



Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No. **04-44412**

54. TITULO USO DE (11,17B)-11-(1,2-BENZODIOXOL-5-IL)-17-HIDROXI-17-(1-PROPINIL)-
ESTRA-4,9-DIEN-3-ONA EN EL TRATAMIENTO DE DESORDEN DEPRESIVO MAYOR

51. CLASIFICACION INTERNACIONAL A61K31/58 // A61K31/05

71. SOLICITANTE AKZO NOBEL N.V.

DOMICILIO Arnhem, Holanda.

74. APODERADO EMILIO FERRERO

Código No. 1092

22. BOGOTA, D.C., 13/05/2004.

GF
(SS)



Industria y Comercio
SUPERINTENDENCIA

PETITORIO

Radicación : 04044412 00000003
Fecha (MD): 2004-05-13 17:43:15
Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE Solicitud DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 SOLICITANTE (71)	Nombre: AKZO NOBEL N.V. sociedad constituida y existente bajo las leyes de Holanda Dirección: Velperweg 78, 6824 BM Arnhem, Holanda Domicilio: Arnhem, Holanda	IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____	
3 REPRESENTANTE O APODERADO	Nombre: EMILIO FERRERO Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 38 11 Fax: 217 92 11 E-mail: clientes@camyo.com. Domicilio: Bogotá, Colombia.	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 438.019 T.P 31.929	
4 INVENTOR (ES) (72)	1. Cornelle SENNEF N.V. Organon, P.O. Box 20, NL-5340 BH Oss, Holanda	2. Bernardus Wijnand Mathys Marie PEETERS N.V. Organon, P.O. Box 20, NL-5340 BH Oss, Holanda	
5 PCT (86) Solicitud Internacional No. PCT/EP02/11732 Fecha: 21 de Octubre de 2002 Publicación Internacional No. WO 03/037354 A1 Fecha: 8 de Mayo de 2003			
6 Título (54) β USO DE (11,178)-11-(1,3-BENZODIOXOL-5-IL)-17-HIDROXI-17-(1-PROPINIL)-ESTRA-4,9-DIEN-3-ONA EN EL TRATAMIENTO DE DESORDEN DEPRESIVO MAYOR			
7 Clasificación Internacional (51) A61K 31/58 // A61K31/05			
8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	EP	26 de Octubre de 2001	01204072.1
9 Comprobante de pago No.: 04 - 28.815 Fecha: Abril 12 de 2004			

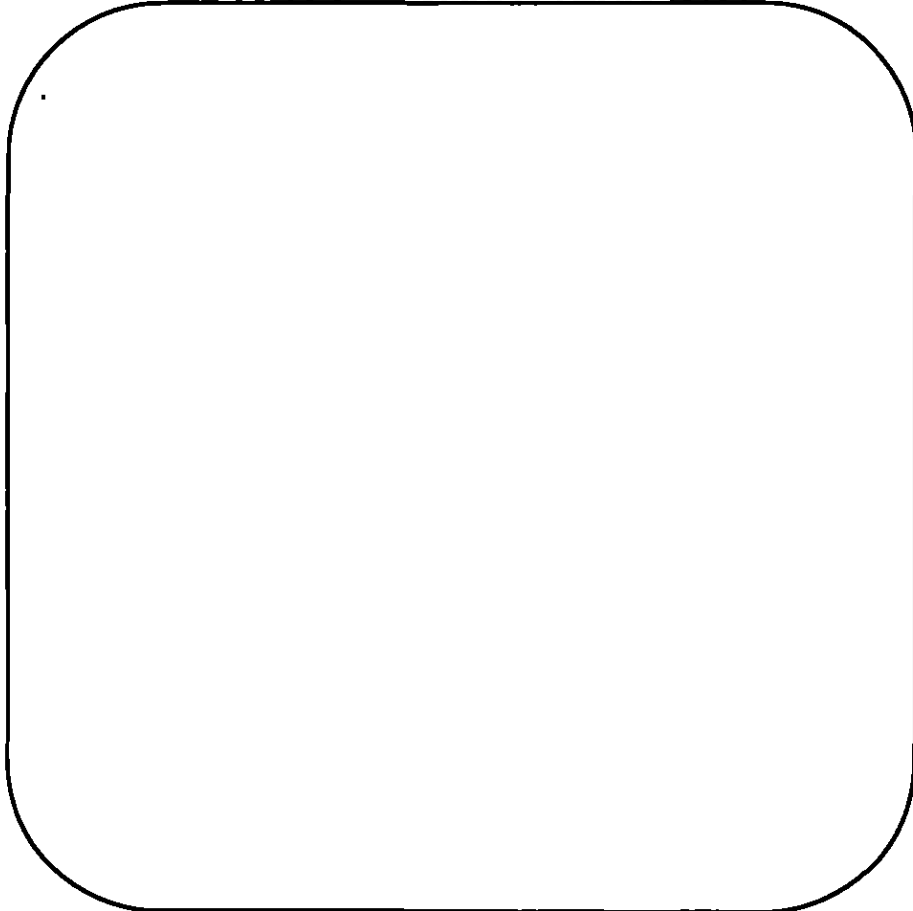
10

An xos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 422.000.00.
- ☐ 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 CARACTERÍSTICA



12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERREROFIRMA: Emilio Ferrero

C.C. 438.019 de Usaquén T.P. 31.929

PRP

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

3

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

REPRESENTACION Y PODER

REPRESENTATION AND
POWER OF ATTORNEY33.16
15.8

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 todos 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 primer o segundo suplente, 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 (nos) 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 (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, especially 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; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court 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 this 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 AffairsCAVELIER ABOGADOS
WPPODERE-179 (MINUTA N° 12.1.1.2.5)TRADUCCION No. 18.11/98
MARIA ELVIRA MAS FLO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2079 Min. Justicia

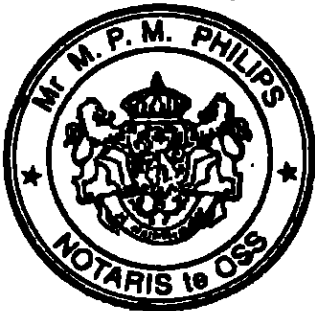
LEGALIZACION

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 las solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a certificate on (1) the legal existence of the company, (2) that it is in accordance with the legal purposes 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.



[Signature]

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

15499



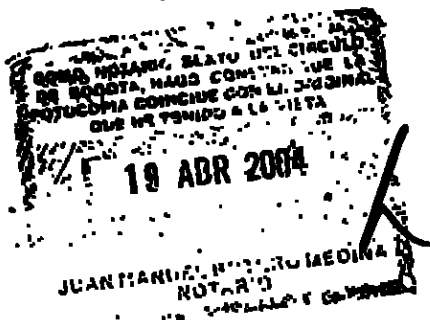
CHAMBER OF COMMERCE AND INDUSTRY
FOR OOST-BRABANT (NEDERLAND)

EXCLUSIVE CHAMBER FOR LEGALIZATION OF
THE SIGNATURE(S)

27 AUG 1998

KAMER VAN KOOPHANDEL
OOST-BRABANT
's-HERTOGENBOSCH

[Signature]
J. Schellekens



Gezien voor legalisatie van de handtekening
van dhr/mw *[Signature]*

'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

0710 112 11-201-001-2

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. 18.11.198
MARIA ELVIRA MARTELO C.
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

19 ABR 2004

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

90 NOV 19 11:56

JEFE DE RELACIONES
SANTO DOMINGO
19 ABR 2004
JUAN PABLO DOMESTICA

MINISTERIO DE RELACIONES
EXTERIORES

300803

ESTA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

5

TRADUCCIÓN FICIAL 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.

(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 25 de agosto de 1998, para legalización de las firmas de F.G.M. Hermans y E.H. Reerink. (Firma ilegible).

SENO NOTARIO PUBLICO DEL CIRCULO
DE OSS, PAISES BAJOS, el 25 de agosto de 1998,
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
19 ABX 2004

(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. 8.11.98
MARIA ELVIRA MARTELO
Traductora e interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

19 ABR 2004

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



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

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

PK①
7

CAVELIER

ABOGADOS
EDIFICIO SISKI
CARRERA 48 Nº 7235
BOGOTÁ, D.C. COLOMBIA

374

2001.673 CO

CESSION

ASSIGNMENT

Yo, (nosotros) abajo firmado (s)

SENNEF, C
Cornells

I (we), the undersigned

PEETERS, B.W.M.M.
Bernardus, Wijnand, Mathys, Marie

domiciliado(s) en

N.V. Organon
Po.Box 20
5340 BH Oss
The Netherlands

of

N.V. Organon
Po.Box 20
5340 BH Oss
The Netherlands

declaro (amos) bajo juramento ser el/los y verdadero(s) inventor(es) de la
invención:

Use of (11B,17B)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one in the
treatment of major depressive disorder

state(s) under oath to be sole and true inventor(s) of the invention:

declaro (amos) así mismo que cada(amos) y transFero(amos), sin
limitación, a favor de la sociedad

- Akzo Nobel N.V.

constituida y existente de conformidad con las leyes de

state as well, that assigns, without reservations or limitations in favour of

Akzo Nobel N.V.

a corporation constituted and existing in conformity with the laws of

domiciliado en

Velperweg 76
6824 BM Arnhem
The Netherlands

Todos los derechos inherentes a dicha invención y que la citada compañía quede
facultada para solicitar en su nombre la patente de invención correspondiente en
la República de Colombia.

domiciled in

Velperweg 76
6824 BM Arnhem
The Netherlands

all rights inherent to said invention and that the above mentioned company hereby
is enabled to apply, in its name, for the corresponding patent invention, in the
Republic of Colombia

Dado y firmado hoy/ Given and signed this

RAVENSTEIN

en/ on

22 MARCH 2004

Firma

Signature

SENNEF, C
Cornells

PEETERS, B.W.M.M.
Bernardus, Wijnand, Mathys, Marie

8

AUTENTICACION NOTARIAL (INDIVIDUAL)

A las _____ días del mes de _____ de
200____ ante mí, Notario Público de _____
compareció(ron) personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s)
firmante(s) del documento que precede, y quien(es) tiene(n) capacidad
legal para otorgarlo.

NOTARIAL AUTHENTICATION (INDIVIDUAL)

On this _____ day of _____, 200____
before me, a Notary Public of _____
personally appeared _____

to me known, and known to me to be the person(s) who executed that
foregoing document, and who has (have) legal capacity to execute it.

Notario Público / Notary Public _____

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country:
This public document
2. has been signed by
3. acting in the capacity of
4. bears the seal/stamp of

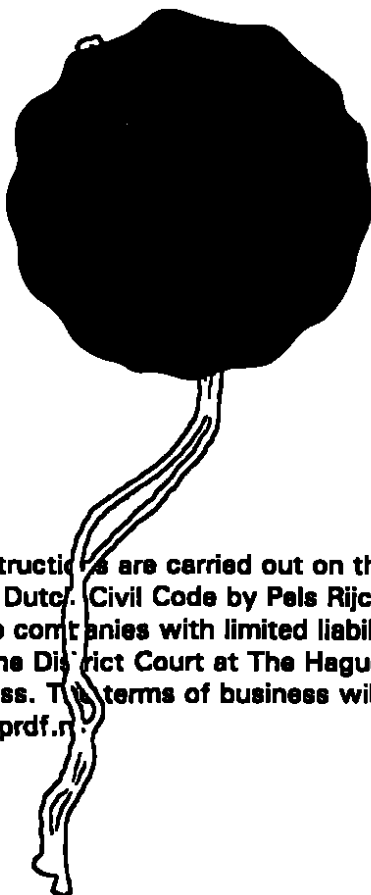
Certified

5. at 6. the
7. by
8. No.
9. Seal/stamp 10. Signature

Seen by me, mr. Robbert Alexander Gallas, civil-law notary practising in The Hague,
for the authentication of the signature on the attached document of:

- Mr Cornelis Sennef, born on the twenty-sixth day of October nineteenhundred
fourty-nine in Veenendaal, The Netherlands, residing at Overlangel, The
Netherlands, holder of a Dutch passport, number N86001963;

The Hague, the thirty-first day of March twothousandfour.



All instructions are carried out on the basis of an agreement as meant in Section 400 of Book 7
of the Dutch Civil Code by Pels Rijcken & Droogleevers Fortuijn, a partnership consisting of
private companies with limited liability. The agreement is subject to terms of business registered
with the District Court at The Hague. A limitation of liability is included in these terms of
business. The terms of business will be provided on request. These can also be accessed at
www.prdf.nl.

D

TRADUCCIÓN OFICIAL No. 20.04/04a realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia, registrado ante el Ministerio de Relaciones Exteriores de Colombia.

Documento de Cesión escrito en inglés y español por medio del cual SENNEF, C., Cornelis y PEETER, B.W.M.M., Bernardus, Wijnand, Mathys, Marie, ambos domiciliados en N.V. Organon, Po. Box 20, 5340 BH Oss, Holanda, declaran bajo juramento ser únicos y verdaderos inventores de la invención:

Uso de (11β-17β)-11-(1,3-benzodioxol-5-il)-17-hidroxi-17-(1-propinil)-estra-4-9-dien-3-ona en el tratamiento del desorden depresivo mayor y declaran así mismo que ceden y transfieren, sin limitación, a favor de la sociedad Akzo Nobel N.V. constituida y existente de conformidad con las leyes de HOLANDA, domiciliada en Velperweg 76, 6824 BM ARNHEM, Holanda, todos los derechos inherentes a dicha invención y que dicha Compañía queda facultada para solicitar a su nombre la patente correspondiente en la República de Colombia.

Dado y firmado en Ravenstein el 22 de marzo de 2004.

SENNEF, C
Cornelis

PEETERS, B.W.M.M.
Bernardus, Wijnand, Mathys, Marie

Firma Ilegible

(Anexo)

Visto por mí, el señor Robbert Alexander Gallas, Notario Público ejerciendo en La Haya, para la autenticación de la firma en el adjunto de:

- El señor Cornelis Sennef, nacido el veintiséis de octubre de mil novecientos cuarenta y nueve en Veenendaal, Holanda,

A P O S T I L L E

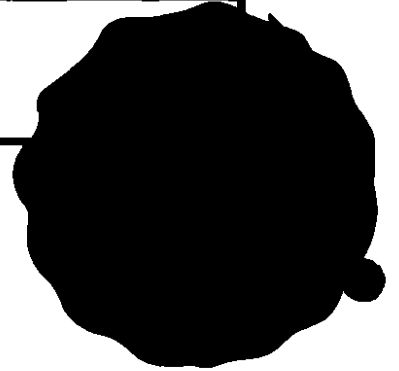
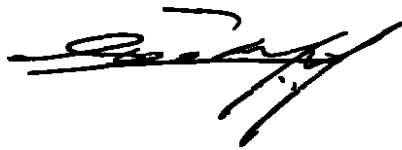
(Convention de La Haye du 5 octobre 1961)

1. Pais: NEDERLAND
El presente documento público
2. ha sido firmado por mr. M.A. Gallas
3. quien actúa en calidad de notario en 's-Gravenhage
4. y está revestido del sello/timbre de el susodicho notario

Certificado

5. en 's-GRAVENHAGE 6. el día 13 april 2004
7. por de Griffier van de Rechtbank
8. bajo el número: 2004-1267
9. Sello/timbre: 10. Firma:

S. Petronilla



/

domiciliado en Overlangel, Holanda, portador del pasaporte
holandés número N86001963;

La Haya, treinta y uno de marzo de dos mil cuatro.

Sello Notarial: Sr. R.A. GALLAS NOTARIS TE 's-GRAVENHAGE

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Todas las instrucciones se realizan basadas en un acuerdo según se establece en la Sección 400 del Libro 7 del Código Civil Holandés por Pels Rijcken & Droogleever Fortuijn, una sociedad conformada por sociedades privadas de responsabilidad limitada. El acuerdo está sujeto a los términos comerciales inscritos en el Tribunal del Distrito en La Haya. Se incluye una limitación de responsabilidad en estos términos comerciales. Los términos comerciales serán suministrados a petición. Estos también pueden ser consultados en www.prd.f.nl.

(RESPALDO)

Apostille en español de Holanda certificada el 13 de abril de 2004 en 's-GRAVENHAGE por de Griffier van de Rechtbank con el número: 2004-1267 y firmado por S. Petronilla.

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

DVZ/ID: 5541/WPCL002G/COLO 11214-841-018-9


DIEGO F. VARGAS
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLÉS - INGLÉS - ESPAÑOL
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SANTAFE DE BOGOTA. 22 ABR 2004

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CESION

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Yo, (nosotros) abajo firmado (s)

SENNEF, C
Cornelis

I (we), the undersigned

PEETERS, B.W.M.M.
Bernardus, Wijnand, Mathys, Marie

domiciliado(a) en

N.V. Organon
Po.Box 20
5340 BH Oss
The Netherlands

of

N.V. Organon
Po.Box 20
5340 BH Oss
The Netherlandsdeclaro(s) bajo juramento ser el/los inventor(es) de la
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state(s) under oath to be sole and true inventor(s) of the invention:

Use of (11B,17B)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one in the
treatment of major depressive disorderdeclaro(s) así mismo que cedo(s) y transfiero(s), sin
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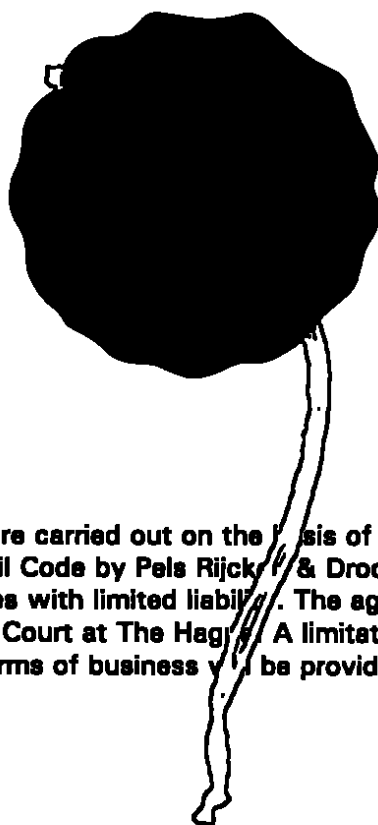
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.....

Seen by me, mr. Robbert Alexander Gallas, civil-law notary practising in The Hague,
for the authentication of the signature on the attached document of:

- Mr Bernardus Wijnand Mathys Marie Peeters, born on the seventh day of June
nineteenhundred sixty-four in Tegelen, The Netherlands, residing at Herpen, The
Netherlands, holder of a Dutch driver licence, number 3127960844; and

The Hague, the thirty-first day of March twothousandfour.



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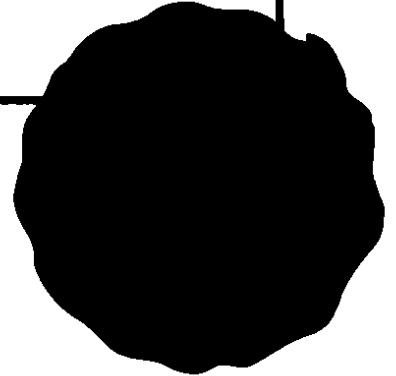
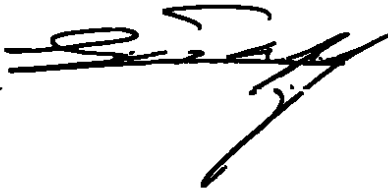
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2. ha sido firmado por **MR. M.A. Gallas**
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Certificado

5. en 's-GRAVENHAGE 6. el día 13 april 2004
7. por de Griffier van de Rechtbank
8. bajo el número: 2004-1267
9. Sello/timbre: 10. Firma:

S. Petronilla



TRADUCCIÓN OFICIAL No. 20.04/04b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia, registrado ante el Ministerio de Relaciones Exteriores de Colombia.

Documento de Cesión escrito en inglés y español por medio del cual SENNEF, C Cornelis y PEETER, B.W.M.M., Bernardus, Wijnand, Mathys, Marie, ambos domiciliados en N.V. Organon, Po. Box 20, 5340 BH Oss, Holanda, declaran bajo juramento ser únicos y verdaderos inventores de la invención:

Uso de (11ß-17ß)-11-(1,3-benzodioxol-5-il)-17-hidroxi-17-(1-propinil)-estra-4-9-dien-3-ona en el tratamiento del desorden depresivo mayor y declaran así mismo que ceden y transfieren, sin limitación, a favor de la sociedad Akzo Nobel N.V. constituida y existente de conformidad con las leyes de HOLANDA, domiciliada en Velperweg 76, 6824 BM ARNHEM, Holanda, todos los derechos inherentes a dicha invención y que dicha Compañía queda facultada para solicitar a su nombre la patente correspondiente en la República de Colombia.

Dado y firmado en Ravenstein el 22 de marzo de 2004.

SENNEF, C
Cornelis

PEETERS, B.W.M.M.
Bernardus, Wijnand, Mathys, Marie

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(Anexo)

Visto por mí, el señor Robbert Alexander Gallas, Notario Público ejerciendo en La Haya, para la autenticación de la firma en el adjunto de:

- El señor Bernardus Wijnand Mathys Marie Peeters, nacido el siete de junio de mil novecientos sesenta y cuatro en Tegelen,

16

Holanda, domiciliado en Herpen, Holanda, portador del pasaporte
holandés número 3127960844; y

La Haya, treinta y uno de marzo de dos mil cuatro.

Sello Notarial: Sr. R.A. GALLAS NOTARIS TE 's-GRAVENHAGE

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DVZ/ID: 5542/WPCL002G/COLO 11214-841-018-9

Diego F. Vargas Z.
DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLÉS - INGLÉS - ESPAÑOL
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 BARRALAS

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(54) Title: USE OF (11 β , 17 β)-11-(1,3-BENZODIOXOL-5-YL)-17-HYDROXY-17-(1-PROPYNYL)-ESTRA-4,9-DIEN-3-ONE
IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

(57) Abstract: The present invention relates to the use of the glucocorticoid receptor antagonist (11 β , 17 β)-11-(1,3-benzodioxol-5-
yl)-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one (Org 34517) for the preparation of a medicament for the treatment of depres-
sion as well as to pharmaceutical preparations of Org 34517 for said use.

18

USE OF (11 β ,17 β)-11-(1,3-BENZODIOXOL-5-YL)-17-HYDROXY-17-(1-PROPYNYL)-
ESTRA-4,9-DIEN-3-ONE IN THE TREATMENT OF MAJOR DEPRESSIVE
DISORDER.

5 The present invention relates to the use of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one (Org 34517) for the preparation of a medicament for the treatment of depression as well as to pharmaceutical preparations of Org 34517 for said use.

10 Major depressive disorder is a psychiatric disorder which has a lifetime prevalence of around 8 %. One of the most consistent findings in psychiatry is that patients with major depression present with alterations in the hypothalamic-pituitary-adrenal (HPA) axis. A significant percentage of depressed patients exhibit hypersecretion of the adrenal glucocorticosteroid cortisol, as manifested by elevated plasma and cerebrospinal fluid
15 concentrations of cortisol and increased urinary free cortisol. In addition many depressed patients exhibit a clear inability to switch off endogenous cortisol release following exogenous challenge with the potent synthetic glucocorticoid dexamethasone (the so-called dexamethasone non-suppressors) (Gold P.W., et al., *Clinical and biochemical manifestations of depression: relation to neurobiology of stress*. New
20 England J. Med. 319, 413-420, 1988). Other abnormalities of the HPA axis found in depressed patients are increased cortisol response to corticotrophin, a blunted corticotrophin response to CRH (corticotrophin releasing hormone), adrenal and pituitary enlargement and diminished glucocorticoid negative feedback (for a review see Holsboer, F. and Barden, N.: *Antidepressants and Hypothalamo-Pituitary-Adrenocortical regulation*. Endocrine Reviews 1996, 17, 187-205). These observations have
25 been interpreted to suggest a causal relationship between disturbed functioning of the HPA axis and the pathology of depression (Murphy, B.E.P.: Steroids and Depression. J. of Steroid Biochem. and Mol. Biol. 1991, 38, 537-559). Therapeutic efficacy of classical antidepressants has been shown to be preceded by or to coincide with
30 restoration of the disturbed HPA axis in depression (Holsboer and Barden, 1996, *supra*). It has been postulated that any intervention which can restore this HPA dysfunction may have antidepressant potential. One type of such intervention is the administration of glucocorticoid synthesis inhibitors; as has been shown in patients suffering from Cushing's syndrome, which is a condition in which high cortisol levels

are reported as a result of adrenal gland malfunction (due to a pituitary tumour or a secondary tumour, both producing the cortisol secretagogue ACTH). The depressive symptoms associated with Cushing's disappear relatively quickly with the return of cortisol levels to normal. Such treatment may involve removal of the offending tumour or treatment with cortisol synthesis inhibitors such as metyrapone, ketoconazole, or aminoglutethimide (Murphy, B.E.P., *Steroids and Depression*, J. Steroid Biochem & Mol. Biol. **38**, 537-558, 1991). Similarly, relatively recent clinical trials have demonstrated that cortisol synthesis inhibitors can be used to ameliorate depressive symptoms in severe, treatment-resistant non-Cushing depressives (Murphy, B.E.P., *Neuroendocrine responses to inhibitors of steroid synthesis in patients with major depression resistant to antidepressant therapy*, Can. J. Psych. **43**, 279-288, 1998; see also US Patent 4,814,333 (Ravaris, C.L.): *Method for treatment of hypercortisolemic, depressed patients*). Drawbacks of the use of cortisol synthesis inhibitors to lower plasma cortisol levels are their high toxicity and their relatively low degree of selectivity for inhibition of cortisol synthesis versus synthesis of other endogenously manufactured steroids (such as mineralocorticoids and sex steroids) combined with the risk for the induction of adrenal insufficiencies. A further serious disadvantage is that the onset of therapeutic effect of these cortisol synthesis inhibitors is as long as that observed with classical antidepressants (e.g., several weeks).

Another type of intervention is the use of direct glucocorticoid receptor (GR) antagonists, which have much more specific pharmacological effects as compared to synthesis inhibitors and which may help restore HPA activity. Small scale pilot clinical studies have been conducted in order to study the antidepressant activity of the non-selective glucocorticoid receptor antagonist RU 486 (mifepristone; 17 β -hydroxy-11 β -(4-dimethylaminophenyl)-17 α -(1-propynyl)estra-4,9-dien-3-one; Murphy, B.E.P. et al. J. Psychiat. Neurosc. **18**, 209-213, 1993). Relatively high doses mifepristone, in the range of 8-12 mg/kg/day, over a relatively short period of time (4 days), was also shown to be effective in the treatment of psychosis associated with psychotic major depression (International Patent Application WO 99/17779; Schatzberg and Belanoff). More recently (Nemerott, C., Remeron Scientific Expert Meeting, Budapest, March 29-April 1, 2001) it was demonstrated in a Phase IIB continuation of this study, that both the number of responders as well as the efficacy of the psychosis treatment increased with increasing daily dose of mifepristone as measured by the change in Brief Psychiatric Rating Scale (50 mg-33% change; 600 mg-40 % change and 1200 mg-52 % change).

These data suggest that a higher dose of glucocorticoid receptor antagonist is correlated with a higher clinical efficacy.

Selective glucocorticoid receptor antagonists, which are structurally related to mifepristone, which lack appreciable affinity for mineralocorticoid, estrogen and androgen receptors, and which have low affinity for the progesterone receptor have been disclosed in European Patent 763 541 B1 (Akzo Nobel N.V.) as being potentially useful in the prevention and treatment of glucocorticoid dependent diseases or symptoms, like Cushing syndrome, diabetes, glaucoma, sleep disturbances, depression, anxiety, atherosclerosis, hypertension, adiposity, osteoporosis and withdrawal symptoms from narcotics.

The antiglucocorticoid activity of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one, a compound specifically disclosed in EP 763 541 B1, and which will be referred to as Org 34517, was found to be dose related as measured by the procedure described by Kloosterboer et al (J. Steroid Biochem 31, 567-571, 1988): the effect (weight gain) of orally applied Org 34517 on body weight, adrenals, thymus and spleen of immature dexamethasone treated male rats proved to increase with the dose (from 10 mg/kg to 40 mg/kg).

Org 34517 was found to be less potent (52%) than mifepristone in *in vitro* binding to the glucocorticoid receptor. The threshold dose for demonstrating *in vivo* (rat) antiglucocorticoid effects was likewise much higher for Org 34517 (20 mg/kg) than for mifepristone (5 mg/kg). In agreement with the relatively lower antiglucocorticoid activity, a clinical study wherein the antiglucocorticoid activity in (healthy) humans was estimated on the basis of the cortisol increase or on the amount of dexamethasone antagonism, upon administration of Org 34517, revealed Org 34517 to have a potency relative to mifepristone of 10-25% and 17%, respectively.

These data would indicate that clinical useful effects during treatment of a glucocorticoid dependent disease should be expected at daily doses of Org 34517 which would be much higher than for the more potent antiglucocorticoid mifepristone.

It has now been unexpectedly found in clinical studies that patients suffering from major depressive disorder should be treated with a daily dosage of Org 34517 which does not exceed 300 mg. Administration of such a relatively low dose of the antiglucocorticoid Org 34517 results in fast onset of antidepressant effect as compared to the onset of antidepressant effect in patients treated with a daily dosage of 450 mg of Org 34517 or more. The preferred daily dosage of Org 34517 ranges between 150 and 300 mg.

An advantage of these low doses is that potential side effects which might result from the residual antiprogesteragenic activity of the compound, and which could lead to interference with the normal female menstrual cycle, are kept to the minimum.

Glucocorticoids are extremely important hormones, which play key roles in the coping mechanisms that animals (including man) have at their disposal against internal and external stressors. Pharmacologically effective dosages of glucocorticoid receptor antagonists, such as Org 34517 and RU 486, will block physiological action of endogenous glucocorticoids and may thereby induce risks when stressors affect the organism. The low dose treatment regimen of the present invention thus warrants minimal increases in susceptibility for the induction of risks.

In a preferred embodiment the invention is concerned with a medicament comprising a daily dosage of Org 34517 which does not exceed 300 mg, for the treatment of patients suffering from a major depressive disorder and who have a plasma cortisol level, as measured by the afternoon cortisol test, which is higher than 10 µg/dl. Such major depressive disorder patients, having a disturbed regulation of the hypothalamus-pituitary-adrenal (HPA) axis, show a short onset of action of the antidepressant effect of Org 34517. The low dosage medicament of the invention is especially effective with regard to the onset of action of the antidepressant effect in patients classified as dexamethasone non-suppressors, i.e. patients which demonstrate non-suppression in the dexamethasone suppression test.

Org 34517, (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one, can be prepared as described in European Patent P 763 541 B1 (Alzo Nobel N.V.), the content of which is hereby entirely incorporated by reference.

In a further aspect the invention relates to a pharmaceutical preparation comprising a daily dosage unit of (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one which does not exceed 300 mg and pharmaceutically acceptable auxiliaries, for the treatment of major depressive disorder.

The pharmaceutical preparations, or compositions, for use according to the invention comprise (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one in admixture with pharmaceutically acceptable auxiliaries. The term "acceptable" means being compatible with the other ingredients of the composition and not deleterious to the recipients thereof. The compositions can be prepared in accordance with standard techniques such as those described in the standard

reference Gennaro A.R. et al., Remington: *The Science and Practice of Pharmacy*, (20th ed., Lippincott Williams & Wilkins, 2000, Part 5: Pharmaceutical Manufacturing). Compositions include e.g. those suitable for oral, sublingual, topical or rectal administration, and the like, all in unit dosage forms for administration.

- 5 For oral administration, which is the preferred route, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, and suspensions.

The invention is illustrated in the following examples:

10 Example 1.

Treatment of major depressive patients with Org 34517

- A double blind, 4 week, paroxetine controlled study of Org 34517 in depressed patients was carried out. Paroxetine is a selective serotonin re-uptake inhibitor which is recognized as an effective antidepressant for major depression. Patients were selected
15 which had a primary depressive disorder fulfilling the diagnostic criteria of a Major Depressive Disorder (MDD) as defined by the DSM-IV for recurrent (296.3) episodes, and who had a severity of depression which resulted in a total score of at least 22 on the HAMD-21 (HAMILton Rating Scale for Depression; see Hamilton, M. "A rating scale for depression." J. Neurol. Neurosurg. Psychiat. 1960, 23, 56-62) scale at baseline.
20 Patient had an episode of depression which had lasted at least 2 weeks before baseline.

- Patients were randomly allocated to one of three treatment groups. Group I patients (Org 150 group: 50 patients) received 2 capsules with 75 mg of Org 34517 and one placebo (total daily dose 150 mg) for the first 2 weeks and 2 capsules with 75 mg Org
25 34517 and 1 capsule with 150 mg (total daily dose 300 mg) the next 2 weeks; Group II patients (Org 450 group: 48 patients) received 3 capsules with 150 mg Org 34517 (total daily dose 450 mg) in the first 2 weeks and 4 capsules of Org 34517 (total daily dose 600 mg) in the next 2 weeks; Group III patients (paroxetine group: 44 patients) received
30 2 capsules with 10 mg paroxetine and one placebo capsule (total daily dose 20 mg) for the first 2 weeks, followed by 2 capsules of 10 mg and one capsule of 20 mg paroxetine (total daily dose 40 mg) in the next 2 weeks. Medication was administered orally in the morning. Efficacy assessment was done on days 4, 7, 10, 14, 21, 28 and 35 by using the 21-item HAMD scale.

Afternoon cortisol plasma levels (ACT=afternoon cortisol test) were measured as described by Halbreich et al (J. Clin. Endocrinol. Metab. 54(6), 1262, 1982).

Results for all the patients are shown in Figure 1. These data demonstrate a faster onset of action of the antidepressant effect for the 150 mg treatment group as compared with paroxetine, measured as an approximate 2 point difference on the Hamilton scale on day 10.

Results for patients who had an afternoon plasma cortisol level at the start of treatment higher than 10 µg/dl are shown in Figure 2. These data again demonstrate a faster onset of action of the antidepressant effect for the 150 mg treatment group as compared with paroxetine, measured as an approximate 4 point difference on the Hamilton scale on day 10.

Results for the patients who were diagnosed at the start of treatment as dexamethason non-suppressors (non-suppression in the dexamethason suppression test) are shown in figure 3. These data demonstrate a pronounced difference in the onset of action of the antidepressant effect for the 150 mg treatment group as compared with the paroxetine treatment group, measured as an approximate 6 point difference on the Hamilton scale on day 10.

Claims.

1. The use of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one for the preparation of a medicament for the treatment of a patient suffering from a major depressive disorder.
- 5 2. The use according to claim 1, wherein the medicament is applied in a daily dosage which does not exceed 300 mg.
3. The use according to claims 1 or 2, wherein the daily dosage ranges between 150
10 and 300 mg.
4. The use according to any one of claims 1-3, wherein the major depressive disorder is characterized by plasma cortisol levels in the patient which are higher than 10 μ g/dl.
- 15 5. The use according to claim 4, wherein the plasma level of cortisol in the patient demonstrates non-suppression in the dexamethason suppression test.
6. A pharmaceutical preparation comprising a daily dosage unit of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one which does not
20 exceed 300 mg and pharmaceutically acceptable auxiliaries, for the treatment of major depressive disorder.
7. The pharmaceutical preparation according to claim 6 wherein the daily dosage unit ranges between 150 and 300 mg.
- 25 8. A method for the treatment of a patient suffering from major depressive disorder by administering to the patient an effective amount of a glucocorticosteroid, said method comprises administration of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one in a daily dosage which does not exceed 300 mg.
- 30 9. The method of claim 8, wherein the daily dosage is between 150 and 300 mg.

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.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference

(if desired) (12 characters maximum)

2001.673 WO

Box No. I TITLE OF INVENTION

"Use of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one in the treatment of major depressive disorder"

Box No. II APPLICANT

Name and address: (Family name followed by given names; 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

6824 BM ARNHEM

The Netherlands

☐ This person is also inventor

Telephone No.

0412-666380

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 for the purposes of:

☐

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 names; 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)

SENNEF, Cornelis

N.V. Organon

P.O. Box 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 for the purposes of:

☐

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 names; for a legal entity, full official designation. The address must include postal code and name of country.)

P.M.G.F. van Wezenbeek

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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 FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

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)

Peeters, Bernardus, Wijnand, Mathys, Marie
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P.O. Box 20
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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 for the purposes of

☐ 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

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)

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:

State (i.e. country) of residence:

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State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of

☐ 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 another continuation sheet.

These data suggest that a higher dose of glucocorticoid receptor antagonist is correlated with a higher clinical efficacy.

Selective glucocorticoid receptor antagonists, which are structurally related to mifepristone, which lack appreciable affinity for mineralocorticoid, estrogen and androgen receptors, and which have low affinity for the progesterone receptor have been disclosed in European Patent 763 541 B1 (Akzo Nobel N.V.) as being potentially useful in the prevention and treatment of glucocorticoid dependent diseases or symptoms, like Cushing syndrome, diabetes, glaucoma, sleep disturbances, depression, anxiety, atherosclerosis, hypertension, adiposity, osteoporosis and withdrawal symptoms from narcotics.

The antiglucocorticoid activity of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propyny)estra-4,9-dien-3-one, a compound specifically disclosed in EP 763 541 B1, and which will be referred to as Org 34517, was found to be dose related as measured by the procedure described by Kloosterboer et al (J. Steroid Biochem 31, 567-571, 1988): the effect (weight gain) of orally applied Org 34517 on body weight, adrenals, thymus and spleen of immature dexamethasone treated male rats proved to increase with the dose (from 10 mg/kg to 40 mg/kg).

Org 34517 was found to be less potent (52%) than mifepristone in *in vitro* binding to the glucocorticoid receptor. The threshold dose for demonstrating *in vivo* (rat) antiglucocorticoid effects was likewise much higher for Org 34517 (20 mg/kg) than for mifepristone (5 mg/kg). In agreement with the relatively lower antiglucocorticoid activity, a clinical study wherein the antiglucocorticoid activity in (healthy) humans was estimated on the basis of the cortisol increase or on the amount of dexamethasone antagonism, upon administration of Org 34517, revealed Org 34517 to have a potency relative to mifepristone of 10-25% and 17%, respectively.

These data would indicate that clinical useful effects during treatment of a glucocorticoid dependent disease should be expected at daily doses of Org 34517 which would be much higher than for the more potent antiglucocorticoid mifepristone.

It has now been unexpectedly found in clinical studies that patients suffering from major depressive disorder should be treated with a daily dosage of Org 34517 which does not exceed 300 mg. Administration of such a relatively low dose of the antiglucocorticoid Org 34517 results in fast onset of antidepressant effect as compared to the onset of antidepressant effect in patients treated with a daily dosage of 450 mg of Org 34517 or more. The preferred daily dosage of Org 34517 ranges between 150 and 300 mg.

reference Gennaro A.R. et al., Remington: *The Science and Practice of Pharmacy*, (20th ed., Lippincott Williams & Wilkins, 2000, Part 5: Pharmaceutical Manufacturing). Compositions include e.g. those suitable for oral, sublingual, topical or rectal administration, and the like, all in unit dosage forms for administration.

- 5 For oral administration, which is the preferred route, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, and suspensions.

The invention is illustrated in the following examples:

10 Example 1.

Treatment of major depressive patients with Org 34517

- A double blind, 4 week, paroxetine controlled study of Org 34517 in depressed patients was carried out. Paroxetine is a selective serotonin re-uptake inhibitor which is recognized as an effective antidepressant for major depression. Patients were selected
15 which had a primary depressive disorder fulfilling the diagnostic criteria of a Major Depressive Disorder (MDD) as defined by the DSM-IV for recurrent (296.3) episodes, and who had a severity of depression which resulted in a total score of at least 22 on the HAMD-21 (HAMILton Rating Scale for Depression; see Hamilton, M. "A rating scale for depression." J. Neurol. Neurosurg. Psychiat. 1960, 23, 56-62) scale at baseline.
20 Patient had an episode of depression which had lasted at least 2 weeks before baseline.

- Patients were randomly allocated to one of three treatment groups. Group I patients (Org 150 group: 50 patients) received 2 capsules with 75 mg of Org 34517 and one placebo (total daily dose 150 mg) for the first 2 weeks and 2 capsules with 75 mg Org
25 34517 and 1 capsule with 150 mg (total daily dose 300 mg) the next 2 weeks; Group II patients (Org 450 group: 46 patients) received 3 capsules with 150 mg Org 34517 (total daily dose 450 mg) in the first 2 weeks and 4 capsules of Org 34517 (total daily dose 600 mg) in the next 2 weeks; Group III patients (paroxetine group: 44 patients) received
30 2 capsules with 10 mg paroxetine and one placebo capsule (total daily dose 20 mg) for the first 2 weeks, followed by 2 capsules of 10 mg and one capsule of 20 mg paroxetine (total daily dose 40 mg) in the next 2 weeks. Medication was administered orally in the morning. Efficacy assessment was done on days 4, 7, 10, 14, 21, 28 and 35 by using the 21-item HAMD scale.

Claims.

1. The use of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one for the preparation of a medicament for the treatment of a patient suffering from a major depressive disorder.
- 5 2. The use according to claim 1, wherein the medicament is applied in a daily dosage which does not exceed 300 mg.
3. The use according to claims 1 or 2, wherein the daily dosage ranges between 150
10 and 300 mg.
4. The use according to any one of claims 1-3, wherein the major depressive disorder is characterized by plasma cortisol levels in the patient which are higher than 10 μ g/dl.
- 15 5. The use according to claim 4, wherein the plasma level of cortisol in the patient demonstrates non-suppression in the dexamethason suppression test.
6. A pharmaceutical preparation comprising a daily dosage unit of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one which does not
20 exceed 300 mg and pharmaceutically acceptable auxiliaries, for the treatment of major depressive disorder.
7. The pharmaceutical preparation according to claim 6 wherein the daily dosage unit ranges between 150 and 300 mg.
- 25 8. A method for the treatment of a patient suffering from major depressive disorder by administering to the patient an effective amount of a glucocorticosteroid, said method comprises administration of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one in a daily dosage which does not exceed 300 mg.
- 30 9. The method of claim 8, wherein the daily dosage is between 150 and 300 mg.

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.

International Filing Date

Name of receiving Office and "PCT International Application"

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

2001.673 WO

Box No. I TITLE OF INVENTION

"Use of (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one in the treatment of major depressive disorder"

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☐ This person is also inventor

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Teleprinter No.

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

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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)

SENNEF, Cornelis

N.V. Organon

P.O. Box 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 for the purposes of: ☐ 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.)

P.M.G.F. van Wazerbeek

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5340 BH Oss

The Netherlands

Telephone No.

0412-666219

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 FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS	
<i>If none of the following sub-boxes is used, this sheet is not to be included in the request.</i>	
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) Peeters, Bernardus, Wijnand, Mathys, Marie N.V. Organon P.O. Box 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 for the purposes of ☐ 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	
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)	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:	State (i.e. country) of residence:
This person is applicant for the purposes of ☐ 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	
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)	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:	State (i.e. country) of residence:
This person is applicant for the purposes of ☐ 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 another continuation sheet.	

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, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
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- ☒ **EP** European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, 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, SK Slovakia, 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, GQ Equatorial 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):

- | | | |
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| ☒ AE United Arab Emirates | ☐ GM Gambia | ☒ NZ New Zealand |
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| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
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| ☒ CR Costa Rica | ☒ LT Lithuania | ☒ TT Trinidad and Tobago |
| ☒ CU Cuba | ☐ LU Luxembourg | ☐ TZ United Republic of Tanzania |
| ☐ CZ Czech Republic | ☒ LV Latvia | ☒ UA Ukraine |
| ☐ DE Germany | ☒ MA Morocco | ☐ UG Uganda |
| ☐ DK Denmark | ☐ MD Republic of Moldova | ☒ US United States of America |
| ☒ DM Dominica | ☒ MG Madagascar | ☐ UZ Uzbekistan |
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| ☐ EE Estonia | ☐ MW Malawi | ☒ ZA South Africa |
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Box No. VI PRIORITY CLAIM		Further priority claims are indicated in the Supplemental Box ☐	
The priority of the following earlier application(s) is hereby claimed:			
Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) EP (designated NL)	26-10-2001	01204072.1	EPO
item (2)			
item (3)			
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):			
☒ 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): 1			
Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) (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): ISA IEPO			
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): EP	Date (day/month/year) 26-10-2001	Number: 01204072.1	
Box No. VIII CHECK LIST			
This international application contains the following number of sheets:		This international application is accompanied by the item(s) marked below:	
1. request	4 sheets	1. ☐ separate signed power of attorney	5. ☒ fee calculation sheet
2. description:	6 sheets	2. ☒ copy of general power of attorney	6. ☐ separate indications concerning deposited microorganisms
3. claims:	1 sheets	3. ☐ statement explaining lack of signature	7. ☐ nucleotide and/or amino acid sequence listing (diskette)
4. abstract:	1 sheets	4. ☐ priority document(s) identified in Box No VI	8. ☒ other (specify): Letter Request Refund copy European Search Report
5. drawings	3 sheets	as item(s)	
6 Sequence listing	0 sheets		
Total :	15 sheets		
Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.			
Box No. IX SIGNATURE OF APPLICANT OR AGENT			
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 request)			
 P.M.G.F. van Wezenbeek			

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1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received ☐ 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. ☐ Transmittal of search copy delayed until search fee is paid

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37

FEE CALCULATION SHEET

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Annex to the Request

International application No.

Applicant's or agent's
file reference 2001.673 WO

Date stamp of the receiving Office

Applicant

Akzo Nobel N.V.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE

EUR 100,=

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
first 30 sheets

15

sheets

EUR 444,=

b₁

EUR 10=

remaining sheets

additional amount

b₂Add amounts entered at b₁ and b₂ and enter total at B.

EUR 444,=

B

Designation Fee

The international application contains 58 designations

number of designation fees
payable (maximum 5)

amount of designation fee

EUR 480,=

D

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(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.)

EUR 924,=

I

4. FEE FOR PRIORITY DOCUMENT

EUR 30,=

P

5. TOTAL FEES PAYABLE

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TOTAL

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18 October 2002

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

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

Schalkwijk, Pieter Cornelis
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Quelle-Fontijn, Monique
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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 Patentrewesens. 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.

☒ Weitere Vertreter sind auf einem gesonderten Blatt angegeben. / Additional representatives indicated on supplementary sheet. Les autres mandataires sont mentionnés sur une feuille supplémentaire.

☒ Untervollmacht kann erteilt werden. / Sub-authorisation may be given. / Le pouvoir pourra être délégué.

☒ Bitte die gelbe Kopie, ergänzt um die Nr. der allgemeinen Vollmacht, an den Vollmachtgeber zurücksenden. Please return the yellow copy, supplemented by the General Authorisation No., to the authoriser. Prière de renvoyer la copie jaune au mandant, munie du n° du pouvoir général.

Ort/Place/Lieu Arnhem, the Netherlands

Datum / Date November 22, 2001

Unterschrift(en) / Signature(s)

P.G. Schalkwijk
(Holder of Proxy)

P.H. van Deursen
(Holder of Proxy)

Das Formular muß von (von den) Vollmachtgeber(n) (bei juristischen Personen vom Unterschriftsberechtigten) eigenhändig unterschrieben sein. Nach der Unterschrift bitte den (die) Namen des (der) Unterzeichneten mit Schreibmaschine wiederholen (bei juristischen Personen die Stellung des Unterschriftsberechtigten innerhalb der Gesellschaft angeben).

The form must bear the personal signature(s) of the authoriser(s). (In the case of legal persons, that of the officer empowered to sign). After the signature, please type the name(s) of the signatory(ies) adding, in the case of legal persons, his (their) position within the company.

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:
concerning:
signed in the name of:
dated:

EPA/EPO/OEB Form 1004. 1 04.92
General Authorisation No. 59 (rev.)
Akzo Nobel N.V.
November 22, 2001

Additional representatives:Address of place of business:

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IPRA/

PCT

CHAPTER II

34

DEMAND

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

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND
------------------------	---------------------------

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 2001.673 WO
International application No. PCT/EP02/11732	International filing date (day/month/year) 21-10-2002	(Earliest) Priority date (day/month/year) 26-10-2001
Title of invention "Use of (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one in the treatment of major depressive disorder"		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) Akzo Nobel N.V. Velperweg 76 6824 BM ARNHEM The Netherlands		Telephone No.: 0412-666380 Facsimile No.: 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 names; for a legal entity, full official designation. The address must include postal code and name of country.) SENNEF, Cornelis N.V. Organon Postbus 20 5340 BH Oss The Netherlands		
State (i.e. country) of nationality: NL		State (i.e. country) of residence: NL
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) PEETERS, Bernardus, Wijnand, Mathys, Marie N.V. Organon Postbus 20 5340 BH Oss The Netherlands		
State (i.e. country) of nationality: NL		State (i.e. country) of residence: NL
☐ 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.)

VAN WEZENBEEK, P.M.G.F.
P.O. Box 20
5340 RH Oss
The Netherlands

Telephone No.:

0412-666219

Facsimile No.:

0412-650592

Teleprinter No.:

☐ Mark this check-box where no agent or common representative before 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 nevered.

(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(4)). (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.)

36

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).



VAN WEZENBEEK, P.M.G.F

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):

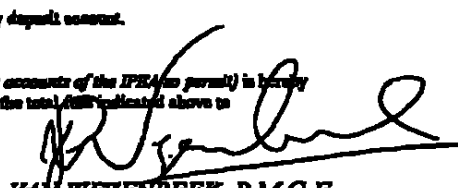
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.☐ The applicant has been informed accordingly.4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 60.5.5. ☐ 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 62.

For International Bureau use only

Demand received from IFPA on:

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/EP02/11732 Applicant's or agent's file reference 2001.673 WO Applicant Akzo Nobel N.V. Calculation of prescribed fees 1. Preliminary examination fee EUR 1530,- P 2. Handling fee (<i>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.</i>) EUR 159,- H 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box..... EUR 1689,- TOTAL	For International Preliminary Examining Authority use only Date stamp of the IPEA								
Modes of Payment <table style="width: 100%;"><tr><td>☒ authorization to charge deposit account with the IPEA (see below)</td><td>☐ cash</td></tr><tr><td>☐ cheque</td><td>☐ revenue stamps</td></tr><tr><td>☐ postal money order</td><td>☐ coupons</td></tr><tr><td>☐ bank draft</td><td>☐ other (specify):</td></tr></table>		☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash								
☐ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								
Deposit Account Authorization (<i>this mode of payment may not be available at all IPEAs</i>) The IPEA / EPO ☒ is hereby authorized to charge the total fees indicated above to my deposit account. ☒ (<i>this check-box may be marked only if the conditions for deposit accounts of the IPEA (see permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.</i>) 2802 0012 Deposit Account Number 26-03-2003 Date (day/month/year)  VAN WEZENBEEK, P.M.G.F Signature									

PATENT COOPERATION TREATY

13 MAR 2003

38

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To: VAN WEZENBEEK, P.M.G. P.O. Box 20 NL-5340 BH Oss NETHERLANDS		Behandeld door CBA
		Adm. expansion AUL
		Bericht d.d.
		Bijlagen d.d.
		Afgegeven
		Date of mailing (day/month/year) 14/03/2003
Applicant's or agent's file reference 2001.673 WO		FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/EP 02/11732		International filing date (day/month/year) 21/10/2002
Applicant AKZO NOBEL N.V.		

- 1.
- ☒
- The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 18:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 48):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

- 2.
- ☐
- The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

- 3.
- ☐
- With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 18 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 18 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3018	Authorized officer Sylvia Hermier
---	---

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 18, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 18 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

70

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 18, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 18 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the POT Applicant's Guide.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2001.673 WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/EP 02/11732	International filing date (day/month/year) 21/10/2002	(Earliest) Priority Date (day/month/year) 26/10/2001
Applicant 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 5 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:

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 02/11732

V3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 17779 A (BELANOFF JOSEPH K ;SCHATZBERG ALAN F (US); UNIV LELAND STANFORD JU) 15 April 1999 (1999-04-15) cited in the application abstract page 2, line 6 - line 22 page 5, paragraph 1 page 9, line 5 - line 29 page 13, line 28 - line 30 page 23, paragraph 1 claims 1-3	1-9
Y	US 4 814 333 A (RAVARIS CHARLES L) 21 March 1989 (1989-03-21) cited in the application column 1, line 52 - line 56 column 2, line 43 - line 52 column 6, line 51 - line 55	1-9
Y	MURPHY B E ET AL: "Possible use of glucocorticoid receptor antagonists in the treatment of major depression: Preliminary results using RU 486" JOURNAL OF PSYCHIATRY AND NEUROSCIENCE, OTTAWA, CA, vol. 18, no. 5, 1 November 1993 (1993-11-01), pages 209-213, XP002091170 ISSN: 1180-4882 abstract page 209, column 1, line 1 -page 210, column 1, line 8	1-9
A	AGARWAL M K, HAINQUE B, MOUSTAID N, LAZER G: "Glucocorticoid antagonists" FEBS LETTERS, vol. 217, no. 2, June 1987 (1987-06), pages 221-226, XP002195329 page 222, column 2, line 11 -page 223, column 1, line 1	1-9
P,X	WO 02 076390 A (BELANOFF JOSEPH K ;CORCEPT THERAPEUTICS INC (US)) 3 October 2002 (2002-10-03) page 6, line 24 - line 27 page 15, line 24 - line 28	1-9
E	WO 02 096433 A (BELANOFF JOSEPH K ;CORCEPT THERAPEUTICS INC (US)) 5 December 2002 (2002-12-05) page 6, line 7 - line 10 page 14, line 6 - line 10	1-9

3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/11732

44

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8 and 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 02/11732 45

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0763541	A	19-03-1997	EP 0763541 A1	19-03-1997
			GR 3031116 T3	31-12-1999
			AT 182596 T	15-08-1999
			AU 711369 B2	14-10-1999
			AU 6211996 A	20-02-1997
			BR 9603429 A	12-05-1998
			CA 2182771 A1	18-02-1997
			CN 1147520 A	16-04-1997
			CZ 9602386 A3	14-05-1997
			DE 69603425 D1	02-09-1999
			DE 69603425 T2	20-01-2000
			DK 763541 T3	28-02-2000
			ES 2137625 T3	16-12-1999
			HK 1002010 A1	07-04-2000
			HU 9602269 A2	28-04-1997
			IL 118974 A	13-09-2001
			JP 9104696 A	22-04-1997
			NO 963427 A	18-02-1997
			NZ 299181 A	22-09-1997
			PL 315733 A1	03-03-1997
			RU 2135514 C1	27-08-1999
			SG 52834 A1	28-09-1998
			TR 970210 A2	21-03-1997
			TW 464654 B	21-11-2001
			US 6011025 A	04-01-2000
WO 9917779	A	15-04-1999	AU 747956 B2	30-05-2002
			AU 9683298 A	27-04-1999
			CA 2302586 A1	15-04-1999
			CN 1272788 T	08-11-2000
			EP 1023074 A1	02-08-2000
			JP 2001518509 T	16-10-2001
			NO 20001744 A	05-04-2000
			NZ 503250 A	28-09-2001
			WO 9917779 A1	15-04-1999
			US 6150349 A	21-11-2000
			US 6362173 B1	26-03-2002
US 4814333	A	21-03-1989	AU 3198589 A	06-09-1989
			WO 8907442 A1	24-08-1989
WO 02076390	A	03-10-2002	WO 02076390 A2	03-10-2002
			US 2002169152 A1	14-11-2002
WO 02096433	A	05-12-2002	WO 02096433 A1	05-12-2002

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/11732

46

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/58

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, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 763 541 A (AKZO NOBEL NV) 19 March 1997 (1997-03-19) cited in the application page 2, line 48 - line 51 page 3, line 2 - line 3 page 3, line 55 - line 56 examples 1,11,12 claims 6,8,10	1-9
Y	the whole document — -/-	1-9

☒ 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 claim or other special reason (see 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.
- "&" document member of the same patent family

Date of the actual completion of the international search

10 March 2003

Date of mailing of the international search report

14/03/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-8018

Authorized officer

Langer, O

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/11732

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT -

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 17779 A (BELANOFF JOSEPH K ;SCHATZBERG ALAN F (US); UNIV LELAND STANFORD JU) 15 April 1999 (1999-04-15) cited in the application abstract page 2, line 6 - line 22 page 5, paragraph 1 page 9, line 5 - line 29 page 13, line 28 - line 30 page 23, paragraph 1 claims 1-3	1-9
Y	US 4 814 333 A (RAVARIS CHARLES L) 21 March 1989 (1989-03-21) cited in the application column 1, line 52 - line 56 column 2, line 43 - line 52 column 6, line 51 - line 55	1-9
Y	MURPHY B E ET AL: "Possible use of glucocorticoid receptor antagonists in the treatment of major depression: Preliminary results using RU 486" JOURNAL OF PSYCHIATRY AND NEUROSCIENCE, OTTAWA, CA, vol. 18, no. 5, 1 November 1993 (1993-11-01), pages 209-213, XP002091170 ISSN: 1180-4882 abstract page 209, column 1, line 1 -page 210, column 1, line 8	1-9
A	AGARWAL M K, HAINQUE B, MOUSTAID N, LAZER G: "Glucocorticoid antagonists" FEBS LETTERS, vol. 217, no. 2, June 1987 (1987-06), pages 221-226, XP002195329 page 222, column 2, line 11 -page 223, column 1, line 1	1-9
P,X	WO 02 076390 A (BELANOFF JOSEPH K ;CORCEPT THERAPEUTICS INC (US)) 3 October 2002 (2002-10-03) page 6, line 24 - line 27 page 15, line 24 - line 28	1-9
E	WO 02 096433 A (BELANOFF JOSEPH K ;CORCEPT THERAPEUTICS INC (US)) 5 December 2002 (2002-12-05) page 6, line 7 - line 10 page 14, line 6 - line 10	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/11732 47**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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8 and 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 02/11732

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0763541	A	19-03-1997	EP 0763541 A1	19-03-1997
			GR 3031116 T3	31-12-1999
			AT 182596 T	15-08-1999
			AU 711369 B2	14-10-1999
			AU 6211996 A	20-02-1997
			BR 9603429 A	12-05-1998
			CA 2182771 A1	18-02-1997
			CN 1147520 A	16-04-1997
			CZ 9602386 A3	14-05-1997
			DE 69603425 D1	02-09-1999
			DE 69603425 T2	20-01-2000
			DK 763541 T3	28-02-2000
			ES 2137625 T3	16-12-1999
			HK 1002010 A1	07-04-2000
			HU 9602269 A2	28-04-1997
			IL 118974 A	13-09-2001
			JP 9104696 A	22-04-1997
			NO 963427 A	18-02-1997
			NZ 299181 A	22-09-1997
			PL 315733 A1	03-03-1997
			RU 2135514 C1	27-08-1999
			SG 52834 A1	28-09-1998
			TR 970210 A2	21-03-1997
			TW 464654 B	21-11-2001
			US 6011025 A	04-01-2000
WO 9917779	A	15-04-1999	AU 747956 B2	30-05-2002
			AU 9683298 A	27-04-1999
			CA 2302586 A1	15-04-1999
			CN 1272788 T	08-11-2000
			EP 1023074 A1	02-08-2000
			JP 2001518509 T	16-10-2001
			NO 20001744 A	05-04-2000
			NZ 503250 A	28-09-2001
			WO 9917779 A1	15-04-1999
			US 6150349 A	21-11-2000
			US 6362173 B1	26-03-2002
US 4814333	A	21-03-1989	AU 3198589 A	06-09-1989
			WO 8907442 A1	24-08-1989
WO 02076390	A	03-10-2002	WO 02076390 A2	03-10-2002
			US 2002169152 A1	14-11-2002
WO 02096433	A	05-12-2002	WO 02096433 A1	05-12-2002

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VAN WEZENBEEK, P.M.G.F.
P.O. Box 20
NL-5340 BH Oss
PAYS-BAS

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

22 DEC 2003	
Behandeld door	CBR
Adm. opgenomen	✓
Besicht d.d. aan:	18
Bescher. d.d.	
Afgegeven	[Signature]

Date of mailing
(day/month/year)

19.12.2003

Applicant's or agent's file reference
2001.673 WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP02/1732

International filing date (day/month/year)
21.10.2002

Priority date (day/month/year)
26.10.2001

Applicant
AKZO NOBEL N.V.

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

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

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

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

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

Name and mailing address of the international
preliminary examining authority:



European Patent Office - P.B. 6818 Patentaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tlx 31 651 epo nl
Fax +31 70 340 - 3016

Authorized Officer

Janzing, M

Tel. +31 70 340-4140



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2001.673 WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP02/11732	International filing date (day/month/year) 21.10.2002	Priority date (day/month/year) 26.10.2001	
International Patent Classification (IPC) or both national classification and IPC A61K31/58			
Applicant AKZO NOBEL N.V.			
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 9 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.			
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application			
Date of submission of the demand 27.03.2003		Date of completion of this report 19.12.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tlx 31 851 epo nl Fax +31 70 340 - 3018		Authorized Officer Langer, O Telephone No. +31 70 340-1972 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP02/1732**

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

1-6 as originally filed

Claims, Numbers

1-9 as originally filed

Drawings, Sheets

1/3-3/3 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:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP02/11732

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)).

(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. 8,9

because:

☒ the said international application, or the said claims Nos. 8,9 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	7
	No: Claims	1-6,8,9
inventive step (IS)	Yes: Claims	7
	No: Claims	1-6,8,9
Industrial applicability (IA)	Yes: Claims	1-7
	No: Claims	

2. Citations and explanations

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No. PCT/EP02/11732

see separate sheet

53

Re Item III

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

Claims 8 and 9 relate 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 Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: EP-A-0 783 541 (AKZO NOBEL NV) 19 March 1997 (1997-03-19) cited in the application
- D2: MURPHY B E ET AL: 'Possible use of glucocorticoid receptor antagonists in the treatment of major depression: Preliminary results using RU 486' JOURNAL OF PSYCHIATRY AND NEUROSCIENCE, OTTAWA, CA, vol. 18, no. 5, 1 November 1993 (1993-11-01), pages 209-213, XP002091170 ISSN: 1180-4882

V.1. Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 8 and 9 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.

V.2. Novelty (Article 33(2) PCT)

The subject-matter of claims 1-6, 8 and 9 is not new in the sense of Article 33(2) PCT in view of the disclosure of document D1:

Document D1

discloses the synthesis of Org 34517 and its use for the treatment or prevention of glucocorticoid-dependent diseases, e. g. depression (page 2, lines 48-51, page 3, lines 2-3, examples 1, 11 and claims 6, 8, 10). A pharmaceutical composition comprising Org 34517 and its use are claimed, too (claims 8 and 10 of D1).

V.2(i) In the second Written Opinion, an objection on lack of novelty with respect to the disclosure of document D1 for the above claims was made, and it was further pointed out that novelty cannot be conferred to the subject-matter of these claims by selection of a group of patients having an increased plasma cortisol level, as in present claims 4 and 5, because this group of patients overlaps with the group of patients in the prior art, in particular D1.

V.2(ii) The applicant replied that such conclusion cannot be drawn by mere assumption.

V.2(iii) However, the above conclusion has not been drawn by assumption but by common knowledge and by documentary evidence in the prior art, which will be further commented on in the following text:

It is generally accepted in psychiatry that a high percentage of depressed patients show elevated concentrations of cortisol in plasma and cerebrospinal fluid. This fact is acknowledged as well-known in the description of the present application, as well (see eg page 1, lines 10-15).

Moreover, document D1 discloses that compounds according to formula (I), including Org 34517 as the most preferred compound (page 3, lines 2-3), can be used "in the prevention and treatment of glucocorticoid diseases or symptoms, like Cushing syndrome, (...) depression" (page 2, lines 48-51). Cushing syndrome, however, is a condition with high cortisol levels associated with depressive symptoms, which is - again - acknowledged as being common knowledge in the description of the present application and not part of the invention (page 1, line 34 to page 2, line 4).

V.2(iv) Consequently, the selection of patients suffering from depression and showing an increased plasma cortisol level is overlapping with the group of patients in the prior art (D1), as already objected on in the second Written Opinion.

V.2(v) Even though the present application provides experimental data comparing effectivity and speed of onset of action between "all patients" (Figure 1), patients with an afternoon plasma cortisol level higher than 10 µg/dl ("ACT-high patients", Figure 2) and dexamethason non-suppressor patients ("DST-non suppressors", Figure 3), no non-overlapping selection of a group of patients with respect to the prior art has been made. Furthermore, the faster onset of action does not seem to bear any significant relation to the cortisol level in the patient. Rather, the concentrations tested seem to be responsible for different speeds of onset of action at different concentrations tested. Selecting a high-cortisol population in claims 4 and 5 therefore seems arbitrary.

V.2(vi) Consequently, the subject-matter of the above claims 1-6, 8 and 9 cannot be considered novel over the prior art.

V.2(vii) The applicant made reference to several decisions of the Enlarged Board of Appeal and the Boards of Appeal of the European Patent Office (G1/83, T0051/93, T0893/90, and T19/86), which will be commented on in a purely illustrative manner, in spite of the fact that these decisions are not relevant to an International Preliminary Examination procedure under the PCT, especially since the PCT does not provide for the so-called "second medical use claim":

V.2(vii)(a) In G1/83 the Enlarged Board of Appeal decided that claims directed to the use are not admissible for the "use of a substance or composition for the treatment of the human or animal body by therapy", but that claims directed to the "use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application" are admissible.

V.2(vii)(b) Requirements for novelty of a therapeutic application have been exemplified in T0893/90 and T0019/86: In both cases it has been decided that a non-overlapping (with respect to the prior art) selection of patients (hemophilic animals vs. non-hemophilic animals, and sero-negative pigs vs. sero-positive pigs, respectively) may fulfil the requirements of a new second medical use within the principle set out in Decision Gr 05/83 (OJ EPO 1985, 64) and may therefore be patentable if such new is inventive.

V.2(vii)(c) Decision T0051/93 relates to the mode of administration of human chorionic gonadotrophin and is of little relevance for the present legal aspect.

V.2(viii) The experimental data in the present application show a quicker onset of action of ORG 34517 when administered at a low dose of 150 mg when compared with 450 mg/day (Figure 1). Such a quicker onset of action is a new technical feature which could confer novelty to an appropriately drafted claim.

Present claim 7 in combination with claim 6, specifying a dosage unit ranging from 150-300 mg ORG 34517, could have formed the basis for an amendment of the second medical use claims.

V.2(ix) For the reasons stated above, a claim relating to the use of ORG 34517 for the preparation of a medicament for the treatment of a patient suffering from a major depressive disorder, the medicament containing a dosage unit of ORG 34517 ranging from 150 mg to 300 mg, could have been considered novel in the sense of a selection invention.

V.2(x) In claim 6, however, no lower limit for the dosage unit of ORG 34517 is specified. Therefore, the subject-matter of claim 6 cannot be recognised as a selection of a sufficiently narrow range from the dosage range disclosed in the prior art (D1).

V.3 Inventive step (Article 33(3) PCT)

V.3(i) For the objections due to lack of inventive step for the subject-matter of claims 1-6, 8 and 9 see the respective passages in the second Written Opinion.

V.3(ii) In the present application, the use of ORG 34517 at a low dosage of 150 mg appears to have unexpected beneficial effects (rapid onset of action) in the treatment of a major depressive disorder. The second medical use of ORG 34517 at a low dosage could therefore be considered as a purposive selection providing an unexpected beneficial effect and thus conferring novelty to such a restricted use. The dosage of 150 mg can be considered as being sufficiently remote from D1 which discloses a large range for the dosage of ORG 34517 from 0.07 to 7000 mg, preferably 0.7-700 mg and a dose of 1400 mg ORG 34517 in example 12 (all doses assuming a patient's body weight of 70 kg).

V.3(iii) Consequently, the presence of an inventive step for a claim according to point V.2.(x) could have been acknowledged in the sense of a selection invention showing an unexpected and beneficial technical effect.

V.3(iv) However, in claim 6 no lower limit for the dosage unit of ORG 34517 is specified. Therefore, the subject-matter of claim 6 cannot be recognised as a selection of a sufficiently narrow range from the dosage range disclosed in the prior art (D1), see also point V.2.(x).

V.3(v) It is not likely, in view of the present application, that very low dosage values (of e.g. 0,00005 mg/unit), which fall within the claimed range of "not exceeding 300 mg", solve the problem posed by the invention. Such embodiments of claim 6, and thus claim 6 in its entirety, therefore lack an inventive step.

Traducción

TRATADO DE COOPERACIÓN DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 del PCT)

Referencia del expediente del agente o solicitante 2001.823 WO	PARA ACTUACIONES ADICIONALES	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA416)
Solicitud internacional No. PCT/EP02/11732	Fecha de presentación internacional (día/mes/año) 21.10.2002	Fecha de prioridad (día/mes/año) 28.10.2001
Clasificación internacional de Patentes (IPC) o clasificación nacional e IPC A61K 31/58		
Solicitante AKZO NOBEL N.V.		

1. Este informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.

2. Este INFORME consta de una total de 9 hojas, incluyendo la portada

☐ Este informe también se acompaña de ANEXOS, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT)

Estos anexos constan de un total de _____ hojas.

3. Este Informe contiene indicaciones relativas a los siguientes aspectos:

I ☒ Fundamentos del Informe

II ☐ Prioridad

III ☒ No se establece concepto relativo a la novedad, nivel inventivo y aplicación industrial

IV ☐ Carencia de unidad de la invención

V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración

VI ☐ Ciertos documentos citados

VII ☐ Ciertos defectos de la solicitud internacional

VIII ☐ Ciertas observaciones respecto a la solicitud internacional

Fecha de presentación de la demanda 27.03.2003	Fecha de terminación de este reporte 19.12.2003
Nombre y dirección de correo de la autoridad encargada del examen preliminar  Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tlx 523856 epmu d Fax +49 89 2399 - 4465	Funcionario Autorizado Langer, O Teléfono No. +31 70 340-1872

59

I. Base del informe

1. Respecto a los elementos de la solicitud internacional:*

La descripción, páginas
1-8, como se presentaron originalmente

Las reivindicaciones, número
1-9, como se presentaron originalmente

Los dibujos, páginas
1/3 – 3/3, como se presentaron originalmente

2. Respecto al lenguaje, todos los elementos marcados anteriormente estuvieron disponibles o fueron enviados a la Administración en el lenguaje en que se presentó la solicitud internacional, a menos que se indique otra cosa en este punto.

Estos elementos estuvieron disponibles o fueron enviados a esta Administración en el siguiente lenguaje _____ el cual es:

- ☐ el lenguaje de la traducción enviada para propósitos de la búsqueda internacional (bajo Regla 23.1 (b)).
- ☐ el lenguaje de la publicación de la solicitud internacional (bajo Regla 48.3(b)).
- ☐ el lenguaje de la traducción entregada con propósitos del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Respecto a cualquier secuencia de nucleótido y/o amino ácidos divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:

- ☐ contenido en la solicitud internacional en forma escrita
- ☐ presentado junto con la solicitud internacional en forma legible por computador
- ☐ entregado posteriormente a esta Administración en forma legible por computador
- ☐ La declaración de que el listado de secuencias posteriormente entregado no va más allá de lo divulgado en la solicitud internacional originalmente presentada, ha sido entregada.
- ☐ La declaración de que la información grabada en la forma legible por computador es idéntica al listado de secuencias escrito que se ha entregado.

4. ☐ Las modificaciones han dado como resultado la cancelación de:

- ☐ la descripción, páginas _____,
- ☐ las reivindicaciones, Nos. _____,
- ☐ los dibujos, página _____.

5. ☐ Este reporte ha sido establecido como si (parte de) las modificaciones no se hubieran realizado, ya que éstas han sido consideradas como una ampliación de lo inicialmente divulgado como se indica en la Casilla Suplementaria (Regla 70.2(c)).**

** Las hojas de reemplazo que han sido entregadas a la Oficina receptora en respuesta a la invitación bajo el Artículo 14 se refieren en este informe como "originalmente presentadas" y no se anexan a este informe ya que ellas no contienen modificaciones (Regla 70.16 y 70.17).*

*** Cualquier hoja de reemplazo que contenga dichas modificaciones deberá ser referida bajo el punto 1 y anexada a este informe.*

III. No establecimiento de opinión con respecto a la novedad, nivel inventivo y aplicabilidad Industrial.

1. La pregunta de si la invención reivindicada parece tener novedad, nivel inventivo (que no sea obvia), o que sea aplicable industrialmente no ha sido examinada con respecto a:

- ☐ la solicitud internacional completa
☒ las reivindicaciones Nos. 8, 9

Porque

- ☒ la solicitud internacional, o las mencionadas reivindicaciones Nos. 8, 9 se relacionan con los siguientes objetos, los cuales no requieren examen preliminar internacional (*especifique*):K

Ver hoja separada

- ☐ la descripción, las reivindicaciones o los dibujos (*indique los elementos particulares abajo*) o las mencionadas reivindicaciones Nos. _____ son demasiado confusas que no se puede formar ninguna opinión significativa (*especifique*):
- ☐ la descripción, o las mencionadas reivindicaciones Nos. _____ no están adecuadamente soportadas por la descripción que no se puede formar ninguna opinión significativa.
- ☐ no se ha establecido un reporte de búsqueda para las mencionadas reivindicaciones Nos. _____

2. No se pudo realizar un examen preliminar internacional significativo debido a fallas en el listado de nucleótidos y/o aminoácidos para dar cumplimiento con los estándares del Anexo C de las Instrucciones Administrativas:

- ☐ El formato escrito no ha sido suministrado o no cumple con los estándares.
- ☐ El formato de lectura por computador no ha sido suministrado o no cumple con los estándares.

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación Industrial; citas y explicaciones que apoyan esta declaración.

1. Declaración

Novedad (N)	Reivindicaciones	<u>7</u>	SI
	Reivindicaciones	<u>1-6, 8, 9</u>	NO
Nivel inventivo (NI)	Reivindicaciones	<u>7</u>	SI
	Reivindicaciones	<u>1-6, 8, 9</u>	NO
Aplicación Industrial (AI)	Reivindicaciones	<u>1-7</u>	SI
	Reivindicaciones		NO

2. Citas y explicaciones (Regla 70.7)

Ver Hoja separada

Continuación Ítem III

No-establecimiento de opinión con respecto a la novedad, nivel inventivo y aplicabilidad industrial.

Esta autoridad considera que el objeto de las reivindicaciones 8 y 9 se encuentran cubiertas dentro de lo provisto por la Regla 67.1 (iv) PCT. Consecuentemente, no se formulará una opinión al respecto de la aplicabilidad industrial del objeto de estas reivindicaciones (Artículo 34(4)(a)(i)PCT).

Continuación Ítem V

Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones que apoyan esta declaración.

Se hace referencia a los siguientes documentos:

- D1: EP-A-0 763 541 (AKZO NOVEL NV) 19 de Marzo de 1997 (1997-03-19) citado en la solicitud.
- D2: MURPHY B ET AL: "Posible use of glucocorticoid receptor antagonists in the treatment of major depression: Preliminary results using RU 486" JOURNAL OF PSYCHIATRY AND NEUROSCIENCE, OTTAWA, CA, vol. 18, no. 5, 1 de Noviembre de 1993 (1993-11-01), páginas 209-213, XP002091170 ISSN:1180-4882.

V.1 Aplicabilidad Industrial (Artículo 33(4) PCT)

Para establecer si las reivindicaciones 8 y 9 son industrialmente aplicables, no existe un criterio unificado entre los países contratantes del PCT. La patentabilidad puede también depender de la redacción de las reivindicaciones. La EPO, por ejemplo, no reconoce como industrialmente aplicable el objeto de reivindicaciones que se refieren al uso de un compuesto en un tratamiento médico, pero puede permitir, sin embargo, reivindicaciones de un compuesto conocido para su primer uso en un tratamiento médico y el uso de dicho compuesto en la manufactura de un medicamento para un nuevo tratamiento médico.

V.2 Novedad (Artículo 33(2) PCT)

El objeto de las reivindicaciones 1-6, 8 y 9 no es novedoso de acuerdo con el Artículo 33(2) del PCT en relación con lo divulgado por el documento D1:

Documento D1

Divulga la síntesis de Org 34517 y su uso para el tratamiento o prevención de enfermedades dependientes de glucocorticoides, por ejemplo depresión (página 2, líneas 48-51, página 3, líneas 2-3, ejemplos 1, 11 y reivindicaciones 6, 8, 10). También se reivindica una composición farmacéutica que comprende Org 34517 y su uso (Reivindicaciones 8 y 10 de D1).

V.2(i) En la segunda Opinión Escrita, se hizo una objeción con respecto a la falta de novedad sobre la base de lo divulgado por D1 para las reivindicaciones arriba mencionadas, y se mencionó mas adelante que no se le puede otorgar la novedad al objeto de dichas reivindicaciones por la selección de un grupo de pacientes que tienen un aumento en los niveles en plasma de cortisol, como en las presentes reivindicaciones 4 y 5, debido a que este grupo de pacientes se superpone con el grupo de pacientes del arte previo, en particular con D1.

V.2(ii) El solicitante respondió que no puede llegarse a esta conclusión por mera suposición.

V.2(iii) Sin embargo, la conclusión de arriba no ha sido obtenida por suposiciones sino por los conocimientos del común y por la evidencia documental del arte previo, el cual será comentado en el siguiente texto:

Se acepta generalmente en psiquiatría que un alto porcentaje de pacientes con depresión muestran concentraciones elevadas de cortisol en plasma y el fluido cerebro espinal. Este hecho también es reconocido como del conocimiento común por la presente solicitud (Ver por ejemplo página 1, líneas 10-15).

Además, el documento D1 divulga que los compuestos de acuerdo con la fórmula (I), incluyendo el Org 34517 como el compuesto más preferido (pág 3, líneas 2-3), puede ser utilizado "en la prevención del tratamiento de enfermedades de glucocorticoides o sus síntomas, como el síndrome de Cushing, (...)depresión" (página 2, líneas 48-51). El síndrome de Cushing, sin embargo, es una condición con altos niveles de cortisol asociada con síntomas depresivos, la cual es, de nuevo, reconocida como del conocimiento común en la descripción de la presente solicitud y no parte de la invención (página 1, línea 34 a página 2, línea 4).

V.2(iv) En consecuencia, la selección de pacientes que sufren de depresión y sufren de niveles altos de cortisol se sobrepone con el grupo de pacientes del arte previo (D1), como ya se había objetado en la segunda Opinión Escrita.

V.2(v) A pesar de que la presente solicitud provee datos experimentales que comparan la efectividad y la velocidad del inicio de la actividad entre "todos los pacientes" (Figura 1), pacientes con niveles de cortisol mayores a 10µg/dL en la tarde ("Pacientes con ACT-elevado", Figura 2) y pacientes no suprimidos con dexametasona ("DST-no suprimidos", Figura 3), no se ha realizado una selección de un grupo de pacientes que no se superponga con respecto al arte previo. Adicionalmente, el alcanzar la actividad mas rápidamente con respecto al arte previo no parece guardar una relación significativa con los niveles de cortisol en los pacientes. En su lugar, las concentraciones ensayadas parecen ser responsables de las diferentes velocidades del inicio de la actividad con las diferentes concentraciones ensayadas. Seleccionar una población con altos niveles de cortisol en las reivindicaciones 4 y 5 parece entonces ser arbitraria.

V.2(vi) Consecuentemente, el objeto de las reivindicaciones 1-6, 8 y 9 arriba mencionadas no pueden ser consideradas novedosas sobre el arte previo.

V.2(vii) El solicitante hace referencia a varias decisiones del Tribunal Superior de Apelaciones y la Corte de Apelación de la Oficina Europea de Patentes (G1/83, T0051/93, T0893/90 y T19/86), la cual será comentada solamente a manera ilustrativa, a pesar que estas decisiones no son relevantes en el procedimiento del Examen Preliminar

Internacional de acuerdo con el PCT, especialmente debido a que el PCT no provee la llamada "reivindicación del segundo uso médico":

V.2(vii)(a) En G1/83 el Tribunal Superior de Apelaciones decidió que las reivindicaciones dirigidas al uso no son admisibles para el "uso de una sustancia o composición para el tratamiento del cuerpo humano o animal como terapia", pero que las reivindicaciones dirigidas al "uso de una sustancia o composición para la manufactura de un medicamento para una aplicación terapéutica específica nueva e inventiva" son admisibles.

V.2(vii)(b) Los requerimientos de novedad de una aplicación terapéutica han sido ejemplificadas en T0893/90 y T0019/86: En ambos casos ha sido decidido que una selección de pacientes (animales hemofílicos vs animales no-hemofílicos, y cerdos sero-negativos vs cerdos sero-positivos, respectivamente) no superpuesta (con respecto del arte previo) puede cumplir con los requerimientos de un nuevo segundo uso médico dentro del principio establecido en la Decisión Gr05/83 (OJ EPO 1985, 64) y puede de esta forma ser patentable si dicho nuevo es inventivo.

V.2(vii)(c) La Decisión T0051/93 se relaciona con el modo de administración de gonodotropina y es de muy poca relevancia para el presente aspecto legal.

V.2(viii) Los datos experimentales de la presente solicitud muestran un inicio mas rápido de la actividad de Org 34517 cuando se administra a una baja dosis de 150 mg cuando se compara con los 450 mg/día (Figura 1). Dicho inicio rápido es una nueva característica técnica la cual le puede conferir novedad a una reivindicación apropiadamente redactada.

La presente reivindicación 7 en combinación con la reivindicación 6, especificando la unidad de dosis de 150 –300 mg de Org 34517, podrían haber formado las bases para una modificación de las reivindicaciones de segundo uso médico.

V.2(ix) Por las razones expresadas arriba, una reivindicación relacionada al uso de Org 34517 para la preparación de un medicamento para el tratamiento de un paciente que sufre de un desorden depresivo mayor, el medicamento que contiene una unidad de dosis

de Org 34517 de entre 150 mg a 300 mg, podría haber sido considerada como novedosa en el sentido de una invención de selección.

V.2(x) En la reivindicación 6, sin embargo, no se especifica un límite inferior para la unidad de dosis de Org 34517. De esta forma, el objeto de la reivindicación 6 no puede ser reconocido como una selección de un rango lo suficientemente específico par el rango de dosis divulgado en el arte previo (D1).

V.3 Nivel Inventivo (Artículo 33(3)PCT)

V.3(i) Para las objeciones debido a la falta de nivel inventivo del objeto de las reivindicaciones 1-6, 8 y 9, ver los respectivos pasajes de la Opinión Escrita.

V.3 (ii) En la presente solicitud, el uso de Org 34517 a una baja dosis de 150 mg parece traer efectos beneficiosos inesperados (inicio rápido de la actividad) en el tratamiento del trastorno depresivo mayor. El segundo uso médico de Org 34517 a una baja dosis puede ser considerado como una selección dirigida que proporciona un efecto benéfico inesperado y así conferirle novedad a tal uso restringido. La dosis de 150 mg puede ser considerada como lo suficientemente remota a partir de D1, el cual divulga un amplio rango de dosis de Org 34517 a partir de 0.07 a 7000 m, preferiblemente 0.7-700 mg y una dosis de 1400 mg de Org 34517 en el ejemplo 12 (todas las dosis asumiendo que el paciente pesa 70 Kg).

V.3(iii) Consecuentemente, la presencia de nivel inventivo para una reivindicación de acuerdo con el punto V.2(x) puede ser aceptada en el sentido de una invención de selección mostrando un efecto técnico inesperado y benéfico.

V.3(iv) Sin embargo, en la reivindicación 6 no se especifica un límite inferior de la unidad de dosis de Org 34517. De esta forma, el objeto de la reivindicación 6 no puede ser reconocido como una selección lo suficientemente específica a partir del rango de dosis divulgado en el arte previo (D1), ver también punto V.2(x).

V.3(v9 No es probable, en vista de la presente solicitud, que valores de dosis muy bajos (por ejemplo 0.00005 mg/unidad), que caen dentro del rango de "no ejecen los 300 mg", solucionen el problema del que trata la invención. Dichas incorporaciones de la reivindicación 6, y así la reivindicación 6 en su totalidad, no cumple el requisito de nivel inventivo.

PRP/WPC11214/ID-000325

USO DE (11,17 β)-11-(1,3-BENZODIOXOL-5-IL)-17-HIDROXI-17-
(1-PROPINIL)-ESTRA-4,9-DIEN-3-ONA EN EL TRATAMIENTO DE
DESORDEN DEPRESIVO MAYOR

La presente invención se relaciona con el uso de (11,17 β)-11-(1,3-benzodioxol-5-il)-17-hidroxi-17-(1-propinil)-estra-4,9-dien-3-ona (Org 34517) para la preparación de un tratamiento de depresión así como también con preparaciones farmacéuticas de Org 34517 para dicho uso.

El desorden depresivo mayor es un desorden psiquiátrico que tiene una prevalencia durante el tiempo de vida de alrededor del 8%. Uno de los hallazgos más consistentes en psiquiatría es que los pacientes con depresión mayor presentan alteraciones en el eje hipotalámico-pituitaria-adrenal (HPA). Un porcentaje significativo de los pacientes deprimidos exhiben hipersecreción de cortisol glucocorticosteroide adrenal, manifestado por plasma elevado y concentraciones de fluido cerebroespinal de cortisol y cortisol libre urinario incrementado. Además muchos pacientes depresivos exhiben una clara incapacidad de desconectar la

liberación de cortisol endógeno y luego de exposición exógeno con el glucocorticoide potente sintético dexametasona la así llamada dexametasona no supresora) (Gold P. W., et al., *Clinical and biochemical manifestations of depression: relation to neurobiology of stress*. New England J. Med. 319, 413-420, 1988). Otras anormalidades del eje HPA encontrado en pacientes deprimidos son la respuesta de cortisol incrementada a corticotropina, una respuesta a corticotropina colmada a CRH (hormona de vibración de corticotropina), agrandamiento adrenal y de la pituitaria y retroalimentación negativa de glucocorticoide disminuido (para una revisión de Holsboer, F. y Barden, N.: *Antidepressants and Hypothalamic-Pituitary-Adrenocortical regulation*. Endocrine Reviews 1996, 17, 187-205). Estas observaciones han sido interpretadas para sugerir una relación causal entre funcionamiento disturbado del eje HPA y la patología de depresión (Murphy, B.E.P.: *Steroids and Depression*. J. of Steroid Biochem. Mol. Biol. 1991, 38, 537-559). La eficacia terapéutica de los antidepresivos clásicos ha sido mostrada por ser precedida o por coincidir con la restauración del eje HPA disturbado en la depresión (Holsboer y Barden, 1996, *Supra*). Se ha postulado que

cualquier intervención que pueda restaurar esta disfunción HPA puede tener potencial antidepresivo. Un tipo de tal intervención es la administración de inhibidores de síntesis de glucocorticoide, como ha sido mostrada en pacientes que sufren del síndrome de Cushing's, la cual es una condición en la cual altos niveles de cortisol son reportados como un resultado de malfuncionamiento de la glándula adrenal (debido a un tumor de la pituitaria o un tumor secundario, ambos produciendo el ACTH secretagogo de cortisol). Los síntomas depresivos asociados con Cushing's desaparecen de manera relativamente rápida cuando se regresa a los niveles de cortisol normales. Tal tratamiento puede involucrar la remoción del tumor ofendiente o el tratamiento con inhibidores de síntesis de cortisol tal como metirapona, cetoconazol, o aminoglutetimida (Murphy, B.E.P., *Steroids and Depressions*. *J. Steroid Biochem & Mol. Biol.* 38, 537-558, 1991). Similarmente, los ensayos clínicos relativamente recientes han demostrado que los inhibidores de síntesis de cortisol pueden ser utilizados para mejorar los síntomas depresivos en depresiones severas diferentes a Cushing resistentes a tratamiento (Murphy, B.E.P., *Neuroendocrine responses to inhibitors of steroid síntesis in patients with major depresión*

resistent to antidepressant therapy. Can J. Psych. 43, 279-286, 1998; ver también patente estadounidense 4,814,333 (Ravaris, C. L.): Method for treatment of hypercorisolemic, depressed patients.). Los inconvenientes del uso de inhibidores de síntesis de cortisol con niveles de cortisol de plasma más bajos son su alta toxicidad y su relativamente bajo grado de selectividad para la inhibición de síntesis de cortisol versus síntesis de otros esteroides endógenamente manufacturados (tal como mineralocorticoides y esteroides sexuales) combinados con el riesgo de la inducción de insuficiencia adrenal. Una desventaja adicional sería es que la irrupción del efecto terapéutico de estos inhibidores de síntesis de cortisol es tan larga como aquella observada con los antidepresivos clásicos (por ejemplo varias semanas).

Otro tipo de intervención es el uso de antagonistas receptores directos de glucocorticoide (GR), los cuales tienen mucho más efectos farmacológicos específicos comparados con los inhibidores de síntesis y que pueden ayudar a restablecer la actividad HPA. Los estudios clínicos pilotos a pequeña escala han sido conducidos con el fin de estudiar la actividad antidepresiva de los

antagonistas de receptor de glucocorticoide no selectivos
RU 486 (mifepristona; 17 β -hidroxi-11 β -(4-dimetilaminofenil-17 α -(1-propinil)estra-4,9-dieno-3-ona; Murphy, B.E.P. et al. J. Psychiat. Neurosc. 18,209-213, 1993). Relativamente altas dosis de mifepristona en el rango de 8-12 mg/kg/día, durante un periodo de tiempo relativamente corto, (4 días), también se mostró efectivo en el tratamiento de psicosis asociadas con depresión mayor sicótica (Solicitud de Patente Internacional Wo 99/17779; Schatzberg and Belanoff). Más recientemente, (Nemeroff, C., Remeron Scientific Expert Meeting, Budapest, March 29-April 1, 2001) se demostró en una continuación de fase IIB de este estudio, que tanto el número de respondedores así como también la eficacia del tratamiento de psicosis incrementada con una dosis diaria creciente de mifepristona medida por el cambio en "Brief Psychiatric Rating Scale (50 mg-33% de cambio; 600 mg-40% de cambio y 1200 mg-52% de cambio). Estos datos sugieren que una mayor dosis de antagonista de receptor de glucocorticoide esta correlacionada con una mayor eficacia clínica.

Los antagonistas de receptores de glucocorticoide selectivos, que son estructuralmente relacionados con

mifepristona, que les falta apreciable afinidad por mineralocorticoide, estrógeno y receptores de andrógeno, y que tienen baja afinidad con el receptor de progesterona se han descrito en la Patente Europea 763 541 B1 (Akzo Nobel N.V.) Por ser potencialmente útiles en la prevención y el tratamiento de enfermedades dependientes de glucocorticoide o síntomas, como el síndrome de Cushing, diabetes, glaucoma, trastornos del sueño, depresión, ansiedad, aterosclerosis, hipertensión, adiposidad, osteoporosis y retiro de los síntomas de narcóticos.

La actividad de antiglucocorticoide de (11 β ,17 β)-11-(1,3-benzodioxol-5-il)-17-hidroxi-17-(1-propinil)-estra-4,9-dien-3-ona, un compuesto específicamente descrito en la EP 763 541 B1, y el cual será denominado como Org 34517, se encontró por estar relacionado con la dosis medida por el procedimiento descrito por Kloosterboer et al (J. Steroid Biochem 31, 567-571, 1988): el efecto (ganancia de peso) de Org 34517 oralmente aplicada sobre el peso del cuerpo, adrenales, timo y vaso de ratas macho inmaduras tratadas con dexametasona probaron incrementarse con la dosis (de 10 mg/kg a 40 mg/kg).

El Org 34517 se encontró que era menos potente (52%) que la mifepristona en u a unión in vivo al receptor de glucocorticoide. La dosis umbral para demostrar los efectos antiglucocorticoides in vivo (rata) fue similarmente mucho mayor para Org 34517 (20 mg/kg) que para mifepristona (5 mg/kg). En acuerdo con la actividad antiglucocorticoide relativamente baja, un estudio clínico en donde la actividad de antiglucocorticoide en humanos (saludables) se estimo sobre la base del incremento de cortisol o sobre la cantidad de antagonismo de dexametason, luego de la administración de Org 34517 reveló que el Org 34517 tiene 8na potencia relativa de mifepristona de 10-25% y 17%, respectivamente.

Estos datos indicarían que los efectos clínicos útiles durante el tratamiento de una enfermedad dependiente de glucocorticoide deben ser esperados en dosis diarias de Org 34517 que serían mucho mayores para la más potente mifepristona antiglucocorticoide.

Se ha encontrado ahora inesperadamente en los estudios clínicos que los pacientes que sufren de desorden depresivo mayor deben ser tratados con una dosis diaria de Org 34517 que no excede en 300 mg. La

administración de tales dosis relativamente bajas de Org 34517 antiglucocorticoide resultan en rápida arremetida del efecto antidepresivo comparado con la arremetida del efecto antidepresivo en pacientes tratados con una dosis diaria de 450 mg de Org 34517 o más. La dosis diariamente preferida de Org 34517 varía entre 150 y 300 mg.

Una ventaja de estas dosis bajas es que los efectos colaterales potenciales que podrían resultar de la actividad antiprogestagénica residual del compuesto, y que podrían conducir a la interferencia con ciclo menstrual femenino normal, son mantenidos en el mínimo.

Los glucocorticoides son hormonas extremadamente importantes, las cuales juegan papeles clave en mecanismos de copiado que los animales (incluyendo el hombre) tienen a su disposición contra estresantes internos y externos. Las dosis farmacológicamente efectivas de antagonistas receptores de glucocorticoide, tales como Org 34517 y RU 486, bloquearan la acción fisiológica de glucocorticoides endógenos y pueden de esta manera inducir riesgos cuando los estresantes afectan el organismo. El régimen de tratamiento de dosis

baja de la presente invención garantiza así el incremento mínimo de la susceptibilidad de la inducción de riesgos.

En una modalidad preferida de la invención está relacionada con un medicamento que comprende una dosis diaria de Org 34517 que no excede de 300 mg, para el tratamiento de pacientes que sufren de desorden depresivo mayor y que tienen un nivel de cortisol de plasma, medido mediante el ensayo de cortisol de la tarde, que es mayor de 10µg/dl. Tales pacientes con desorden depresivo mayor, que tienen una regulación afectada del eje hipotálamo-pituitaria-adrenal (HPA), muestran una arremetida corta de la acción del efecto antidepresivo del Org 34517. El medicamento de dosis baja de la invención es especialmente efectivo con relación a la arremetida de la acción del efecto antidepresivo en pacientes clasificados como no supresores de dexametasona, es decir pacientes que demuestran no supresión en el ensayo de supresión de dexametasona.

El Org 34517, (11β,17β)-11-(1,3-benzodioxol-5-il)-17-hidroxí-17-(1-propinil)-estra-4,9-dien-3-ona, se puede preparar como se describió en la Patente Europea P 763

541 B1 (Akzo Nobel N.V.), cuyo contenido se incorpora aquí totalmente como referencia.

Un aspecto adicional de la invención se relaciona con una preparación farmacéutica que comprende una unidad de dosis diaria de ((11 β ,17 β)-11-(1,3-benzodioxol-5-il)-17-hidroxi-17-(1-propinil)-estra-4,9-dien-3-ona, que no excede 300 mg y auxiliares farmacéuticamente aceptables, para el tratamiento de desorden depresivo mayor.

Las preparaciones farmacéuticas, o las composiciones, para uso de acuerdo con la invención comprenden ((11 β ,17 β)-11-(1,3-benzodioxol-5-il)-17-hidroxi-17-(1-propinil)-estra-4,9-dien-3-ona, en mezcla con auxiliares farmacéuticamente aceptables. El término medios "aceptable" significa ser compatible con otros ingredientes de la composición y no deletéreos a los receptores de esta. Las composiciones se pueden preparar de acuerdo con técnicas estándar tales como aquellas descritas en la referencia estándar Gennaro A.R. et al., Remington: The Science and Practice of Pharmacy, (20ava edición., Lippincott Williams & Wilkins, 2000, Parte 5: Pharmaceutical Manufacturing). Las composiciones incluyen por ejemplo, aquellas adecuadas para administración oral,

sublingual, tópica o rectal, y similares, todas en formas de dosis unitarias para administración.

Para la administración oral, que es la ruta preferida, el ingrediente activo puede ser presentado como unidades discretas, tales como tabletas, cápsulas, polvos, granulados, soluciones, y suspensiones.

La invención se ilustra en los siguientes ejemplos:

Ejemplo 1

Tratamiento con Org 34517 de pacientes con depresión mayor.

Un estudio controlado de paroxetin de 4 semanas doble ciego de Org 34517 en pacientes depresivos fue llevado a cabo. La paroxetina es un inhibidor de retoma de serotonina selectivo que es reconocido como un antidepresivo efectivo para depresión mayor. Los pacientes fueron seleccionados los cuales tenían un desorden depresivo primario que llenaba los criterios de diagnóstico de un desorden depresivo mayor (MDD) como se definió mediante el DMS-IV para episodios recurrentes (296,3), y que tenían una severidad de depresión que dieron como resultado un marcador total de al menos 22

sobre el HAMD-21 (Hamilton Rating Scale for Depresión; ver Hamilton, M. "A rating Scale for depresión." J. Neurol. Neurosurg. Psychiat. 1960, 23, 56-62) escala en línea base. El paciente tuvo un episodio de depresión que había durado al menos dos semanas antes de la línea base.

Los pacientes fueron localizados aleatoriamente en uno de tres grupos de tratamiento. Los pacientes del grupo I (grupo Org 150: 50 pacientes) recibieron dos cápsulas con 75 mg de Org 34517 y un placebo (dosis diaria total 150 mg) para las primeras 2 semanas y 2 cápsulas con 75 mg de Org 34517 y 1 cápsula con 150 mg (dosis diaria total 300 mg) las siguientes 2 semanas; los pacientes del grupo II (grupo Org 450 46 pacientes) recibieron 3 cápsulas con 150 mg de Org 34517 (dosis diaria total 450 mg) en las primeras 2 semanas y 4 cápsulas de Org 34517 (dosis diaria total 600 mg) en las siguientes 2 semanas; los pacientes del grupo III, (grupo paroxetina: 44 pacientes) recibieron 2 cápsulas con 10 mg de paroxetina y una cápsula de placebo (dosis diaria total 20 mg) para las primeras 2 semanas, seguidas de 2 cápsulas de 10 mg y una cápsula de 20 mg de paroxetina (dosis diaria total 40 mg) en las siguientes 2 semanas. La medicación se administró oralmente en la mañana. Las evaluaciones de eficacia

fueron hechas en los días 4, 7, 10, 14, 21, 28 y 35 al utilizar una escala HAMD de 21 ítem.

Los niveles de plasma de cortisona en la tarde (ACT=ensayo de cortisol de la tarde) fueron medidos como se describió por Halbreich et al (J. Clin. Endocrinol. Metab. 54(6), 1262, 1982).

Los resultados para todos los pacientes son mostrados en la figura 1. Estos datos demuestran una arremetida más rápida de la acción del efecto antidepresivo para el grupo de tratamiento de 150 mg comparado con el de paroxetina, medido como una diferencia de 2 puntos aproximados sobre la escala de Hamilton en el día 10.

Los resultados para los pacientes que tenían un nivel de cortisol de plasma en la tarde al inicio de tratamiento mayor de 10 µg/dl son mostrados en la figura 2. Estos datos demuestran de nuevo una arremetida rápida de la acción del efecto antidepresivo del grupo de tratamiento de 150 mg comparado con la paroxetina, medida como una diferencia de 4 puntos aproximado sobre la escala de Hamilton en el día 10.

Los resultados para los pacientes que fueron diagnosticados al inicio del tratamiento como no supresores de dexametasona (no supresión en el ensayo de supresión de dexametasona) son mostrados en la figura 3. Esos datos demuestran una diferencia pronunciada en la arremetida de la acción del efecto antidepresivo para el grupo de tratamiento de 150 mg comparado con el grupo de tratamiento de paroxetina, medido como una diferencia de 6 puntos aproximados sobre la escala de Hamilton en el día 10.

REIVINDICACIONES

1. El uso de (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hidroxi-17-(1-propinil)-estra-4,9-dien-3-ona, para la preparación de un medicamento para el tratamiento de un paciente que sufre de un desorden depresivo mayor.
2. El uso de acuerdo a la reivindicación 1, en donde el medicamento se aplica en una dosis diaria que no excede 300 mg.
3. El uso de acuerdo a la reivindicación 1 o 2, en donde la dosis diaria varía entre 150 y 300 mg.
4. El uso de acuerdo a cualquiera a las reivindicaciones 1-3, en donde el desorden depresivo mayor se caracteriza por niveles de cortisol de plasma en el paciente que son mayores de 10 μ g/dl.
5. El uso de acuerdo a la reivindicación 4, en donde el nivel de plasma de cortisol en el paciente demuestra no supresión en ensayo de supresión de dexametasona.

6. Una preparación farmacéutica que comprende una unidad de dosis diaria de (11 β ,17 β)-11-(1,3-benzodioxol-5-il)-17-hidroxi-17-(1-propinil)-estra-4,9-dien-3-ona, que no excede en 300 mg y auxiliares farmacéuticamente aceptables, para el tratamiento de desorden depresivo mayor.

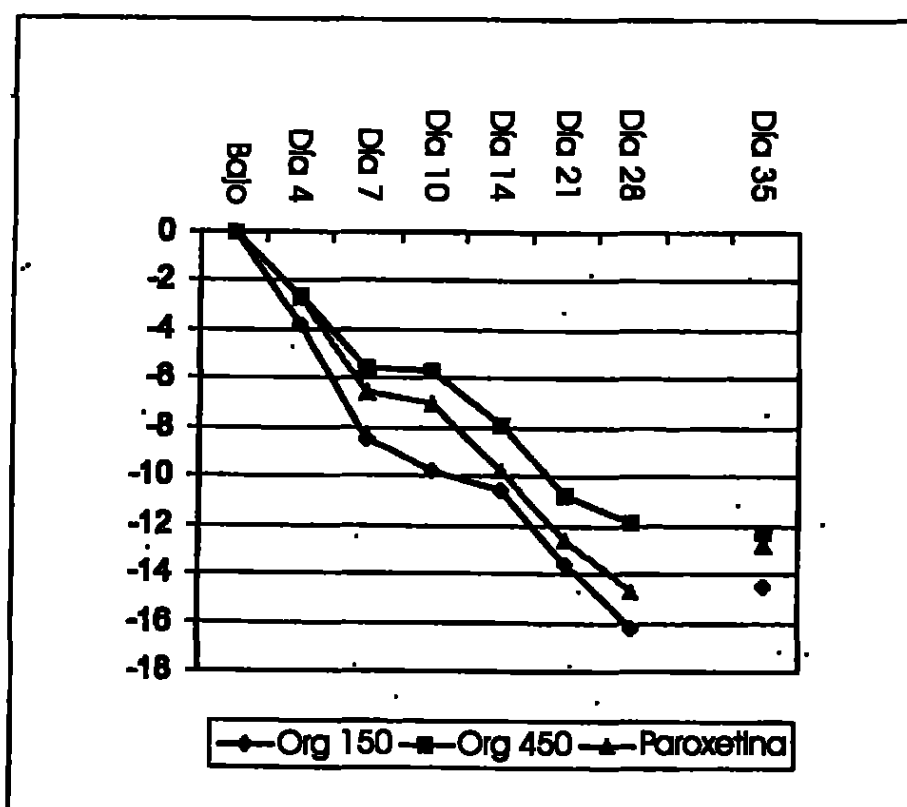
7. La preparación farmacéutica de acuerdo a la reivindicación 6 en donde la unidad de dosis diaria varía en 350 y 300 mg.

8. Un método para el tratamiento de un paciente que sufre de un desorden depresivo mayor mediante la administración al paciente de una cantidad efectiva de glucocorticosteroide, dicho método comprende la administración de (11 β ,17 β)-11-(1,3-benzodioxol-5-il)-17-hidroxi-17-(1-propinil)-estra-4,9-dien-3-ona, en una dosis diaria que no excede 300 mg.

9. El método de la reivindicación 8, en donde la dosis diaria está en 350 y 300 mg.

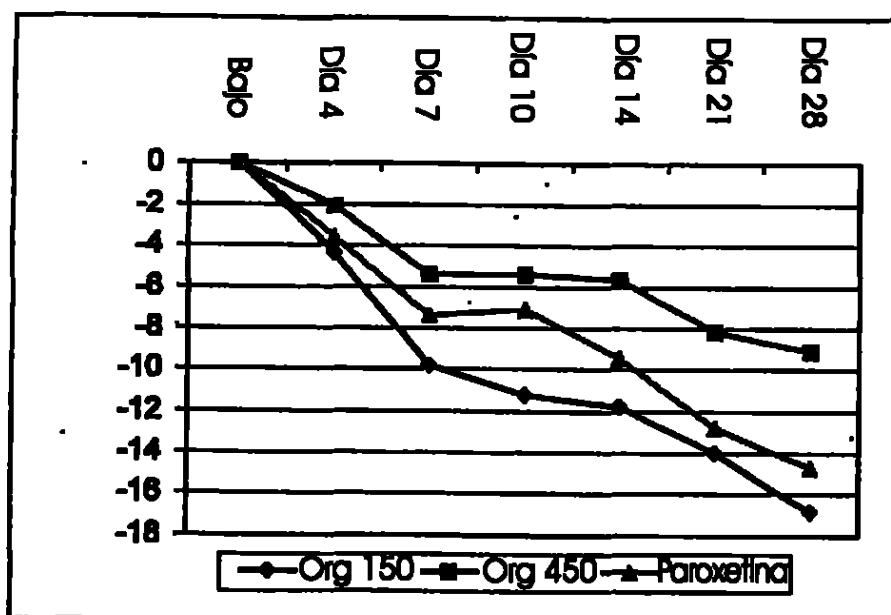
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Figura 1. Cambio de HAMD-21 desde la línea base: todos los pacientes



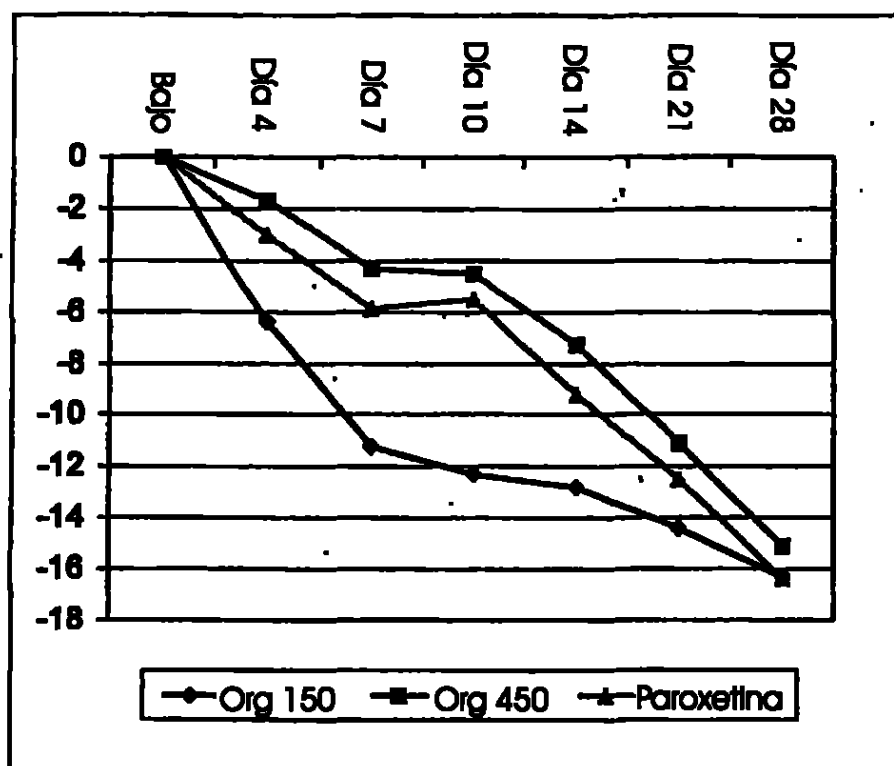
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Figura 2. Cambio de HAMD-21 desde la línea base: pacientes con alto ACT.



3 / 3

Figura 3. Cambio de HAMD-21 desde la línea base: no supresores DST



86

SUPERINTENDENCIA Y LABORAL
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Fecha (UTC): 2004-05-13 17:43:15
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 20,815
FECHA : ABRIL 12 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	22156877	12/04/2004	53,734,000.00

***** CONCEPTO *****

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 90005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.
	TOTAL :	422,000.

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Cdo 11214-841-018-9

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 presenta la solicitud. | () | () |
| - Descripción de la invención. | () | () |
| - Dibujos de ser estos pertinentes. | () | () |
| - Comprobante de pago de las tasas establecidas. | () | () |

COMPLETA ()

INCOMPLETA ()

DISEÑO INDUSTRIAL ()

- | | | |
|--|-----|-----|
| - 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 o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. | () | () |
| - Comprobante de pago de las tasas establecidas | () | () |

COMPLETA ()

INCOMPLETA ()

ESQUEMA DE TRAZADO ()

- | | | |
|--|-----|-----|
| - Indicación de que solicita el registro de un Esquema de trazado. | () | () |
| - 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. | () | () |

COMPLETA

INCOMPLETA ()

Firma Responsable:

Fecha:

SUPERINTENDENCIA Y COGERCIO

Radicación : 04044412 00000000

Folios: 0

Fecha (AÑO): 2004-05-13 17:43:15

Trámite : 411 PCT-PATENT 379 FASE NACI 411 PRESENTI

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

2020
Bogotá D C

Doctor(a)
EMILIO FERRERO
Apoderado(a)
AKZO NOBEL N.V.

REFERENCIA:	Radicación N°	04-044412
	Solicitud internacional	PCT/EP02/11732
	Fecha inicio fase nacional	26/05/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	883
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486.

Cúmplase

Dado en Bogotá D C,

17.5 JUL 2004


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones.

202044