



Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

05-588822

21. EXPEDIENTE No.

54. TITULO

TABLETAS FARMACEUTICAS QUE CONTIENEN TIBOLONA Y UN

RECUBRIMIENTO

51. CLASIFICACION INTERNACIONAL

71. SOLICITANTE

AKZO NOBEL N.V.

DOMICILIO

Arnhem, Holanda.

74. APODERADO

EMILIO FERRERO

C.C. 438,019 de Usaquén,

22. BOGOTA, D.C.,



Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINDUSTRIA Y COMERCIO

Radicación : 05050422 00000000

Folios: 78

Fecha (ORA): 2005-06-16 17:56:54

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL 20-06-05

SOLICITUD DE:

1

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

2

S LICITANTE
(71)

Nombre: **AKZO NOBEL N.V.**
sociedad constituida y existente bajo las
leyes de Holanda

Dirección: Velperweg 76,
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: 211 86 50
E-mail: clientes@camyp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒

NIT ☐

C.E. ☐

Otro ☐

Cual

Número 438.019 T.P 31.929

4

INVENTOR (ES)
(72)

1. **Pieter DE HAAN**
N.V. Organon, P.O. Box 20
NL-5340 BH Oss,
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2. **Cornelis Elisabeth Johannus VAN LARE**
N.V. Organon, P.O. Box 20
NL-5340 BH Oss,
Holanda

5

PCT (86)

Solicitud Internacional No. PCT/EP2003/050829

Fecha: 13 de Noviembre de 2003

Publicación Internacional No. WO 2004/045587 A1

Fecha: 3 de Junio de 2004

6

Título (54)

TABLETAS FARMACÉUTICAS QUE CONTIENEN TIBOLONA Y UN
RECUBRIMIENTO

7

Clasificación Internacional (51) A61K 9/36

8

Prioridad

SI ☒ NO ☐

(33) País de Origen

US
EP

(32) Fecha

20 de Noviembre de 2002
20 de Noviembre de 2002

(31) Número de Solicitud

60/427.740
02079920.1

9

Comprobante de pago No.: 05 - 41.103

Fecha: 7 de Junio de 2005

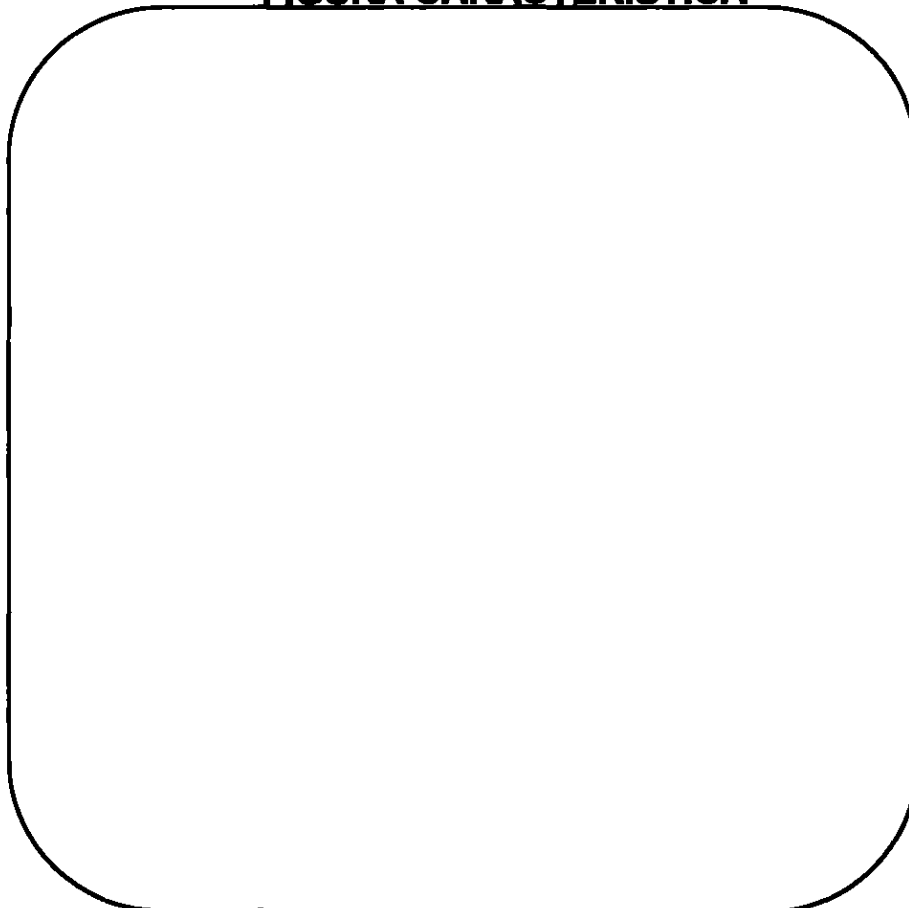
10

Anex s:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 443.000.00.
- ☐ 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: (Ver Hoja de documentos anexos)

11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

NOMBRE:

EMILIO FERRERO

FIRMA :

C.C. 438.019 de Usaquén T.P. 31.929

DOCUMENTOS ANEXOS

1. ☒ **Publicación Internacional WO 2004/045587 A1**

Descripción:

Páginas 1-14 en el idioma original

Páginas 1-19 en español

Reivindicaciones: Número (s) 1-10

Figuras: Número (s) _____

2. ☒ **Forma PCT/RO/101. PCT Request**
3. ☐ **Forma PCT/RO/106. Invitation to Correct Defects.**
4. ☒ **Forma PCT/ISA/210. Informe de Búsqueda Internacional.**
5. ☒ **Forma PCT/ISA/220. Notificación De La Transmisión Del Informe De Búsqueda Internacional Y De La Opinión Escrita De La Administración Encargada De La Búsqueda Internacional, O De La Declaración.**
6. ☐ **Forma PCT/ISA/237. Opinión Escrita De La Administración Encargada De La Búsqueda Internacional.**
7. ☐ **Forma PCT/IB/304. Notification Concerning Submission Or Transmittal Of Priority Document.**
8. ☐ **Forma PCT/IB/306. Notification Of The Recoding Of A Change.**
Descripción De Modificación:

9. ☐ **Forma PCT/IB/308. Notice Informing The Applicant Of The Communication Of The International Application To The Designated Offices.**
10. ☐ **Forma PCT/IB/332. Information Concerning Elected Offices Notified Of Their Election.**
11. ☒ **Forma PCT/IPEA/401. PCT Demand**
12. ☐ **Forma PCT/IPEA/402. Notification Of Receipt Of Demand By Competent International Preliminary Examining Authority.**
13. ☐ **Forma PCT/IPEA/408. Written Opinion.**
14. ☒ **Forma PCT/IPEA/416. Notification Of Transmittal Of The International Preliminary Examination Report.**
15. ☒ **Forma PCT/IPEA/409. Informe Del Examen Preliminar Internacional.**
16. ☐ **Traducción Al Español Del Informe Del Examen Preliminar Internacional.**
17. ☐ **Traducción Al Español De Los Anexos Presentados Junto Con El Informe Del Examen Preliminar Internacional.**

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

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

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

3324
1538

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. 891; 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 al se tratara 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 suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (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. 891; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates; in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property, and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, especially before 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 Day of August 1998

F.G.M. Hermans

E.H. Reerink

In/en Director Patents Pharma

Deputy Director

Legal Affairs

Signature

AKZO NOBEL N.V.

CAVELIER ABOGADOS
WPPODERE-179 (MINUTA N° 12.1.12.5)

TRADUCCION No. 18.11.98
MARIA ELVIRA MACIELLO
Traductora e Intérprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

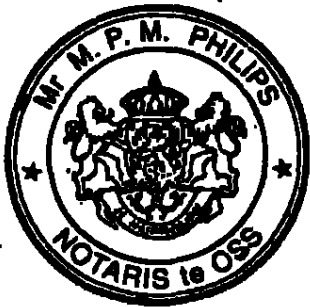
LEGALIZACION

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

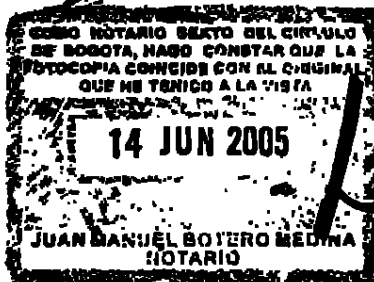
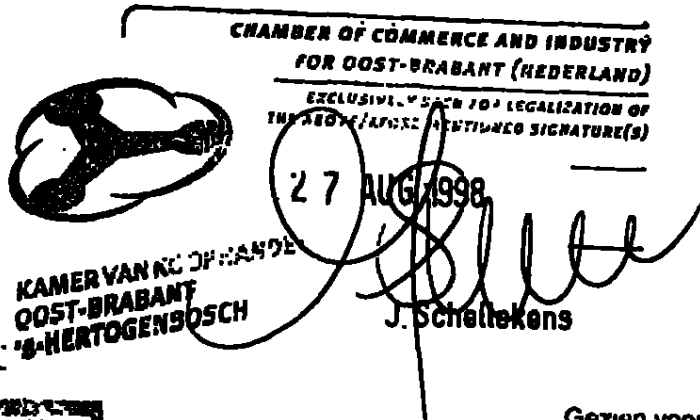
The Colombia Consul must issue a certificate the legal existence of the company, (1) the Power-of-Authority, (2) that it is in accordance of its company purposes, and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect, we show the Consul the evidence to prove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

Seen for legalization of the signatures of Mr. P.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.



TRADUCCION No: 18/1/98
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

15499



Gezien voor legalisatie van de handtekening van dhr/mw ... Schellekens

's-Gravenhage, 9 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

COLO 11214-201-001-3

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.

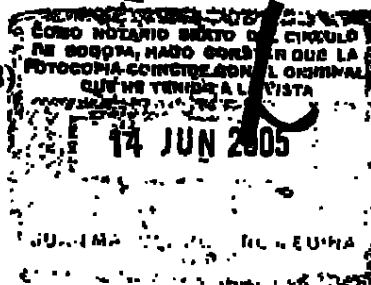
Esta certificación se expide en La Haya, Países Bajos, a los seis (06) días del mes de Noviembre de mil novecientos noventa y ocho (1998).

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

Certificación No. 206

Jose Ignacio Villagas Cortes
JOSE IGNACIO VILLEGAS CORTES
CONSUL DE COLOMBIA
LA HAYA

TRADUCCION No. 18.11 68
MARIA ELVIRA MARTELO
Traductora e interprete Oficial
Inglés - Español Inglés
Res. No. 2879 Min. Justicia



NO SE ASUME
RESPONSABILIDAD DEL TEXTO

98 NOV 19 AM 11:56

BOGOTÁ D.C.

NOTARIO JUAN MANUEL BOTERO MEDINA
14 JUN 2005
NOTARIO

MINISTERIO DE RELACIONES
EXTERIORES

300803

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES INDICADAS

6

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

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

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

(Legalización) CAMARA DE INDUSTRIA Y COMERCIO PARA OOST-BRABANT (PAISES 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

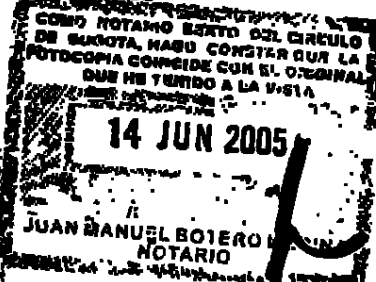
Nov. 20/98

Maria E. Martelo
TRADUCCION No. 15.11.98
MARIA ELVIRA MARTELO
Traductora e interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LOS ANTERIORES (ES) FIRMAS (S) FUERON IDENTIFICADOS CON C.C. No. (s)

Maria E. Martelo
23 NOV 1998

ES (SON) AUTENTICA(S)
SANTAFE DE BOGOTA, 23 NOV. 1998



MINISTERIO DE RELACIONES EXTERIORES

198457

Maria E. Martelo

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

98 NOV 24 PM 12:06

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

ABOGADOS

EDIFICIO SISKI
CARRERA 4ª N° 72-35
BOGOTÁ, 8- COLOMBIA

CESION

Yo.(nosotros). abajo firmado(s)

DE HAAN,
Pieter
N.V. Organon
P.O. Box 20
5340 BH Oss
The Netherlands

domiciliado (s) en

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

"PHARMACEUTICAL TABLETS CONTAINING TIBOLONE AND A COATING"

Tabletas Farmacéuticas que contienen tibolona y un recubrimiento

declaro(amos) así mismo que cedo(amos) y transfiero
(erimos), 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 ARNHEM, Holanda

todos los derechos inherentes a dicha invención y
que los citada Compañía queda facultada para
solicitar en su nombre la patente correspondiente
en la República de Colombia.

ASSIGNMENT

I (we), the undersigned

VAN LARE,
Cornelis, Elisabeth, Johannes
N.V. Organon
P.O. Box 20
5340 BH Oss
The Netherlands
Akzo Nobel Chemicals bv
PO Box 9300
6800 SB Arnhem

ot.

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

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

Akzo Nobel N.V.

a corporation constituted and existing in conformity
with the laws of

The Netherlands

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 in the
Republic of Colombia

Dado y firmado hoy/Given and signed this

Arnhem, 29 March 2005

en/in

DE HAAN,
Pieter

Firma

VAN LARE,
Cornelis, Elisabeth, Johannes

Signature

© CAVELIER ABOGADOS
WPPODERE-343

(Legalization required)

(Legalización necesaria)

AUTENTICACION NOTARIAL (INDIVIDUE)

NOTARIAL AUTHENTICATION (INDIVIDUAL) 9

A los ¹ días del mes de _____ de _____
ante mí, Notario Público de _____
compareció(eron) personalmente _____

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

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

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

.....

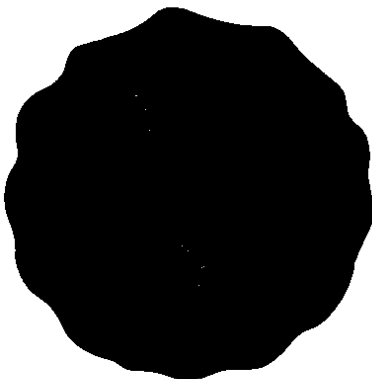
Seen by me, mr. Robbert Alexander Gallas, civil-law notary practising in The Hague,
for the authentication of the signatures on the attached document of:

- Mr Cornelis Elisabeth Johannes van Lare, born on the twentieth day of August
nineteenhundred sixty-four in Horn, The Netherlands, residing at Oss, The
Netherlands, holder of a Dutch divers-licence, number 3105574828;

The Hague, the first day of April twothousandfive.



A long, flowing handwritten signature in black ink, extending from the notary seal to the right.



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.prd.nl.

TRADUCCIÓN OFICIAL 101/2005 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL PIETER DE HAAN, DOMICILIADO EN N.V. ORGANON, P.O. BOX 20, 5340 BH OSS, HOLANDA Y CORNELIS, ELIZABETH, JAHANNUS VAN LARE, DOMICILIADO AKZO NOBEL CHEMICALS, DOMICILIADO EN P.O. BOX 9300, 6800 SB, ARNHEM, HOLANDA, INVENTORES ÚNICOS Y VERDADEROS DE LA INVENCION: TABLETAS FARMACÉUTICAS QUE CONTIENEN TIBULONA Y UN RECUBRIMIENTO, DECLARAN POR EL PRESENTE QUE CEDEN DICHA INVENCION A AKZO NOBEL N.V, EMPRESA ORGANIZADA Y EXISTENTE BAJO LAS LEYES DE HOLANDA, DOMICILIADA EN VELPERWEG 76, 6824 BM, ARNHEM, HOLANDA, JUNTO CON TODOS LOS DERECHOS INHERENTES Y QUE DICHA COMPAÑÍA QUEDA FACULTADA PARA SOLICITAR EN SU NOMBRE LA PATENTE CORRESPONDIENTE EN LA REPÚBLICA DE COLOMBIA.

DADO Y FIRMADO EN ARNHEM, HOY 20 DE MARZO DE 2005.

FIRMADO: CORNELIS, ELIZABETH, JOHANNUS VAN LARE

VISTO POR MI, ROBBERT ALEXANDER GALLAS, NOTARIO DE LEY CIVIL QUE PRACTICA EN LA HAYA, PARA LA AUTENTICACIÓN DE LA FIRMA EN EL DOCUMENTO ADJUNTO DE CORNELIS ELIZABETH JOHANNES VAN LARE, NACIDO EL 20 DE AGOSTO DE 1964 EN HORN, HOLANDA, RESIDENTE EN OSS, HOLANDA, PORTADOR DE UNA LICENCIA DE CONDUCCIÓN HOLANDESA, NÚMERO 3105574828

LA HAYA, PRIMERO DE ABRIL DE 2005

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SELLO: MR. R. A. GALLAS, NOTARIO

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sujeto a las condiciones de negocios registradas ante el tribunal de distrito de La Haya. En estas condiciones de negocios se incluye una limitación de responsabilidad. Estas condiciones de negocios se suministrarán si así se solicita. También se las puede consultar en www.prdf.nl.

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5. en La Haya
6. el 5 de abril de 2005
7. por el registrador del tribunal del distrito
8. Número 2005-342/11
9. Sello: Tribunal del distrito
10. Firma: S. Petronilla

COLO-11214-841-030-4

WPCL002G. ID 6720

Bogotá, 3 de mayo de 2005

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Eduardo Calado Regan
TRADUCTOR OFICIAL
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Bog. 312. Febrero de 1991

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Eduardo Calado
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CARRERA 4ª N° 72-35
BOGOTÁ, 8- COLOMBIA

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Yo.(nosotros). abajo firmado(a)

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N.V. Organon
P.O. Box 20
6540 BH Oss
The Netherlands

I (we), the undersigned

VAN LARE,
Cornelia, Elisabeth, Johannes
N.V. Organon
P.O. Box 20
6540 BH Oss
The Netherlands

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of

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

"PHARMACEUTICAL TABLETS CONTAINING TIBOLONE AND A COATING"

Tabletas farmacéuticas que contienen tibolona y un recubrimiento

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(crimos), sin limitación, a favor de la sociedad

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Pieter

VAN LARE,
Cornelia, Elisabeth, Johannes

Firma

Signature

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WPPODERE-343

(Legalization required)

(Legalización necesaria)

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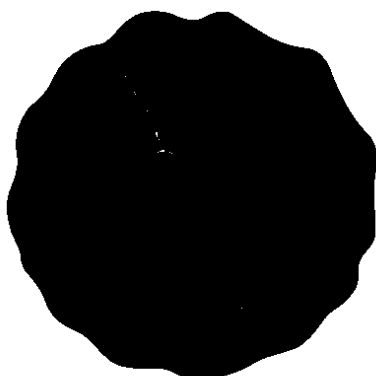
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- Mr Pieter de Haan, born on the twenty-eighth of October nineteenhundred
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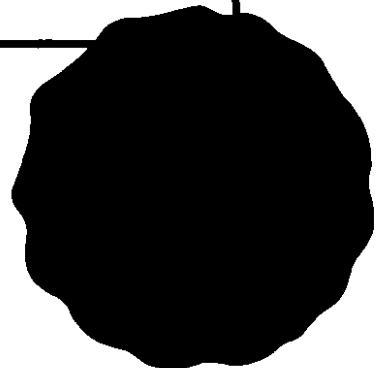
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TRADUCCIÓN OFICIAL 102/2005 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL PIETER DE HAAN, DOMICILIADO EN N.V. ORGANON, P.O. BOX 20, 5340 BH OSS, HOLANDA Y CORNELIS, ELIZABETH, JAHANNUS VAN LARE, DOMICILIADO EN AKZO NOBEL CHEMICALS, DOMICILIADO EN P.O. BOX 9300, 6800 SB, ARNHEM, HOLANDA, INVENTORES ÚNICOS Y VERDADEROS DE LA INVENCION: TABLETAS FARMACÉUTICAS QUE CONTIENEN TIBULONA Y UN RECUBRIMIENTO, DECLARAN POR EL PRESENTE QUE CEDEN DICHA INVENCION A AKZO NOBEL N.V, EMPRESA ORGANIZADA Y EXISTENTE BAJO LAS LEYES DE HOLANDA, DOMICILIADA EN VELPERWEG 76, 6824 BM, ARNHEM, HOLANDA, JUNTO CON TODOS LOS DERECHOS INHERENTES Y QUE DICHA COMPAÑÍA QUEDA FACULTADA PARA SOLICITAR EN SU NOMBRE LA PATENTE CORRESPONDIENTE EN LA REPÚBLICA DE COLOMBIA.

DADO Y FIRMADO EN ARNHEM, HOY 20 DE MARZO DE 2005.

FIRMADO: PIETER DE HAAN

VISTO POR MI, ROBBERT ALEXANDER GALLAS, NOTARIO DE LEY CIVIL QUE PRACTICA EN LA HAYA, PARA LA AUTENTICACIÓN DE LA FIRMA EN EL DOCUMENTO ADJUNTO DE PIETER DE HAAN, NACIDO EL 28 DE OCTUBRE DE 1953 EN ZIJPE, HOLANDA, RESIDENTE EN BERNHEZE, HOLANDA, PORTADOR DEL PASAPORTE HOLANDÉS, NÚMERO NC0914502

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COLO-11214-841-030-4

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Bogotá, 3 de mayo de 2005

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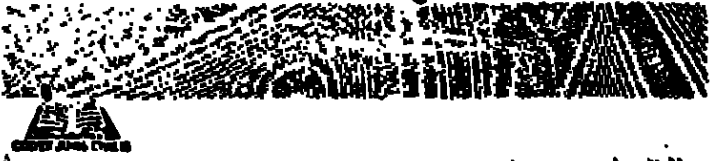
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- (71) Applicant (*for all designated States except US*): AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): DE HAAN, Pieter [NL/NL]; N.V. Organon, P.O. Box 20, NL-5340 BH Oss (NL). VAN LARE, Cornelia, Elisabeth, Johannes [NL/NL]; N.V. Organon, P.O.Box 20, NL-5340 BH Oss (NL).
- Published:
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

04/045587 A1

(54) Title: PHARMACEUTICAL TABLETS CONTAINING TIBOLONE AND A COATING

(57) Abstract: The present invention relates to a stabilized pharmaceutical tablet comprising an amount of from 0.1 to 10% by weight of tibolone provided with a coating, such as a film coating, a sugar coating, a sugar film coating or a "wrap" coating. The invention further relates to the use of a coating for stabilizing a pharmaceutical tablet comprising tibolone. Preferably, the coating is a sugar coating or a sugar film coating. Preferably, the sugar comprises sucrose. These tablets were shown to have a lower amount V38, i.e. an isomerization degradation product of tibolone, after storage as compared to uncoated tibolone tablets.

PHARMACEUTICAL TABLETS CONTAINING TIBOLONE AND A COATING

The present invention relates to a pharmaceutical tablet comprising an amount of
5 from 0.1 to 10% by weight of tibolone.

Compositions comprising tibolone, the chemical name of which is (7 α ,17 α)-17-
hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (also denoted as Org OD
14) and a pharmaceutically acceptable solid carrier have been described in EP
10 389 035.

A known formulation for tibolone is a 100 mg tablet having 2.5 mg of tibolone
contained therein, a relatively small amount (e.g. approx. 1% by weight) of
pharmaceutically acceptable auxiliaries, and a carrier making up the body of the
15 tablet. The carrier typically is composed of approx. 10% by weight of starch, e.g.
potato starch, and approx. 90% by weight of lactose. Tablets of 100 mg containing
2.5 mg of tibolone are available in medical practice under the name of Livial®.

Upon long-term storage of tibolone-containing tablets degradation products of
20 tibolone appear. The major degradation product is (7 α ,17 α)-17-hydroxy-7-methyl-
19-nor-17-pregn-4-en-20-yn-3-one (Org OM38). OM38 differs from tibolone in that
the double bond in the steroid skeleton is located between positions 4 and 5,
whereas in tibolone it is located between positions 5 and 10. This isomerization
product is identified as the major impurity in tibolone and in tibolone-containing
25 tablets and limits (at a maximum of 5% by weight of OM38) the approved shelf life
of the presently available Livial® tablets to a maximum of two years. Considerable
advantage is achieved in prolonging the shelf life of tibolone-containing tablets. It
is therefore advantageous to find means to reduce the formation of OM38 and to
provide more stable tibolone tablets with respect to the amount of OM38 formed
30 after storage.

The problem of reducing OM38 formation in tibolone and tibolone-containing
products was addressed earlier in WO 00/23460, providing high purity tibolone
containing less than 0.5% by weight of OM38, and in WO 98/47517, providing a
35 composition comprising tibolone and a pharmaceutically acceptable carrier, said
carrier having a high starch content, i.e. more than 10%, preferably at least 40%
by weight. Despite these contributions to the art, there still is a need to further

improve the shelf life of tibolone tablets and for alternatives to the solutions presented in WO 00/23460 and WO 98/47517.

In accordance with the present invention a stabilized pharmaceutical tablet comprising an amount of from 0.1 to 10% by weight of tibolone provided with a coating is made available for the first time. Surprisingly, such a tablet has a lower content of OM38 after storage, in particular after several months of storage, than a similar tablet without a coating. It is unexpected that a coating reduces the formation of the tibolone-derived isomerisation degradation product OM38.

10

The present invention further resides in an unexpected new use of a coating for stabilizing a pharmaceutical tablet comprising an amount of from 0.1 to 10% by weight of tibolone.

15 In the context of the present invention with the term "stabilized" thus is meant "stabilized with respect to the formation of OM38 upon storage." Hence, the coating of tibolone-containing tablets serves to reduce the formation of OM38 as compared to uncoated tablets. Further, in the context of the present invention the term "tablets" is meant to refer to "solid dosage forms" which can technically be
20 provided with a coating and which typically are applied for oral administration. Thus, apart from compressed or molded tablets, powders, granules, nonpareils, and capsules are also comprised in the term "tablets." Compressed tablets, however, are the most frequently used solid dosage forms.

25 Incidentally, in WO 98/47517 reference is made to provide tablets of tibolone with a film coat if required (see page 5, lines 14-16). The tablets made in accordance with WO 98/47517 make use of a pharmaceutically acceptable carrier containing more than 10%, preferably at least 40% by weight of starch. In this document, no teaching or suggestion is made with respect to the technical effect of a coating on
30 the formation of OM38 during storage of tibolone-containing tablets. Tibolone tablets stabilized by application of a coating are neither disclosed nor exemplified in this document. With respect to the words "if required" in line 14 it should be noted that the Livial® tablets that are currently on the market are neither coated nor require a coating with a view to typical reasons for coating pharmaceutical
35 tablets (taken from Remington, page 894, cited below), i.e. protecting the drug from its surrounding environment (particularly air, moisture, and light), masking of

unpleasant taste or odor, increasing the ease by which the product can be ingested by a patient, improving product identity, facilitating handling, improving product appearance, reducing the risk of interaction between incompatible components, improving product mechanical integrity or modifying drug release.

- 5 Further, WO 98/47517 only mentions a film coat and makes no reference to any other type of coating.

In the context of the present invention with "coating" is meant any coating which achieves a stabilizing effect with respect to the formation of OM38 upon storage of
10 a coated tablet as compared to an uncoated tablet. Whether or not a coating achieves a stabilizing effect can easily be determined by one skilled in the art on the basis of the present specification. The amount of OM38 present in a tablet is determined via HPLC analysis in a conventional way.

- 15 Suitable examples of coatings that can be used in accordance with the present invention include a film coating, a sugar coating, a sugar film coating, for example, a sugar film coating according to US 2002/0044970, and a "wrap" coating according to US 5146730. The compositions of these coatings and the methods and equipment by which they are applied onto tablets are well-known to a person
20 skilled in the art and they are described, for example, by Stuart C. Porter in Chapter 48: Coating of pharmaceutical dosage forms in Remington: The Science and Practice of Pharmacy, 20th ed., 2000; Alfonso R. Gennaro, Editor, Lippincott Williams & Wilkins, Baltimore, USA, as well as in US 2002/0044970 and US 5146730. Preference is given to aqueous coating compositions, including mixtures
25 of water and an organic solvent such as an alcohol. Most preferably, coating compositions containing water as the only solvent or vehicle are used.

In particular, the coating to be used in accordance with the present invention is a sugar coating, a sugar film coating or a "wrap" coating. Particularly, the coating of
30 the present invention is a film coating, a sugar coating or a sugar film coating. In a preferred embodiment of the present invention the coating is a sugar coating or a sugar film coating. The sugar coating may be used with or without a seal coat and/or subcoat.

- 35 With respect to a film coating, the present inventors have found that not all film coatings give the desired stabilizing effect on tibolone tablets. In particular,

fibrolone tablets coated with Eudragit® E PO and Eudragit® L100, which are acrylic polymer-containing coatings used for moisture protection, taste and odor masking and for drug delivery in the jejunum, respectively, showed a higher content of OM38 after storage as compared to uncoated tablets. Accordingly, these film coating should not be used.

As explained in Chapter 46 of Remington (cited above), the major components in any film coating formulation usually consist of a polymer, a plasticizer, a colorant, and a solvent. In accordance with the present invention, a plasticizer and a colorant are optional ingredients and – as stated above – the solvent or vehicle preferably is an aqueous solvent or vehicle or most preferably it is water.

Suitable examples of polymers include cellulose ethers, such as hydroxypropyl cellulose, methylcellulose, and ethylcellulose, and particularly hydroxypropyl methylcellulose. Suitable cellulose ether-containing coating compositions are commercially available under the name of Sepifilm™, Opadry®, and Aquacoat®. Acrylic polymers such as methacrylate and methyl methacrylate copolymers, vinyl polymers such as polyvinyl alcohol and polyvinyl pyrrolidone, gelatin or starches, may also be used. Suitable acrylic polymer-containing coating compositions are commercially available under the name of Eudragit®. Suitable vinyl polymer-containing coating compositions are commercially available under the name of, Opaglos®, Opalux™, and Opadry®. In particular in accordance with the present invention use is made of a cellulose ether, a vinyl polymer or gelatin, more in particular a cellulose ether or a vinyl polymer.

Typical plasticizers include glycerin (or glycerol), propylene glycol, polyethylene glycol, triacetin (or glyceryl triacetate), acetylated monoglyceride, citrate esters (e.g. triethyl citrate), and phthalate esters (e.g. diethyl phthalate). Preferred plasticizers are glycerin or glycerol, propylene glycol, and polyethylene glycol.

As explained in Chapter 46 of Remington (cited above), a sugar coating typically consists of a seal coating or sealing, a subcoating, and a sugar coating. In said latter sugar coating a polymer typically is not present. In accordance with the present invention the seal coating and the subcoating are optional coatings and need not be used in combination with a sugar coating in order to obtain the technical effect of the present invention. In particular, the stabilizing effect on

5

OM38 formation can already be observed in sugar coated tablets without a seal coat and/or subcoat.

The sugar used in a sugar coating typically is sucrose (or saccharose), but other
5 saccharides such as glucose, fructose, and lactose or polyalcohols such as sorbitol, mannitol, and xylitol may also be used in accordance with the present invention. Either one or more sugars may be used in accordance with the invention. Preferably, the sugar comprises sucrose.

10 A sugar film coating is a coating comprising a polymer and a sugar as defined above. For example, the sugar film coating according to US 2002/0044970 makes use of an aqueous sugar coating liquid containing 30-54% by weight of saccharides (preferably sucrose), 2-10% by weight of polyethylene glycol, and 0.2-
15 2% by weight of polyvinyl pyrrolidone, giving rise to a mono-layered sugar coated tablet. JP 2001026534 describes a sugar film coat comprising sucrose, pullulan, and hydroxypropyl methylcellulose. Based on this, a person skilled in the art will find no trouble in making suitable variations in a sugar film coating.

The "wrap" coating according to US 5146730 typically makes use of a water-based
20 gelatin preparation having about 45% by weight of gelatin and about 9% by weight of a plasticizer (glycerin and/or sorbitol). With the method of US 5146730, tablets are enrobed or "wrapped" in a gelatin coating formed by application of respective layers of elastic gelatin film to opposite sides of the tablet. The applied gelatin layers conform tightly to the tablet surface, bond securely to the tablet, and are
25 sealed together in essentially edge-to-edge manner at a seal line which extends around the tablet at a desired place on the tablet. The coating is applied by feeding a tablet into a cavity formed between a pair of dies over two elastic self-adherent films. A tablet, which is enveloped in this manner between the films is finally coated by sealing the films to each other along the lines contiguous to the tablet.
30 Instead of gelatin, (modified) starches, alginates, modified gelatin, acrylates, polyvinyl pyrrolidone, cellulose derivatives both esters and ethers, and polysiloxanes may also be used. The details of this method and of the "wrap" coating composition are described in US 5146730.

35 The coating to be used in accordance with the present invention typically also contains pharmaceutically acceptable auxiliaries such as arabic gum (or acacia),

calcium carbonate, magnesium stearate, talc, china clay, and/or titanium dioxide. Such auxiliaries may be used in conventional quantities if desired. A colorant may also be used if desired.

5 As is known to the person skilled in the art of coating and as exemplified in the examples below, either one or more than one coating layers may be used and if more than one layer is used, the layers may be of the same or different composition. Particularly, in accordance with the present invention a single layer coating is used.

10

If desired, the coated pharmaceutical tablet of the present invention can be subjected to smoothing, polishing or printing as is known in the art.

The pharmaceutical tablets to be used in accordance with the present invention
15 may vary in weight and/or in tibolone content. Particularly, 100 mg tablets containing 2.5 mg of tibolone (i.e. 2.5% by weight) are currently on the market and 65 mg tablets containing 1.25 mg of tibolone (i.e. 1.9% by weight) are currently under investigation. Results on both are provided in the examples given below. The pharmaceutically acceptable carrier may vary in composition and be
20 composed of approx. 10% by weight of starch and approx. 90% by weight of lactose, or contain higher amounts of starch as described in WO 98/47517. In particular, the carrier contains less than 40%, more in particular 10% or less by weight of starch. In a preferred embodiment of the invention, stabilized coated Livial® tablets are provided.

25

The present invention is illustrated by the following Examples.

Example 1

30 Tablets of 65 mg total weight, containing 1.25 mg of tibolone, were prepared from purified tibolone. The latter was obtained according to the method described in WO 00/23460.

A basic granulate, consisting of 10% potato starch and 90% lactose, was manufactured in a Fluid Bed Granulator, using a starch mucilage as binding liquid.

35

Uncoated tibolone tablets

65 mg tablets having the composition: 1.25 mg tibolone, 63.29 mg basic granulate, 0.13 mg ascorbyl palmitate, and 0.33 mg magnesium stearate, were prepared as follows: approximately 10% of the basic granulate was premixed with tibolone and ascorbyl palmitate. After screening the premix through a 250 µm sieve, the rest of the basic granulate was added and mixing was continued. Finally, magnesium stearate was admixed and the final mixture was tableted to tablets with a diameter of 5 mm.

10 Film coating

Tablets prepared as described above were provided with a film coat (1.2 mg per tablet) having the following composition: 0.75 mg hydroxypropyl methyl cellulose E15, 0.15 mg polyethylene glycol 400, 0.11 mg titanium dioxide, and 0.19 mg talc. An aqueous dispersion of the coating excipients was sprayed onto the tablets using standard film coating equipment (Accela Cota™ 24") at a rotation speed of the coating pan of 12.5 rpm, an inlet temperature of approx. 60°C, and an airflow of approx. 300 m³/hour.

Sugar coating I

20 A batch of approx. 16 kg of tablets film coated as described above (now having the function of a seal coat) was further provided with a sugar-containing subcoat, a sugar-containing layering powder, and a sugar coat.

For application of the coats, tablets were added to a sugar coat pan. The rotating pen had a diameter of about 0.7 m and a rotation speed of 42 rpm. Room conditions were 21°C and 46% relative humidity.

A subcoat consisting of an aqueous 60.2 w/w % dispersion of approx. 20% arabic gum and approx. 80% saccharose was added manually to the tablets in the sugar coat pan step by step. After each addition, a total of a few hundred grams of a layering powder consisting of 64.3% talc, 21.4% calcium carbonate, 7.1% saccharose, and 7.1% titanium dioxide was added manually. Between the addition of subcoat and layering powder, the tablets were dried in open air without forced drying. After finalizing the subcoat (subcoat and layering powder approx. 26 mg per tablet), a sugar coat dispersion with the composition indicated in Table 1 was

added in a number of sequential steps and finally the batch of sugar coated tablets was dried (sugar coat approx. 39 mg per tablet).

Table 1

Arabic gum	3.4
Saccharose	43.6
Calcium carbonate	6.7
Talc	10.7
Titanium dioxide	4.7
Polyethylene glycol	0.7
Glucose syrup	0.7
Glycerol 86.5%	0.1
China clay	6.7
Purified water	22.7

5 The amount of the components are provided in weight percentages of the total weight of the composition.

Sugar coating II

A batch of 8 kg of tablets film coated as described above was provided with a
10 sugar coat, but now without a subcoat, as described above.

Tablets prepared and coated as described above were packed in open brown glass bottles and were subjected to the storage condition of 25°C and 60% relative humidity (RH) or 40°C and ambient relative humidity.

15 After six months, the amount of the isomerization degradation product OM38 was measured in the tablets via HPLC analysis as a percentage of the declared amount of fibolone in the tablets. The results are depicted in Table 2.

Table 2

	At 25°C, 60% RH ¹⁾		At 40°C, ambient RH	
	% OM38	SD ²⁾	% OM38	SD ²⁾
Uncoated tablets	2.83	0.02	6.53	0.02
Film coated	2.45	0.03	4.83	0.09
Sugar coated I	2.32	0.02	3.19	0.04
Sugar coated II	2.39	0.01	3.44	0.05

20 ¹⁾ RH is Relative Humidity of the environment.

²⁾ SD is the standard deviation in the mean obtained from three measurements from pooled tablets of 10 tablets per pool.

The results in Table 2 show that the coating of tibolone tablets in accordance with the present invention results in a decrease in the formation of the isomerization degradation product OM38 and thus leads to stabilized tibolone tablets. Sugar coating gave better results than just film coating.

Example 2

10

Sugar coating

A batch of approx. 20 kg of uncoated tablets (65 mg, see Example 1) was provided with a sugar coat.

For application of the coat, tablets were added to a conventional film coat pan equipped with an air bypass (Dumoulin IDA 30 X). The rotating pan had a diameter of about 1 m and a rotation speed of 3 to 5 rpm.

A sugar coat dispersion with the composition indicated in Table 3 was added in a number of sequential steps until a sugar coat of approx. 35 mg per tablet was reached and finally the batch of sugar coated tablets was dried and analysed as described in Example 1. The results after two months of storage are depicted in Table 4.

Table 3

Arabic gum	1.8
Saccharose	59.5
Talc	3.0
Titanium dioxide	0.9
Sunset yellow	0.002
Purified water	34.8
Total	100
Carnauba wax ¹⁾	0.1

¹⁾ Added after the application of the coat to obtain a shiny appearance

The amount of the components are provided in weight percentages of the total weight of the composition.

Film coating II

Tablets prepared as described above were provided with a film coat having the following composition: 5.2 mg Septifilm™ LP770, consisting of hydroxypropyl methylcellulose, stearic acid, and talc. An aqueous dispersion (solids content 8 w/w%) of the coating excipients was sprayed onto the tablets using standard film coating equipment (Glatt® GC300) at a rotation speed of the coating pan of approx. 15 rpm, an inlet temperature of approx. 60°C, and an airflow of approx. 100 m³/hour.

- 10 The tablets were analysed as described in Example 1 and the results after six months of storage are depicted in Table 6.

Table 6

	At 25°C, 60% RH ¹⁾		At 40°C, 40% RH	
	% OM38	SD ²⁾	% OM38	SD ²⁾
Uncoated tablets	4.84	0.08	17.10	0.60
Film coated I	3.57	0.02	10.69	0.14
Film coated II	3.51	0.06	6.77	0.05

¹⁾ RH is Relative Humidity of the environment.

- 15 ²⁾ SD is the standard deviation in the mean obtained from three measurements from pooled tablets of 10 tablets per pool.

The results in Table 6 show that the coating of tibolone tablets in accordance with the present invention results in a decrease in the formation of the isomerization degradation product OM38 and thus leads to stabilized tibolone tablets.

Example 5**Uncoated tibolone tablets**

- 25 65 mg tablets with a diameter of 5 mm having the composition: 0.644 mg tibolone, 63.9 mg basic granulate, 0.13 mg ascorbyl palmitate, and 0.325 mg magnesium stearate, were prepared following the procedure described in Example 1.

Film coating I

- 30 Tablets prepared as described above were provided with 5.2 mg per tablet of a film coat having the following composition: 3.07 mg Eudragit® E PO, 0.31 mg

sodium lauryl sulfate, 0.78 mg stearic acid, and 1.04 mg magnesium stearate. An aqueous dispersion (solids content 16 w/w%) of the coating excipients was sprayed onto the tablets using standard film coating equipment (Glatt® GC300) at a rotation speed of the coating pan of approx. 15 rpm, an inlet temperature of approx. 45°C, and an airflow of approx. 100 m³/hour.

Film coating II

Tablets prepared as described above were provided with 5.2 mg per tablet of a film coat using an aqueous film coat dispersion having the following composition (in w/w% of the total dispersion): 11.1% Eudragit® L 100, 5.6% triethyl citrate, 3.7% 1N NH₃, 74% purified water, and 5.6% talc. The aqueous dispersion was sprayed onto the tablets using standard film coating equipment (Glatt® GC300) at a rotation speed of the coating pan of approx. 20 rpm, an inlet temperature of approx. 45°C, and an airflow of approx. 80 m³/hour.

15

Film coating III

Tablets prepared as described above were provided with 5.2 mg per tablet of a film coat using an aqueous film coat dispersion having the following composition (in w/w% of the total dispersion): 39.2% Eudragit® RL 30D, 2.4% triethyl citrate, 52.5% purified water, and 5.9% talc. The aqueous dispersion was sprayed onto the tablets using standard film coating equipment (Glatt® GC300) at a rotation speed of the coating pan of approx. 15 rpm, an inlet temperature of approx. 45°C, and an airflow of approx. 80 m³/hour.

25 Film coating IV

Tablets prepared as described above were provided with 5.2 mg per tablet of a film coat using an aqueous film coat dispersion having the following composition (in w/w% of the total dispersion): 41.7% Eudragit® NE 30D, 45.8% purified water, and 12.5% talc. The aqueous dispersion was sprayed onto the tablets using standard film coating equipment (Glatt® GC300) at a rotation speed of the coating pan of approx. 20 rpm, an inlet temperature of approx. 45°C, and an airflow of approx. 80 m³/hour.

The tablets were analysed as described in Example 1 and the results after two months of storage are depicted in Table 7.

35

Table 7

	At 25°C, 60% RH ¹⁾		At 40°C, 40% RH	
	% OM38	SD ²⁾	% OM38	SD ²⁾
Uncoated tablets	1.72	0.01	4.27	0.02
Film coated I	2.65	0.03	6.71	0.07
Film coated II	3.05	0.06	8.89	0.33
Film coated III	1.27	0.01	4.06	0.05
Filmcoated IV	1.70	0.02	4.86	0.02

¹⁾ RH is Relative Humidity of the environment.

²⁾ SD is the standard deviation in the mean obtained from three measurements from pooled tablets of 10 tablets per pool.

5

The results in Table 7 show that not all coatings of tibolone tablets result in a decrease in the formation of the isomerization degradation product OM38, in particular when using Eudragit® E PO or Eudragit® L 100 worse results were obtained as compared to uncoated tablets.

10

CLAIMS

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- 30
1. A stabilized pharmaceutical tablet comprising an amount of from 0.1 to 10% by weight of tibolone provided with a coating.
2. A tablet according to claim 1 wherein the coating is a film coating, a sugar coating, a sugar film coating or a "wrap" coating.
3. A tablet according to claim 2 wherein the coating is a sugar coating or a sugar film coating.
4. A tablet according to claim 1 or 2 wherein the film coating contains a cellulose ether, a vinyl polymer or gelatin.
5. A tablet according to claim 3 wherein the sugar comprises sucrose.
6. A tablet according to any one of claims 1-5 wherein the coating contains a plasticizer selected from the group consisting of glycerin, propylene glycol, and polyethylene glycol.
7. Use of a coating for stabilizing a pharmaceutical tablet comprising an amount of from 0.1 to 10% by weight of tibolone.
8. Use according to claim 7 wherein the coating is a film coating, a sugar coating, a sugar film coating or a "wrap" coating.
9. Use according to claim 8 wherein the coating is a sugar coating or a sugar film coating.
10. Use according to claim 9 wherein the sugar comprises sucrose.

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 03/50829

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/36 A61K31/569

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

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

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

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/47517 A (MORITA RYOICHI ;AKZO NOBEL NV (NL); HAAN DE PIETER (NL); LAMBREGTS) 29 October 1998 (1998-10-29) cited in the application page 5, line 14-16; claim 1	1
A	page 1, line 26 - page 2, line 14	1-10
A	WO 00/23460 A (KIRCHHOLTES PETER HUUB GERARD ;SAS GERARD ARNOUD JOZEF MARIA (NL);) 27 April 2000 (2000-04-27) cited in the application page 2, line 1-6; page 3, line 9-15	1-10
A	EP 0 927 556 A (AKZO NOBEL NV) 7 July 1999 (1999-07-07) '0004!	1-10
	-/-	

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

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- "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

2 February 2004

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/50829

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2002/044970 A1 (TAKEUCHI TOSHIO) 18 April 2002 (2002-04-18) cited in the application '0009!	11-3, 5-10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/50829

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/50829

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PCT REQUEST

2002.745_WO

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0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/ROH101 PCT Request	
0-4-1	Prepared using	epoline® online filing PCT plug-in (updated 13.11.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	2002.745 WO
I	Title of invention	COATED PHARMACEUTICAL TABLETS CONTAINING TIBOLONE
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	AKZO NOBEL N.V.
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II-7	State of residence	NL
II-8	Telephone No.	+31 (0) 412 666380
II-9	Facsimile No.	+31 (0) 412 650 592
II-10	e-mail	patent@organon.com
II-11	Applicant's registration No. with the Office	0200751.6

PCT REQUEST

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III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	DE HAAN, Pieter
III-1-5	Address:	N.V. Organon P.O. Box 20 NL-5340 BH Oss Netherlands
III-1-6	State of nationality	NL
III-1-7	State of residence	NL
III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	VAN LARE, Cornelis, Elisabeth, Johannus
III-2-5	Address:	N.V. Organon P.O.Box 20 NL-5340 BH Oss Netherlands
III-2-6	State of nationality	NL
III-2-7	State of residence	NL
IV-1	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
IV-1-1	Name (LAST, First)	VAN DEN BROEK, Ludovicus A.G.M.
IV-1-2	Address:	P.O. BOX 20 NL-5340 BH OSS Netherlands
IV-1-3	Telephone No.	+31 412 66380
IV-1-4	Facsimile No.	+31 412 650592
IV-1-5	e-mail	patent@organon.com
IV-1-6	Agent's registration No.	0098170.4

30

PCT REQUEST

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V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-3	Precautionary Designation Statement In addition to the designations made under Items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under Item V-3 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-4	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	20 November 2002 (20.11.2002)
VI-1-2	Number	60/427,740
VI-1-3	Country	US

PCT REQUEST

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VI-2	Priority claim of earlier regional application		
VI-2-1	Filing date	20 November 2002 (20.11.2002)	
VI-2-2	Number	02079920.1	
VI-2-3	Regional Office	EP	
VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-2	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VII-2	Request to use results of earlier search; reference to that search		
VII-2-1	Date	25 February 2003 (25.02.2003)	
VII-2-2	Number	02079920.1	
VII-2-3	Country (or regional Office)	EP	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	14	2002.745_wo_descr.pdf
IX-3	Claims	1	2002.745_wo_descr.pdf
IX-4	Abstract	1	2002.745_wo_descr.pdf
IX-2b	Pre-conversion archive	-	2002.745.zip
IX-5	Drawings	0	-
IX-7	TOTAL	21	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	-	Fees.PDF
IX-11	Copy of general power of attorney	reference no. 59.6	general_authorization_59.pdf
IX-18	Other (specified):	ADD REPRESENTATIVES	add_sheet_representatives.pdf

5/5

PCT REQUEST

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IX-18	Figure of the drawings which should accompany the abstract	
IX-20	Language of filing of the international application	English

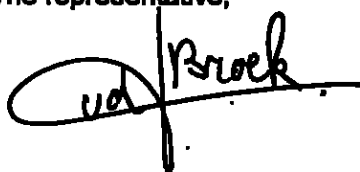
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10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

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------	--	--

The representative,



L.A.G.M van den Broek
Global Patent Department
N.V. Organon

**Power of Attorney
(Concerning a Given International Application)**

**PATENT CO-OPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE**

POWER OF ATTORNEY

The undersigned applicant(s):

DE HAAN,
Pieter
N.V. Organon
P. . Box 20
5340 BH Oss
The Netherlands

VAN LARE,
Cornells, Ellsabeth, Johannes
N.V. Organon
P.O. Box 20
5340 BH Oss
The Netherlands

hereby appoints (appoint) Mr. (Ms., Miss, Mrs.) (Name, address):

H. Kraak

M. Hogenbirk

P.M.G.F. van Wezenbeek

A.M.A. Rovers

L.A.G.M. van den Broek

All residing at:

Postbus 20
5340 BH Oss
The Netherlands

☒ [X] as agent

☐ [] as common representative

to act on his (her, their) behalf before the competent International Authorities in connection with the international application on [title of the invention, applicant's or agent's file reference, if any has been indicated in the request, international application number, if already available]:

Our ref.: 2002.745 WO

International application number : PCT/EP03/50829

Title: "COATED PHARMACEUTICAL TABLETS CONTAINING TIBOLONE"

filed with the [name of the Office]: *EPO*

as receiving Office and to make or receive payments on his (her,their) behalf.

Place.....*Oss*.....

Date:.....*19 - november 2003*.....

Signature of the applicant (where there are several applicants, each of them must sign):

DE HAAN,
Pieter

VAN LARE,
Cornells, Ellsabeth, Johannes

[Type the name under the (each) signature and add, in case of legal persons, an indication of the capacity in which the person signs]

34

**Power of Attorney
(Concerning a Given International Application)**

**PATENT CO-OPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE**

POWER OF ATTORNEY

The undersigned applicant(s):

**DE HAAN,
Pieter
N.V. Organon
P.O. Box 20
5340 BH Oss
The Netherlands**

**VAN LARE,
Cornells, Elisabeth, Johannus
N.V. Organon
P.O. Box 20
5340 BH Oss
The Netherlands**

hereby appoints (appoint) Mr. (Ms., Miss, Mrs.) [Name, address]:

H. Kraak

M. Hogenbirk

P.M.G.F. van Wezenbeek

A.M.A. Rovers

L.A.G.M. van den Broek

All residing at:

*Postbus 20
5340 BH Oss
The Netherlands*

☒ as agent

☐ as common representative

to act on his (her, their) behalf before the competent International Authorities in connection with the international application on [title of the invention, applicant's or agent's file reference, if any has been indicated in the request, international application number, if already available]:

Our ref.: 2002.745 WO

International application number : PCT/EP03/50829

Title: "COATED PHARMACEUTICAL TABLETS CONTAINING TIBOLONE"

filed with the [name of the Office]: *EPO*
as receiving Office and to make or receive payments on his (her, their) behalf.

Place.....

Date:.....19- 11 - 2003.....

Signature of the applicant (where there are several applicants, each of them must sign):

**DE HAAN,
Pieter**

**VAN LARE,
Cornells, Elisabeth, Johannus**

[Type the name under the (each) signature and add, in case of legal persons, an indication of the capacity in which the person signs]

35

1a

ADDITIONAL SHEET

Additional Representatives:

H. Kraak

P.M.G.F. van Wezenbeek

A.M.A. Rovers

M. Hogenblirk

L.A.G.M. van den Broek

All residing at:

**P.O. Box 20
5340 BH OSS
The Netherlands**

All authorized under G.A. No. 59

Bitte übermitteln Sie 3 Blätter 1004.1-3 dem EPA in München, Direktion 5.1.1, und beachten Sie Blatt 1004.4, insbesondere Nr.3 b.
Please forward the 3 sheets 1004.1-3 to the EPO at Munich, Directorate 5.1.1 and pay attention to sheet 1004.4, especially point 3 b.
Veuillez faire parvenir les 3 feuilles 1004.1-3 à l'OEI à Munich, Direction 5.1.1 et de tenir compte de la feuille 1004.4, notamment du point 3 b.

**ALLGEMEINE VOLLMACHT
GENERAL AUTHORISATION
POUVOIR GENERAL**

Nur für amtlichen Gebrauch / For official use only
Cadre réservé à l'administration
Nr. der allgemeinen Vollmacht / General Authorisation No.
N° du pouvoir général

59 (rev.)

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

Alzo Nobel N.V.
Velperweg 78
8824 BM Amhem
The Netherlands

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

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

Address of place of business:
Alzo Nobel N.V.
Intellectual Property Department (Dept. AIP)
P.O. Box 9300
6800 SB Amhem
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 Patentrechts.
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.
Veuillez renvoyer la copie jaune au mandant, munie du n° du pouvoir général.

Ort/Place/Lieu Amhem, the Netherlands

Datum / Date December 4 2002

Unterschrift(en) / Signature(s)

P.C. Schalkwijk
(Holder of Proxy)

P.H. van Deursen
(Holder of Proxy)

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

The form must bear the personal signature(s) of the authorizer(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. 69 (rev.)
Akzo Nobel N.V.
December 4, 2002

Additional representatives:

Address of place of business:

KRAAK, Hajo
HOGENBIRK, Marijke
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Gerardus Franciscus
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PATENT COOPERATION TREATY

09 FEB. 2004

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

JK

To:
VAN DEN BROEK, Ludovicus A. G. M.
P.O. Box 20
NL-5340 BH Oss
NETHERLANDS

Date of mailing
(day/month/year) 10/02/2004

Applicant's or agent's file reference
2002.745_WO

Beentje, d.d.
Aleggen

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/EP 03/50829

International filing date
(day/month/year) 13/11/2003

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 19:
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) 740.14.36

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) 340-3016	Authorized officer Natalia Morancho Alcaine
---	---

NOTES TO FORM PCT/ISA/220

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 19, 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 16 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 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.

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NOTES TO FORM PCT/ISA/220 (continued)

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 19, 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 19 may have to be furnished to the designated/elected Office, 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.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2002.745 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 03/50829	International filing date (day/month/year) 13/11/2003	(Earliest) Priority Date (day/month/year) 20/11/2002
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:

PHARMACEUTICAL TABLETS CONTAINING TIBOLONE AND A COATING

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 36.2(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.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50829

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/36 A61K31/569

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

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

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/47517 A (MORITA RYOICHI ;AKZO NOBEL NV (NL); HAAN DE PIETER (NL); LAMBREGTS) 29 October 1998 (1998-10-29) cited in the application page 5, line 14-16; claim 1	1
A	page 1, line 26 - page 2, line 14	1-10
A	WO 00/23460 A (KIRCHHOLTES PETER HUUB GERARD ;SAS GERARD ARNOUD JOZEF MARIA (NL);) 27 April 2000 (2000-04-27) cited in the application page 2, line 1-6; page 3, line 9-15	1-10
A	EP 0 927 556 A (AKZO NOBEL NV) 7 July 1999 (1999-07-07) '0004!	1-10
	----- -/-	

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

2 February 2004

Date of mailing of the international search report

10/02/2004

Name and mailing address of the ISA

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

Borst, M

43

International Application No
PCT/EP 03/50829

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2002/044970 A1 (TAKEUCHI TOSHIO) 18 April 2002 (2002-04-18) cited in the application '0009!	11-3, 5-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/50829

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9847517	A	29-10-1998	AU 742037 B2 13-12-2001
			AU 8014698 A 13-11-1998
			BR 9809268 A 27-06-2000
			CN 1253503 T 17-05-2000
			WO 9847517 A1 29-10-1998
			EP 0975348 A1 02-02-2000
			HU 0001780 A2 28-12-2000
			ID 22763 A 09-12-1999
			JP 10316573 A 02-12-1998
			NO 995127 A 21-10-1999
			NZ 338028 A 26-10-2001
			PL 336658 A1 03-07-2000
			RU 2207133 C2 27-06-2003
			TR 9902530 T2 22-05-2000
			US 6514958 B1 04-02-2003
			US 2003119801 A1 26-06-2003
			US 2001005513 A1 28-06-2001
			ZA 9803169 A 20-10-1998
WO 0023460	A	27-04-2000	AT 239032 T 15-05-2003
			AU 763232 B2 17-07-2003
			AU 6202999 A 08-05-2000
			BR 9914441 A 26-06-2001
			CA 2344686 A1 27-04-2000
			CN 1322210 T 14-11-2001
			CZ 20010976 A3 15-08-2001
			DE 69907495 D1 05-06-2003
			DK 1121375 T3 04-08-2003
			WO 0023460 A1 27-04-2000
			EP 1275379 A2 15-01-2003
			EP 1121375 A1 08-08-2001
			HK 1039620 A1 22-08-2003
			HU 0104206 A2 29-04-2002
			ID 28463 A 24-05-2001
			JP 2002527525 T 27-08-2002
			NO 20011664 A 03-04-2001
			NZ 510501 A 31-10-2003
			PL 347264 A1 25-03-2002
			PT 1121375 T 31-07-2003
			SK 4932001 A3 03-12-2001
			TR 200101083 T2 21-08-2001
			ZA 200101952 A 10-06-2002
EP 0927556	A	07-07-1999	EP 0927556 A1 07-07-1999
			AT 195871 T 15-09-2000
			AU 738996 B2 04-10-2001
			AU 1147099 A 12-04-1999
			CA 2304331 A1 01-04-1999
			CN 1271286 T 25-10-2000
			DE 69702985 D1 05-10-2000
			DE 69702985 T2 15-02-2001
			DK 927556 T3 20-11-2000
			WO 9915180 A1 01-04-1999
			ES 2152065 T3 16-01-2001
			GR 3034842 T3 28-02-2001
			HK 1019048 A1 29-12-2000
			ID 24436 A 20-07-2000
			JP 2001517629 T 09-10-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/50829

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0927556	A		NO 20001474 A	22-03-2000
			NZ 503400 A	30-11-2001
			PT 927556 T	29-12-2000
US 2002044970	A1	18-04-2002	JP 2002068965 A	08-03-2002
			CA 2336432 A1	28-02-2002

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

IPEA/EPO

PCT

CHAPTER II

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 and hereby elects all eligible States (except where otherwise indicated).

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 2002.745 WO	
International application No. PCT/EP03/50829	International filing date (day/month/year) 13-11-2003 (Earliest) Priority date (day/month/year) 20-11-2002
Title of invention COATED PHARMACEUTICAL TABLETS CONTAINING TIBOLONE	
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. Applicant's registration No. with the Office	
State (that is, country) of nationality: NL	State (that is, 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.) DE HAAN, Pieter N.V. Organon P.O. Box 20 NL-5340 BH OSS The Netherlands	
State (that is, country) of nationality: NL	State (that is, 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.) VAN LARE, Cornelis, Elisabeth, Johannus N.V. Organon P.O. Box 20 NL-5340 BH OSS The Netherlands	
State (that is, country) of nationality: NL	State (that is, country) of residence: NL
☐ Further applicants are indicated on a continuation sheet.	

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ 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.)*L.A.G.M. van den Broek
P.O. BOX 20
5340 BH OSS
THE NETHERLANDS

Telephone No.

0412-668456

Facsimile No.

0412-650592

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

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

Language for the purposes of international preliminary examination:

☐ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**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)*

excluding the following States which the applicant wishes not to elect:

Sheet No. 3.

International application No.
PCT/EP03/50829

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

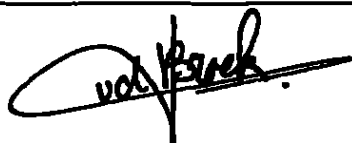
- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

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

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (specify): |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

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).



L.A.G.M. van den Broek

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

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

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

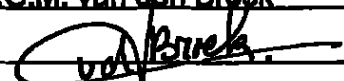
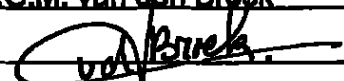
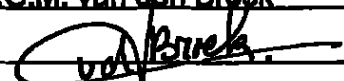
Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">International application No.</td> <td>PCT/EP03/50829</td> </tr> <tr> <td>Applicant's or agent's file reference</td> <td>2002.745 WO</td> </tr> </table>	International application No.	PCT/EP03/50829	Applicant's or agent's file reference	2002.745 WO	For International Preliminary Examining Authority use only				
International application No.	PCT/EP03/50829								
Applicant's or agent's file reference	2002.745 WO								
Applicant AKZO NOBEL N.V.									
CALCULATION OF PRESCRIBED FEES <table style="width: 100%;"> <tr> <td style="width: 50%;">1. Preliminary examination fee</td> <td style="width: 50%; text-align: right;">EURO 1530 P</td> </tr> <tr> <td>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>)</td> <td style="text-align: right;">EURO 159 H</td> </tr> <tr> <td>3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box</td> <td style="text-align: right;">EURO 1689</td> </tr> <tr> <td></td> <td style="text-align: center; border: 1px solid black;">TOTAL</td> </tr> </table>		1. Preliminary examination fee	EURO 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>)	EURO 159 H	3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EURO 1689		TOTAL
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	TOTAL								
MODE 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):								
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs) <table style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> ☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. </td> <td style="width: 50%; vertical-align: top;"> IPEA/ <u>EPO</u> Deposit Account No.: <u>2809 0012</u> Date: <u>05-02-2004</u> Name: <u>L.A.G.M. van den Broek</u> Signature: <u></u> </td> </tr> </table>		☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ <u>EPO</u> Deposit Account No.: <u>2809 0012</u> Date: <u>05-02-2004</u> Name: <u>L.A.G.M. van den Broek</u> Signature: <u></u>						
☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ <u>EPO</u> Deposit Account No.: <u>2809 0012</u> Date: <u>05-02-2004</u> Name: <u>L.A.G.M. van den Broek</u> Signature: <u></u>								

SD

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

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

To:

VAN DEN BROEK, Ludovicus A. G. M.
P.O. Box 20
NL-5340 BH Oss
PAYS-BAS

Date of mailing
(day/month/year)

07.03.2005

Applicant's or agent's file reference
2002.745 WO *Allegger*

IMPORTANT NOTIFICATION

International application No.
PCT/EP 0350829

International filing date (day/month/year)
13.11.2003

Priority date (day/month/year)
20.11.2002

Applicant
AKZO NOBEL N.V. et al.

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

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

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

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

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
D-80298 Munich
Tel. +49 89 23699 - 0 Tx: 523656 epmu d
Fax: +49 89 23699 - 4465

Authorized Officer

Senkel, H

Tel. +49 89 23699-5071



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

Applicant's or agent's file reference 2002.745 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/50829	International filing date (day/month/year) 13.11.2003	Priority date (day/month/year) 20.11.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/38		
Applicant AKZO NOBEL N.V. et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 6 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 09.02.2004	Date of completion of this report 07.03.2005	
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tlx 523656 epmu d Fax +49 89 2399 - 4465	Authorized Officer Borst, M Telephone No. +49 89 2399-8648	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50829

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

1-14 as originally filed

Claims, Numbers

1-10 as originally filed

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

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

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

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

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

4. The amendments have resulted in the cancellation of:

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

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

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

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/50829**

**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	2-10
	No: Claims	1
Inventive step (IS)	Yes: Claims	3-5,9,10
	No: Claims	1,2,6-8
Industrial applicability (IA)	Yes: Claims	1-10
	No: Claims	

2. Citations and explanations

see separate sheet

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/50829

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

- D1: WO-A-9847517 (AKZO NOBEL N.V.) 29 October 1998 (1998-10-29)**
D2: WO 00/23460 A (KIRCHHOLTES PETER HUUB GERARD ;SAS GERARD ARNOUD JOZEF MARIA (NL);) 27 April 2000 (2000-04-27)
D3: EP-A-0 927 556 (AKZO NOBEL NV) 7 July 1999 (1999-07-07)
D4: US 2002/044970 A1 (TAKEUCHI TOSHIO) 18 April 2002 (2002-04-18)

1. Novelty (Article 33(2) PCT)

The subject-matter of present claim 1 is not new in the light of D1.

D1 (claim 1) discloses pharmaceutical dosage units comprising 0.1 to 10% by weight of tibolone. According to D1 (page 5, line 14-16) the dosage unit can take the form of tablet provided with a film coat. Thus, the subject-matter of claim 1 on file can be arrived at after one selection only.

Lack of novelty occurs when the subject-matter on file can be derived directly and unambiguously from the prior art document. This is the case for D1, from the disclosure of which a film-coated tablet comprising 0.1 to 10% by weight of tibolone can be directly and unambiguously derived. It is not necessary for being pertinent to novelty that the relevant disclosure is in the form of working examples or already marketed products.

Moreover, the term "stabilized" as used in claim 1 is a relative term and cannot be used for establishing novelty as long as the claim fails to define a reference point or the structural features providing the stabilisation. In fact the particular definition given to the term "coating" (cf. page 3, line 8-10) is not part of the claims. Once this is the case, it appears that a tablet comprising an amount of from 0.1 to 10% by weight tibolone and provided with a coating which achieves a stabilizing effect with respect to the formation of OM38 upon storage of a coated tablet as compared to an uncoated tablet cannot be derived from D1. D1 only in a general way discloses coated tablets. As is apparent from the experimental data on file (table 7) not any coating provides the stabilizing effect.

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

The subject-matter of claims 1-10 does not involve an inventive step, since the

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/50829

problem posed is not solved for whole range of the claim.

The problem to be solved according to the present application (page 1, line 31-36) is to reduce degradation of tibolone in dosage forms. By comparison to uncoated tablet cores containing tibolone the applicant has shown (cf. examples) that said problem can be solved by the provision of the following film coatings:

HPMC coat

HPMC coat + sucrose subcoat + sucrose topcoat

HPMC coat + sucrose topcoat

sucrose coat

PVA coat

Eudragit RL 30 D

For the claims on file the results of these experiments have been generalised to *any* kind of tablet core and to *any* kind of coating applied. However, it has been stated in the application (cf. page 3, line 35ff and example 5) that not all film coatings give the desired stabilizing effect on tibolone tablets. Moreover, it has been shown that the above problem is not solved by the provision of the following film coatings:

Eudragit E PO

Eudragit L 100

Eudragit NE 30 D

Thus, the alleged effect of stabilising tibolone is not provided by all variants covered by the claims. The technical problem not being solved over the whole scope of the claims, inventive step cannot be acknowledged.

Due to the relative character of the term "stabilized" the claims are not restricted to those embodiments which actually provide a stabilisation in comparison to uncoated tablets. As already pointed out the particular definition given to the term "coating" (cf. page 3, line 8-10) is not part of the claims.

In view of 6 coatings that work versus 3 coatings that do not work, incorporating said definition into the claims and, thereby, restricting the claims to those coatings that "achieve a stabilizing effect with respect to the formation of OM38 upon storage of a coated tablet as compared to an uncoated tablet", would amount to claiming the underlying problem (Article 6 PCT). Therefore, for establishing inventive step, either further experimental data showing that the failure experienced with Eudragit E PO, Eudragit L 100, Eudragit NE 30 D is only exceptional, or restriction to those embodiments that actually work (page 4, line 22-24; claims 3-5, 9, 10) would be required.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/50829

This being the case, the requirements of inventive step appear to be met: D1 (page 1, line 26 - page 2, line 14) and D2 (page 2, line 1-6; page 3, line 9-15) both deal with the degradation of tibolone. According to D1 said drawback can be overcome by increasing the amount of starch in the carrier. D2 tends to achieve the same result by aging tibolone crystals in water for at least 24 hours. The objective technical problem to be solved in the light of the closest prior art D1 or D2 is to provide an alternative solution for minimising the degradation of tibolone in dosage forms, such as tablets. None of the prior art documents available suggests a tablet coating for solving said problem. D3 ([0004]) proposes to apply a coating, however not for the purpose of reducing degradation of the steroids, but for the purpose of inhibiting migration of the steroids from the tablet core.

TABLETAS FARMACEUTICAS QUE CONTIENEN TIBOLONA Y UN RECUBRIMIENTO

La presente invención se relaciona con una tableta farmacéutica que comprende una cantidad de 0.1 % a 10% en peso de tibolona.

Los compuestos que incluyen tibolona, el nombre químico es (7 α , 17 α)-17-hidroxi-7-metil-19-nor-17-pregn-5(10)-en-20-yn-3-uno (también denominado como Org OD14) y un vehículo sólido farmacéuticamente aceptable han sido descritas en EP 389 035.

Una formulación conocida de tibolona es una tableta de 100 mg que tiene 2.5 mg de tibolona allí contenida, una cantidad relativamente pequeña (por ejemplo, 1 % en peso) de auxiliares farmacéuticamente aceptables, y un vehículo que conforma el cuerpo de la tableta. El vehículo esta típicamente compuesto de aproximadamente un 10% en peso de almidón, por ejemplo, almidón de papa, y aproximadamente 90% en peso de lactosa. Tabletas de 100 mg que contiene 2.5 mg de tibolona están disponibles a la práctica médica bajo el nombre de Livial®.

Luego de almacenamiento de largo plazo, en las tabletas que contienen tibolona aparecen productos de degradación. El mayor producto de degradación es (7 α , 17 α)-17-hidroxi-7-metil-19-nor-17-pregn-4-en-20-yn-3-uno (Org OM 38). OM 38 es diferente de la tibolona en que el doble enlace en el esqueleto esteroide esta localizado entre las posiciones 5 y 10. Este producto de isomerización se identifica como una impureza mayor en tibolona y en las tabletas que contienen tibolona y limita (a un máximo del 5 % en peso de OM38) el tiempo de expiración de las actualmente disponibles tabletas de Livial® a un máximo de dos años. Una considerable ventaja es alcanzada prolongando el tiempo de expiración de la tabletas que contienen tibolona. Es en consecuencia ventajoso encontrar medios para reducir la formación de OM38 y para proveer tabletas

de tibolona mas estables en relación con la cantidad de OM38 que se forma después de almacenamiento.

El problema de reducir la formación de OM38 en tibolona y en los productos que contienen tibolona fue abordado antes en WO 00/23460, proveyendo tibolona de alta pureza que contiene menos del .5% en peso de =M38, y en WO 98/47517, proveyendo un compuesto que contiene tibolona y un vehículo farmacéuticamente aceptable, tal vehículo con un alto contenido de almidón, por ejemplo, mas del 10% preferiblemente al menos 40 % en peso. A pesar de estas contribuciones al arte, hay todavía una necesidad para mejorar mas el tiempo de expiración de las tabletas de tibolona y por alternativas a las soluciones presentadas en WO 00/23460 y WO 98/47517.

De acuerdo con la presente invención, una tableta farmacéuticamente estabilizada que incluye una cantidad de 0.1 a 10 % en peso de tibolona proveída de un recubrimiento se hace disponible por primera vez. Sorprendentemente, tal tableta tiene un mas bajo contenido de OM38 despajes del almacenamiento, en particular después de varios meses en almacenamiento, y en comparación con una tableta similar sin el recubrimiento. Es inesperado que un recubrimiento reduzca la formación del producto de degradación por isomerización derivado de la tibolona, OM 38

La presente invención reside además en el inesperado nuevo uso de un recubrimiento para estabilizar una tableta farmacéutica que comprende una cantidad de 0.1 a 10 % en peso de tibolona.

En el contexto de la presente invención con el término " estabilizado" se significa " estabilizado con respecto a la formación de OM 38 una vez almacenada ". Por lo tanto, el recubrimiento de las tabletas que contienen tibolona sirven para reducir la formación de OM38 en comparación a tabletas no recubiertas. Mas aún, en el contexto de la

presente invención el término " tabletas " se utiliza para referir a " formas de dosificación sólidas " que pueden ser técnicamente proveídas con un recubrimiento que típicamente son utilizadas para administración oral. Así, aparte de comprimidos o tabletas moldeadas, polvos, granulos, grageas, y cápsulas están también comprendidas en el término " tabletas " . Tabletas comprimidas, sin embargo, son la formas mas frecuentemente usadas de dosis sólidas.

Incidentalmente, en WO 98/47517 se hace referencia a proveer tabletas de tibolona con una película de recubrimiento si se requiere (ver pagina 5, renglones 14-16) . Las tabletas hechas de acuerdo con WO 98/47517 hacen uso de un vehículo farmacéuticamente aceptable que contiene mas del 10 % preferiblemente al menos 40% en peso de almidón. En este documento, no enseñanzas ni sugerencias son hechas con respecto a los efectos técnicos de un recubrimiento en la formación de OM 38 durante el almacenamiento de las tabletas que contienen tibolona. Las tabletas de tibolona estabilizadas por la aplicación de un recubrimiento no son descubiertas ni ejemplarizadas en este documento. Con respecto a las palabras " si se requiere " en el región 14 debe ser notado que las tabletas de Livial® que actualmente están en el mercado ni están recubiertas , ni requieren un recubrimiento a la luz de razones típicas para recubrir tabletas farmacéuticas (tomado de Remington, página 894, citadas abajo), por ejemplo, proteger la droga de su entorno ambiental (particularmente aire, humedad, y luz), enmascarar un sabor u olor desagradable, incrementar la facilidad con que el producto puede ser ingestado por el paciente, mejorar la identidad del producto, facilitar manipulación, mejorar la apariencia del producto, reducir el riesgo de interacción entre componentes incompatibles, mejorar la integridad mecánica del producto y modificar la liberación de la droga. Mas aún, WO 98/47517 solo menciona un película de recubrimiento y no hace referencia a ningún otro tipo de recubrimiento.

En el contexto de la presente invención con " recubrimiento " se significa cualquier recubrimiento que logra un efecto estabilizante con respecto a la formación de OM38 durante almacenamiento de la tableta recubierta en comparación con la tableta no recubierta. Si un recubrimiento alcanza o no un efecto estabilizante puede ser fácilmente determinado por un habilidoso en el arte sobre la base de la presente especificación . La cantidad de OM38 presente en una tableta es determinada vía análisis de HPLC en una manera convencional.

Ejemplos adecuados de recubrimientos que pueden ser usados de acuerdo con la presente invención incluye una película de recubrimiento, un recubrimiento de azúcar, una película de recubrimiento de azúcar, por ejemplo, una película de recubrimiento de azúcar de acuerdo con US 2002/0044970, y un recubrimiento " empaque" de acuerdo a la US 5146730. La composición de estos recubrimientos y de los métodos y equipos por los cuales son aplicados sobre las tabletas son bien conocidos a una persona habilidosa en el arte y ellos son descritos, por ejemplo, por Stuart C. Potter en el Capítulo 46: Coating of pharmaceutical dosage forms in Remington: The Science and Practice of Pharmacy; 20 th ed., 2000; Alfonso R. Gennaro, Editor, Lippincott William & Wilkins; Baltimore, USA, así como en US 2002/0044970 y en US 5146730. Preferencia es dada a las composiciones de recubrimiento acuosas, incluyendo mezclas de agua y un solvente orgánico tal como un alcohol. Mas preferiblemente son usadas las composiciones de recubrimiento que contienen agua como el único solvente o vehículo.

En particular, el recubrimiento a ser usado de acuerdo con la presente invención es un recubrimiento de azúcar, una película de recubrimiento de azúcar o un recubrimiento de " empaque ". Particularmente, el recubrimiento de la presente invención es una película de recubrimiento, un recubrimiento de azúcar y una película de recubrimiento de azúcar . En una incorporación preferida de la presente invención el recubrimiento es un

recubrimiento de azúcar o una película de recubrimiento de azúcar. El recubrimiento de azúcar puede ser usado con o sin un recubrimiento y/o subrecubrimiento de sello.

Con respecto a una película de recubrimiento, los inventores han encontrado que no todos las películas de recubrimiento dan el efecto estabilizante deseado en las tabletas de tibolona. En particular, las tabletas de tibolona cubiertas con Eudragit® E PO y Eudragit® L100, los cuales son recubrimientos que contienen polímeros acrílicos usados para protección de la humedad, enmascarar gusto y olor y para entrega de la droga en el yeyuno, respectivamente, mostraron un mas alto contenido de OM38 después de almacenamiento en comparación a tabletas no recubiertas. En consecuencia, estas películas de recubrimiento no deben ser usadas.

Como se explica en el capítulo 46 de Remington (citado arriba) los componentes principales en cualquier formulación de una película de recubrimiento consisten usualmente en un polímero , un plastificante, un colorante y un solventes. De acuerdo con la presente invención, un plastificante y un colorante son ingredientes opcionales y – como se estableció arriba- el solvente o vehículo es preferiblemente un solvente o vehículo acuoso o mas preferiblemente es agua.

Ejemplos adecuados de polímeros incluyen eters de celulosa, tales como celulosa de hidroxipropil, metilcelulosa, y etilcelulosa, y particularmente hidroxipropil metilcelulosa. Compuestos de recubrimiento adecuados que contengan éter celulosa son comercialmente disponibles bajo el nombre de Sepifilm™ Opadry®, y Aquacoat®. Polímeros de acrílico tales como metacrilato y copolímeros de metil metacrilato, polímeros de vinilo tales como alcohol de polivinilo y pirrolidona de polivinilo, gelatina o almidones, pueden también ser usado. Compuestos de recubrimiento adecuados que contienen polímeros de acrílico están disponible comercialmente bajo el nombre de Eudragit®. Compuestos de recubrimiento adecuados que contienen polímeros de vinilo

están disponible comercialmente bajo el nombre de Opaglos®, Opalux™ y Opadry®. En particular de acuerdo con la presente invención se hace uso de un éter de celulosa, un polímero de vinilo o gelatina, mas en particular un éter de celulosa o un polímero de vinilo.

Los plastificantes típicos incluyen glicerina (o glicol), propileno glicol, polietileno glicol, triacetina (o gliceril triacetato), monoglicerido acetilado, esteres de citrato (por ejemplo, trietil citrato), y esteres de fatalato (por ejemplo. dietil fatalato) . Los plastificantes preferidos son glicerina o glicerol, propileno glicol, y polietileno glicol.

Como se explica en el capítulo 26 de Remington (citado arriba), un recubrimiento ad bazucar consiste típicamente en un recubrimiento de sello o sello, un subrecubrimiento y un recubrimiento de azúcar. En el último recubrimiento de azúcar mencionado no esta presente un polímero típicamente. De acuerdo con la presente invención el sello de cubrimiento y el subrecubrimiento son recubrimientos opcionales y no necesitan ser utilizados con un recubrimiento de azúcar para obtener los efectos técnicos de la presente invención. En particular, el efecto estabilizante sobre la formación de OM38 puede ser ya observado en tabletas recubiertas de azúcar sin un recubrimiento y/o subrecubrimiento de sello.

El azúcar usado en recubrimientos de azúcar es típicamente sucrosa (o sacarosa), pero otros sacáridos tales como glucosa, fructuosa, y lactosa o polialcoholes tales como sorbitol, manitol, y xilitol pueden ser usados de acuerdo con la presente invención. O uno o mas azucares pueden ser usado de acuerdo con la invención. Preferiblemente, el azúcar comprende sucrosa.

Una película de recubrimiento de azúcar es un recubrimiento que comprende un polímero y un azúcar como se definió arriba. Por ejemplo, la película de recubrimiento

de azúcar de acuerdo a US 2002/0044970 hace uso de un líquido de recubrimiento de azúcar acuoso que contiene 30-54% en peso de sacáridos (preferiblemente sucrosa), 2-10% en peso de polietileno glicol, y 0.2-2 % en peso de pirrolidona de polivinilo, lo que da lugar a una tableta con un recubrimiento de azúcar monocapa. JP 2001026534 describe una película de recubrimiento que comprende sucrosa, pullulan y hidroxipropil metilcelulosa. Basado en esto, una persona habilidosa en el arte no encontrará problema en hacer variaciones adecuadas en la película de recubrimiento de azúcar.

El recubrimiento de "empaquetado" de acuerdo a US 5146730 hace uso típicamente de una preparación de gelatina basada en agua que tiene cerca del 45 % en peso de gelatina y cerca del 9% en peso de un plastificador (glicerina y/o sorbitol). Con el método de US 5146730, las tabletas son envueltas o "empacadas" en un recubrimiento de gelatina formado por la aplicación de capas respectivas de película de gelatina elástica en los lados opuestos de la tableta. Las capas de gelatina aplicadas se acomodan ajustadamente sobre la superficie de la tableta, pegándose en forma segura a la tableta y son selladas entre sí en una manera borde a borde en una línea de sellado que se extiende alrededor de la tableta en el lugar deseado sobre la tableta. El recubrimiento es aplicado mediante la alimentación de la tableta dentro de una cavidad formada entre un par de cuñas sobre dos películas auto adherentes elásticas. Una tableta, que es envuelta en esta manera entre películas es finalmente cubierta por sellado de las películas entre sí a lo largo de líneas contiguas a la tableta. A cambio de gelatina, almidones (modificados), alginatos, gelatinas modificadas, acrilatos, pirrolidona de polivinilo, derivados de la celulosa ambos ésteres o éteres y polisiloxanos pueden también ser usados. Los detalles de este método y de la composición de los recubrimientos de "empaquetado" son descritos en US 5146730.

El recubrimiento a ser usado de acuerdo con la presente invención contiene también típicamente auxiliares farmacéuticos aceptables tales como goma arábiga (o acacia),

carbonato de calcio, estereato de magnesio, talco, arcilla caolinita, y/o dióxido de titanio. Tales auxiliares pueden ser usados en cantidades convencionales si se desea. Un colorante puede también ser usado si se desea.

Como es conocido para una persona habilidosa en el arte el recubrimiento como se ejemplariza en lo ejemplos de abajo, o una o mas de una capa de recubrimiento pueden ser usadas y si mas de una capa es usada, las capas pueden ser de la misma o de diferente composición. Particularmente, de acuerdo con la presente invención una sola capa de recubrimiento es usada.

Si se desea, la tableta farmacéutica recubierta de la presente invención, puede ser sometida a suavizado, brillado o impresión como es conocido en el arte.

Las tabletas farmacéuticas a ser usadas de acuerdo a la presente invención pueden variar en peso y/o en contenido de tibolona. Particularmente, tabletas de 100 mg que contienen 2.5 mg de tibolona (equivalente a 2.5 % en peso) están actualmente en el mercado y tabletas de 65 mg que contienen 1.25 mg de tibolona (equivalente a 1.9 % en peso) están actualmente en investigación. Resultados sobre ambas son suministrados en los ejemplos dados mas adelante. El vehículo farmacéuticamente aceptable puede variar en composición y esta compuesto aproximadamente de 10 % en peso de almidón, 90 % en peso de lactosa, o contiene mayores cantidades de almidón como se describe en WO 98/47517. En particular, el vehículo contiene menos del 40% en particular 10% o menos en peso de almidón. En una incorporación preferida de la presente invención, tabletas de Livial® estabilizadas son proveídas.

La presente invención es ilustrada por los siguientes ejemplos:

Ejemplo 1

Tabletas de 65 mg de peso total, que contiene 1.25 mg de tibolona, fueron preparadas de tibolona purificada. Esta última fue obtenida de acuerdo al método descrito en WO 00/23460.

Un granulado básico, consistente de 10% de almidón de papa y 90 % de lactosa fue manufacturado en un granulador de cama fluida , usando un almidón viscoso como fluido aglutinante.

Tabletas no recubiertas de tibolona.

Tabletas de 65 mg que tienen la composición: 1.25 mg de tibolona, 63.29 mg de granulado básico, 0.13 mg de palmitato de ascorbil, y 0.33 mg de estereato de magnesio fueron preparadas como sigue: aproximadamente 10 % del granulado básico fueron premezclados con tibolona y palmitato de ascorbil. Después de tamizar a través de una malla de 250 μ m, el resto del granulado básico fue adicionado y el mezclado fue continuado. Finalmente, el estereato de magnesio fue adicionado y mezclado y la mezcla final fue llevada a tabletas con un diámetro de 5 mm.

Película de recubrimiento.

Las tabletas preparadas como se describió arriba fueron proveídas con una película de recubrimiento (1.3 mg por tabletas) con la siguiente composición: 0.75 mg de celulosa de hidroxipropil metil E15, 0.15 mg de polietileno glicol 400, 0.11 mg de dióxido de titanio, y 0.19 mg de talco. Una dispersión acuosa de los excipientes de recubrimiento fue rociada sobre las tabletas usando equipo estándar de recubrimiento con película (Accela Cota™ 24") a una velocidad de rotación de la paila de recubrimiento de 12.5 rpm, una temperatura de entrada de aproximadamente 60 °C, y una corriente de aire de aproximadamente . 300 m³/hora.

Recubrimiento de Azúcar I

Una cochada de aproximadamente 16 kg. de tabletas recubiertas con película como se describió arriba (ahora teniendo la función de un recubrimiento de sello) fue proveída adicionalmente con un subrecubrimiento conteniendo azúcar, una capa de polvo conteniendo azúcar, y un recubrimiento de azúcar.

Para la aplicación de los recubrimientos, las tabletas fueron colocadas en una paila para recubrimiento de azúcar. La paila rotatoria tenía un diámetro de cerca de 0.7 m y una velocidad de rotación de 42 rpm. Las condiciones ambientales fueron 21 °C y una humedad relativa del 46%.

Un subrecubrimiento que consiste en una dispersión acuosa 60.2 % w/w se aproximadamente 20% de goma arábica y aproximadamente 80 % de sacarosa fue adicionado manualmente a las tabletas en la paila de recubrimiento de azúcar, paso por paso. Después de cada adición, un total de unos pocos cientos de gramos de una capa de polvo consistente de 64.3 % de talco, 21.4 % de carbonato de calcio, 7.1 % de sacarosa, y 7.1 % de dióxido de titanio fue adicionada manualmente. Entre la adición del subrecubrimiento y la capa de polvo, las tabletas fueron secadas al aire abierto sin secado forzado. Después de terminar el subrecubrimiento (subrecubrimiento y capa de polvo aproximadamente 26 mg por tableta), una dispersión de recubrimiento de azúcar con la composición indicada en la Tabla 1 fue adicionada en una serie de pasos secuenciales y finalmente la cochada de tabletas recubiertas de azúcar fue secada (recubrimiento de azúcar aproximadamente 39 mg por tableta)

Tabla 1

Goma arabiga	3.4
Sacarosa	43.6
Carbonato de Calcio	6.7
Talco	10.7
Dioxido de Titanio	4.7
Polietileno Glicol	0.7
Jarabe de Glucosa	0.7
Glicerol 86.5%	0.1
Caolinita	6.7
Agua purificada	22.7

La cantidad de los componentes es proveída en porcentajes en peso del peso total de la composición.

Recubrimiento de Azúcar II

Una cochada de 8 kg de tabletas recubiertas de película como se describió arriba fueron proveídas con un recubrimiento de azúcar, pero ahora sin subrecubrimiento, como se describió arriba.

Las tabletas preparadas y recubiertas como se describió arriba fueron colocadas en botellas de vidrio café abiertas y sometidas a una condición de almacenamiento de 25 °C y 60 % de humedad relativa (RH) o 40 °C y la humedad relativa del ambiente.

Después de seis meses, la cantidad de producto de degradación por isomerización OM38 fue medido en la tabletas vía análisis HPLC como un porcentaje de la cantidad declarada de tibolona en las tabletas. Los resultados son reseñados en la Tabla 2.

Tabla 2.

	A 25 °C y 60 % RH ¹⁾		A 40 °C y RH ambiental	
	% OM38	SD ²⁾	% OM38	SD ²⁾
Tabletas no recubiertas	2.83	0.02	6.53	0.02
Recubiertas de película	2.45	0.03	4.83	0.09
Recubrimiento de Azúcar I	2.32	0.02	3.19	0.04
Recubrimiento de Azúcar II	2.39	0.01	3.44	0.05

¹⁾ RH es humedad relativa del ambiente

²⁾ SD es la desviación estándar en la media obtenida de tres mediciones de tabletas agrupadas, 10 tabletas por grupo.

Los resultados en la tabla 2 muestran que el recubrimiento de tabletas de tibolona de acuerdo con la presente invención resulta en una disminución en la formación del producto de degradación por isomerización OM38 y en consecuencia conduce a tabletas de tibolona estabilizadas. Los recubrimientos de azúcar dieron mejores resultados que los simples recubrimientos de película.

Ejemplo 2

Recubrimiento de Azúcar

Una cochasa de aproximadamente 20 kg de tabletas no recubiertas (65 mg, ver Ejemplo 1) fue proveída con un recubrimiento de azúcar.

Para la aplicación del recubrimiento, las tabletas fueron colocadas en una paila de recubrimiento de película convencional equipado con un bypass de aire (Dumoulin IDA 30X). La paila rotativa tenía un diámetro de cerca de 1 m y una velocidad de rotación de 3 a 5 rpm.

Una dispersión de recubrimiento de azúcar con la composición indicada en la tabla 3 fue adicionada en un número de pasos secuenciales hasta que un recubrimiento de aproximadamente 35 mg. por tableta fue alcanzado y finalmente la cochada de tabletas

recubiertas de azúcar fue secada y analizada como se describió en el ejemplo 1. Los resultados después de dos meses de almacenamiento son registrados en la Tabla 4.

Tabla 3

Goma arábica	1.8
Sacarosa	59.5
Talco	3.0
Dióxido de Titanio	0.9
Amarillo puesta del sol	0.002
Agua purificada	34.8
Total	100
Cera de carnauba ¹⁾	0.1

¹⁾ Adicionada después de la aplicación del recubrimiento para obtener una apariencia brillante

La cantidad de los componentes son proveldos en porcentajes en peso del peso total de la composición.

Tabla 4

	A 40 °C y RH ambiental	
	% OM38	SD ¹⁾
Tabletas no recubiertas	2.65	0.09
Recubiertas de Azúcar	1.66	0.02

¹⁾ SD es la desviación estándar en la media obtenida de tres mediciones de tabletas agrupadas, 10 tabletas por grupo

Los resultados en la tabla 4 muestran que las tabletas de tibolona recubiertas de acuerdo con la presente invención resultan en un decrecimiento en la formación del producto de degradación de isomerización OM38 y así conduce a tabletas de tibolona estabilizadas.

Ejemplo 3

Tabletas de 100 mg de peso total, que contienen 2.5 mg. de tibolona, fueron preparadas siguiendo el procedimiento descrito en el Ejemplo 1.

Tabletas de tibolona no recubiertas

Tabletas de 100 mg con un diámetro de 6 mm que tienen una composición de Tabletas de 65 mg que tienen la composición: 2.5 mg de tibolona, 96.8 mg de granulado básico, 0.2 mg de palmitato de ascorbil, y 0.5 mg de estereato de magnesio fueron preparadas como se describió en el ejemplo 1.

Película de recubrimiento

Tabletas preparadas como se describió arriba fueron proveídas con una capa de recubrimiento (1.51 mg por tableta) que tienen la siguiente composición: 0.94 mg de celulosa de hidroxipropil metil E15, 0.19 mg de polietileno glicol 400, 0.14 mg de dióxido de titanio, y 0.24 mg. de talco. Una dispersión acuosa de los excipientes de recubrimiento fue rociada sobre las tabletas usando equipo estándar de recubrimiento con película (Accela Cota™ 24") a una velocidad de rotación de la paila de recubrimiento de 12.5 rpm, una temperatura de entrada de aproximadamente 60 °C, y una corriente de aire de aproximadamente . 300 m³/hora.

Recubrimiento de Azúcar

Una cochada de 14 kg de tabletas con película de recubrimiento como se describió arriba fueron proveídas con un recubrimiento de azúcar en la misma manera como se describió en " Recubrimiento de Azúcar 1" del Ejemplo 1 (aproximadamente 35 mg por tableta de subrecubrimiento y capa de polvo y aproximadamente 8 mg por tableta de recubrimiento de azúcar).

Las tabletas fueron analizadas como se describió en el ejemplo 1 y los resultados después de seis meses de almacenamiento son registrados en la Tabla 5.

Tabla 5

	A 25 °C y 60 % RH ¹⁾		A 40 °C y RH ambiental
	% OM38		% OM38
Tabletas no recubiertas	3.07		6.05
Recubierta de película	2.74		4.88
Recubierta de Azúcar	2.72		3.83

¹⁾ RH es la humedad relativa del ambiente

Los resultados de la tabla 5 muestran que el recubrimiento de las tabletas de tibolona de acuerdo con la presente invención resultan en una disminución de la formación del producto de degradación por isomerización OM38 y así conducen a tabletas de tibolona estabilizadas.

Ejemplo 4

Tabletas de 65 mg de peso total, que contienen 0.625 mg de tibolona , fueron preparadas siguiendo el procedimiento descrito en el Ejemplo 1.

Tabletas de tibolona no recubiertas

Tabletas de 65 mg que tienen la composición: 0.625 mg de tibolona, 63.29 mg de granulado básico, 0.13 mg de palmitato de ascorbil, y 0.325 mg de estereato de magnesio fueron preparadas como se describió en el Ejemplo 1.

Película de recubrimiento I

Las tabletas preparadas como se describió arriba fueron proveídas con una película de recubrimiento que tiene la siguiente composición: 5.3 mg de Opadry® AMB, que

consiste de alcohol de polivinilo, dióxido de titanio, talco, óxido de hierro amarillo, lecitina, goma de xanthan y óxido de hierro rojo. Una dispersión acuosa (contenido de sólidos 15 % w/w) de los excipientes de recubrimiento fue rociada sobre las tabletas usando equipo estándar para película de recubrimiento (Glatt® GC 300) a una velocidad de rotación de la paila de recubrimiento de aproximadamente 15 rpm, una temperatura de entrada de aproximadamente 60 °C y un flujo de aire de aproximadamente 100 m³/hora.

Película de recubrimiento II

Tabletas preparadas como se describió arriba fueron proveídas con una película de recubrimiento que tiene la siguiente composición: 5.2 mg de Sepifilm™ LP770, que consiste de hidroxipropil metilcelulosa, ácido esteárico y talco. Una dispersión acuosa (contenido de sólidos 8 % w/w) de los excipientes de recubrimiento fueron rociados sobre las tabletas usando equipo estándar de recubrimiento con película (Glatt® GC300) a una velocidad de rotación de la paila de recubrimiento de aproximadamente 15 rpm, una temperatura de entrada de aproximadamente 60 °C , y un flujo de aire de aproximadamente 100 m³/ hora.

Las tabletas fueron analizadas como se describió en el Ejemplo 1 y los resultados después de seis meses de almacenamiento se muestran en la Tabla 6.

Tabla 6

	A 25 °C y 60 % RH ¹⁾		A 40 °C y RH ambiental	
	% OM38	SD ²⁾	% OM38	SD ²⁾
Tabletas no recubiertas	4.84	0.08	17.10	0.60
Recubiertas de película I	3.57	0.02	10.69	0.14
Recubiertas de película II	3.51	0.06	5.77	0.05

¹⁾ RH es humedad relativa del ambiente

²⁾ SD es la desviación estándar en la media obtenida de tres mediciones de tabletas agrupadas, 10 tabletas por grupo.

Los resultados de la tabla 6 muestran que el recubrimiento de las tabletas de tibolona de acuerdo con la presente invención resultan en una disminución de la formación del producto de degradación por isomerización OM38 y así conducen a tabletas de tibolona estabilizadas.

Ejemplo 5

Tabletas de tibolona no recubiertas

Tabletas de 65 mg de 5 mm de diámetro que tienen la composición: 0.644 mg de tibolona, 63.29 mg de granulado básico, 0.13 mg de palmitato de ascorbil, y 0.325 mg de estereato de magnesio fueron preparadas como se describió en el Ejemplo 1.

Película de recubrimiento I

Las tabletas preparadas como se describió arriba fueron proveídas con 5.2 mg por tableta de un película de recubrimiento que tiene la siguiente composición: 3.07 mg de Eudragit® E PO, 0.31 mg de sulfato de lauril de sodio, 0.78 mg de ácido esteárico y 1.04 mg de estereato de magnesio. Una dispersión acuosa (contenido de solidos 16 % w/w) de los excipientes de recubrimiento fue rociada sobre las tabletas usando equipo estándar para película de recubrimiento (Glatt® GC 300) a una velocidad de rotación de la paila de recubrimiento de aproximadamente 15 rpm, una temperatura de entrada de aproximadamente 45 °C y un flujo de aire de aproximadamente 100 m³/hora.

Película de recubrimiento II

Las tabletas preparadas como se describió arriba fueron proveídas con 5.2 mg por tableta de un película de recubrimiento usando una dispersión acuosa de película de recubrimiento que tiene la siguiente composición (en w/w % de la dispersión total) :

11.1 % de Eudragit® L 100, 5.6 % de citrato de trietil, 3.7 % 1N NH₃, 74 % de agua purificada, y 5.6 % de talco. La dispersión fue rociada sobre las tabletas usando equipo estándar para película de recubrimiento (Glatt® GC 300) a una velocidad de rotación de la paila de recubrimiento de aproximadamente 20 rpm, una temperatura de entrada de aproximadamente 45 °C y un flujo de aire de aproximadamente 80 m³/hora.

Película de recubrimiento III

Las tabletas preparadas como se describió arriba fueron proveídas con 5.2 mg por tableta de un película de recubrimiento usando una dispersión acuosa de película de recubrimiento que tiene la siguiente composición (en w/w % de la dispersión total) : 39.2 % de Eudragit® RL 30D, 2.4 % de citrato de trietil , 52.5 % de agua purificada, y 5.9 % de talco. La dispersión fue rociada sobre las tabletas usando equipo estándar para película de recubrimiento (Glatt® GC 300) a una velocidad de rotación de la paila de recubrimiento de aproximadamente 15 rpm, una temperatura de entrada de aproximadamente 45 °C y un flujo de aire de aproximadamente 80 m³/hora.

Película de recubrimiento IV

Las tabletas preparadas como se describió arriba fueron proveídas con 5.2 mg por tableta de un película de recubrimiento usando una dispersión acuosa de película de recubrimiento que tiene la siguiente composición (en w/w % de la dispersión total) : 41.7 % de Eudragit® NE 30D, 45.8 % de agua purificada, y 12.5 % de talco. La dispersión fue rociada sobre las tabletas usando equipo estándar para película de recubrimiento (Glatt® GC 300) a una velocidad de rotación de la paila de recubrimiento de aproximadamente 15 rpm, una temperatura de entrada de aproximadamente 45 °C y un flujo de aire de aproximadamente 80 m³/hora.

Las tabletas fueron analizadas como se describió en el Ejemplo 1 y los resultados después de dos meses de almacenamiento se registran en la Tabla 7.

Tabla 7

	A 25 °C y 60 % RH ¹⁾		A 40 °C y 40% RH	
	% OM38	SD ²⁾	% OM38	SD ²⁾
Tabletas no recubiertas	1.72	0.01	4.27	0.02
Recubiertas de película I	2.65	0.03	6.71	0.07
Recubiertas de película II	3.05	0.06	8.89	0.33
Recubiertas de película III	1.27	0.01	4.06	0.05
Recubiertas de película IV	1.70	0.02	4.86	0.02

¹⁾ RH es humedad relativa del ambiente

²⁾ SD es la desviación estándar en la media obtenida de tres mediciones de tabletas agrupadas, 10 tabletas por grupo.

Los resultados de la Tabla 7 muestran que el recubrimiento de las tabletas de tibolona de acuerdo con la presente invención resultan en una disminución de la formación del producto de degradación por isomerización OM38, en particular cuando se usa Eudragit® E PO o Eudragit® L100 peores resultados fueron obtenidos en comparación con las tabletas no recubiertas.

REIVINDICACIONES

1. Una tableta farmacéutica estabilizada que comprende una cantidad de 0.1 a 10 % en peso de tibolona proveída con un recubrimiento.
2. Una tableta de acuerdo con la reivindicación 1 donde el recubrimiento es una película de recubrimiento, un recubrimiento de azúcar, una película de recubrimiento de azúcar o un recubrimiento de "empaquetado".
3. Una tableta de acuerdo con la reivindicación 2 donde el recubrimiento es un recubrimiento de azúcar o una película de recubrimiento de azúcar.
4. Una tableta de acuerdo con la reivindicación 1 y 2 donde la película de recubrimiento contiene un éter de celulosa, un polímero de vinilo o gelatina.
5. Una tableta de acuerdo a la reivindicación 3 donde la azúcar comprende sucrosa.
6. Una tableta de acuerdo con cualquiera de las reivindicación 1 - 5 donde el recubrimiento contiene un plastificador seleccionado de un grupo consistente de glicerina, propileno glicol y polietileno glicol.
7. Uso de un recubrimiento para estabilizar una tableta farmacéutica que comprende una cantidad de 0.1 a 10 % en peso de tibolona.
8. Uso de acuerdo a la reivindicación 7 donde el recubrimiento es una película de recubrimiento, un recubrimiento de azúcar, una película de recubrimiento de azúcar o un recubrimiento de "empaquetado"

9. Uso de acuerdo a la reivindicación 8 donde el recubrimiento es un recubrimiento de azúcar o una película de recubrimiento de azúcar.
10. Uso de acuerdo a la reivindicación 9 donde el azúcar comprende sucrosa.

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 05053022 00000000 Folios: 78
Fecha (ANS): 2005-06-16 17:36:54
Tramite : 011 PCI-PATENT 379 FASE HACI 411 PRESENTAR
Dependencia: 2020 DIVISION LE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 41,103
FECHA : JUNIO 7 DE 2005

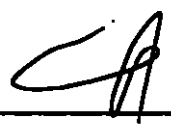
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	40114854	07/06/2005	17,825,200.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
	TOTAL :	443,000.00

SOM: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Cdo 11214-841-030-4

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()

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 COMERCIO
Radicación: 05050022 00601000 Folios: 76
Fecha (HH): 2005-06-16 17:36:54
Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENIM
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

40

Folio 80

2020
Bogotá DC

Doctor(a)
EMILIO FERRERO
Apoderado(a) y/o Representante
AKZO NOBEL N.V.

REFERENCIA:	Radicación No.	05 58822
	Solicitud Internacional	PCT/EP2003/050829
	Fecha límite inicio fase Nacional	20 - 06 - 2005
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	1063
	Follos	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 la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC

21 OCT. 2025


ALIX CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Al contestar favor indique el número de
radicación consignado en el sticker

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Commutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153265 al 69
Fax: 3 505220. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-058822

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 559

DE FECHA 30 DE DICIEMBRE DEL 2005, EL TERMINO HABIL SEÑALADO

POR LA LEY EXPIRA EL 28 DE MARZO DEL 2006

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud calga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI **__ X __** **_____**

NO **__** **_____** **-----**

Bogotá D.C, ABRIL DE 2006