000.00 |

\*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. RENTISTICO          | CONCEPTO                            | TOTAL CONCEPTO |
|---------------------------|-------------------------------------|----------------|
| 1 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 400,000.00     |
|                           | TOTAL :                             | \$ 400,000.00  |

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : \_\_\_\_\_

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

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# REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

## PATENTE DE INVENCION

## MODELO DE UTILIDAD

USUARIO

RADICADOR

- Indicación de que se solicita la concesión de una patente.
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.
- Descripción de la invención.
- Dibujos de ser estos pertinentes.
- Comprobante de Pago de las tasas establecidas.

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## DISEÑO INDUSTRIAL

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- Indicación de que se solicita el registro de Diseño Industrial
- Datos de identificación del solicitante o de la persona que presenta la solicitud.
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.
- Comprobante de pago de las tasas establecidas

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## ESQUEMA DE TRAZADO

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- Datos de identificación del solicitante o de la persona que presenta la solicitud.
- Representación gráfica del esquema de trazado
- Comprobante de pago de las tasas establecidas.

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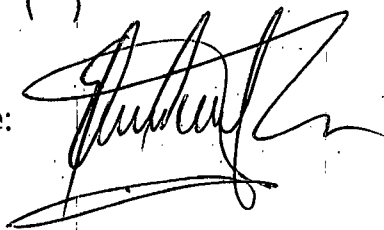
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Firma Responsable:



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Folios: 50

Fecha (AMD): 2003-06-04 16:50:28

Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES