



No. 08-067103- -00003-0000

Fecha: 2010-02-25 17:04:00 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 42

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

②

**SOLICITUD
PUBLICADA**

Numero del expediente: **08 067103**

Solicitante: **WORLD-TRADE IMPORT-EXPORT WTIE, A.G**

Apoderado: **DILIA MARIA RODRIGUEZ D ALEMAN**

**COMPOSICIONES FARMACEUTICAS QUE COMPRENDEN DERIVADOS DE ESTEROIDES SINTETICOS
MINERALES Y METABOLITO ACTIVO DE LA VITAMINA D, 1,25(OH)2D3(CALCITRIOL) PARA LA PREVENCIÓN Y
TRATAMIENTO DE LA OSTEOPOROSIS Y EL CONTROL DE LOS SINTOMAS DE LA MENOPAUSIA**

Gaceta: **610**

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE	Nombre: GYNOPHARM Dirección: Carrera 14 N° 94-44 piso 7 torre b Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA Teléfono: 2 36 84 95 Fax: E-mail:	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual Número 802,006,279-4
REPRESENTANTE O APODERADO	Nombre: CIELO ANGELA PEÑA RODRIGUEZ Dirección: CARRERA 13 No. 119-95 Teléfono: (571)213 12 13 Fax: (571)612 19 79 E-mail: negocios@optimum-co.com	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual Número 51.940.252 TP82701

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: **No cumple con los requisitos de patentabilidad.**

Signo opositor:

Justificación:

**La presente solicitud no cumple con los requisitos de patentabilidad dado que lo
revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la
misma tal y como se demostrará en el capítulo "Fundamento de Hechos".**

⑤ Comprobante de pago No. _____

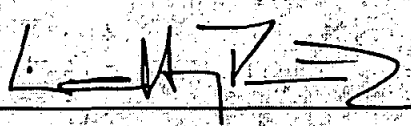
Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: CIELO ANGELA PEÑA RODRIGUEZ

FIRMA: 

C.C. 51.940.252

TP. 82701

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 067103

Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIONES FARMACEUTICAS QUE
COMPRENDE DERIVADOS DE ESTEROIDES
SINTETICOS, MINERALES Y METABOLITO ACTIVO DE
LA VITAMINA D, 1,25(OH)2D3 (CALCITRIOL) PARA LA
PREVENCION Y TRATAMIENTO DE LA
OSTEOPOROSIS Y EL CONTROL DE LOS SINTOMAS DE
LA MENOPAUSIA. (WORLD-TRADE IMPORT-EXPORT,
WTIE, AG)."

Solicitante : WORLD-TRADE IMPORT-EXPORT WTIE, A.G.

Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 610 del 30 de noviembre de 2009

Yo, **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. **82701** del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **GYNOPHARM S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley

y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "COMPOSICIONES FARMACEUTICAS QUE COMPRENDEN DERIVADOS DE ESTEROIDES SINTETICOS, MINERALES Y METABOLITO ACTIVO DE LA VITAMINA D, 1,25(OH)2D3 (CALCITRIOL) PARA LA PREVENCIÓN Y TRATAMIENTO DE LA OSTEOPOROSIS Y EL CONTROL DE LOS SINTOMAS DE LA MENOPAUSIA", cuyo titular es WORLD-TRADE IMPORT-EXPORT WTIE, A.G., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular TIBOLONA Y CALCITRIOL. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 1 de julio de 2008 reivindicando prioridad bajo la solicitud MX2005PA14091 del 2005-12-20; y fue

publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 610 del 30 de Noviembre de 2009, cuya publicación internacional corresponde a la WO2007073135 del 2007-06-28.

2.2. La solicitud colombiana 08 67103 objeto de la presente oposición, se refiere a una composición farmacéutica sinérgica que comprende una combinación sinérgica de un esteroide sintético, minerales y el metabolito activo de la vitamina D, 1,25(OH)₂ D₃ (calcitriol) para la prevención y tratamiento de la Osteoporosis; donde además la combinación de un esteroide sintético es Tibolona, minerales conocidos como calcio, y el metabólico activo de la vitamina D₃ conocido como 1, 25(OH)₂ D₃ (calcitriol); en el que el calcio se encuentra como carbonato de calcio; y en la que la vitamina D₃ se encuentra como colecalciferol.

2.3. En primera instancia, se debe advertir que la reivindicación 9 de la solicitud objeto de la presente oposición, se refiere a un uso y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso no sería patentable.

2.4. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*, tenemos que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad



de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

- D1: US2004229854 publicada el 18 de noviembre de 2004.
- D2: WO9906051 publicada el 11 de febrero de 1999.

2.5. La tibolona es conocida ampliamente en el estado de la técnica. Ahora bien, el documento D1, particularmente en la descripción revela una formulación de Tibolona útil en el tratamiento de problemas asociados a la menopausia y osteoporosis. Particularmente, este documento anterior D1 revela dosis similares, con 2,5 mg de este principio activo por unidad de dosificación (ver ejemplo 1, párrafo [0140]; y, reivindicación 16). Por otro lado, el documento D2 se refiere a una composición farmacéutica que contiene entre otros ingredientes vitamina D y calcio. Según el documento D2, la vitamina D puede aparecer como vitamina D2 (ergocalciferol) o vitamina D3 (colecalciferol) y entre las sales de calcio utiliza el carbonato. Considerando los documentos D1 y D2, no es posible reconocer altura inventiva ya que sería obvio para un experto en la materia la combinación de la información del documento D1 con el documento D2 de similar propósito, apoyado por el hecho de utilizar la misma dosis de tibolona en la solicitud y en D1. Así entonces la presente solicitud a la luz de la combinación de los documentos D1 y D2, no comprenden el requisito de ALTURA o NIVEL INVENTIVO.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 67103 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- "Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.". A la fecha de prioridad, 20 de diciembre de 2005, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a una composición formada por una combinación de un derivado de esteroides sintéticos como lo es la Tibolona, minerales con el calcio y el metabolito activo de la vitamina D 1,25 (OH)₂ (calcitriol), para la prevención y tratamiento de la Osteoporosis, sobre la cual busca protección en el capítulo reivindicatorio.

2.7.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, en el apartado 9 del capítulo reivindicatorio se reclama el uso y este no es aplicable industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos, no cumple con el requisito de la aplicación industrial.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "Los Países Miembros otorgarán



patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial. La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada **"COMPOSICIONES FARMACEUTICAS QUE COMPRENDEN DERIVADOS DE ESTEROIDES SINTETICOS, MINERALES Y METABOLITO ACTIVO DE LA VITAMINA D, 1,25(OH)2D3 (CALCITRIOL) PARA LA PREVENCION Y TRATAMIENTO DE LA OSTEOPOROSIS Y EL CONTROL DE LOS SINTOMAS DE LA MENOPAUSIA"**, cuyo titular es WORLD-TRADE IMPORT-EXPORT WTIE, A.G, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 610 del 30 de noviembre de 2009.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US2004229854 publicada el 18 de noviembre de 2004.
- D2: WO9906051 publicada el 11 de febrero de 1999.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

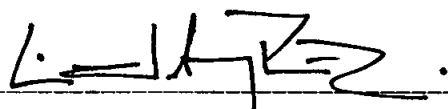
1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de GYNOPHARM S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: US2004229854 publicada el 18 de noviembre de 2004.
- D2: WO9906051 publicada el 11 de febrero de 1999.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



CIELO ANGELA PEÑA RODRIGUEZ
C.C. 51'940.252 de Bogotá
T.P.A. 82701 del C.S. de la J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 15,536
FECHA : FEBRERO 25 DE 2010



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	45812362	29/01/2010	295,000.00

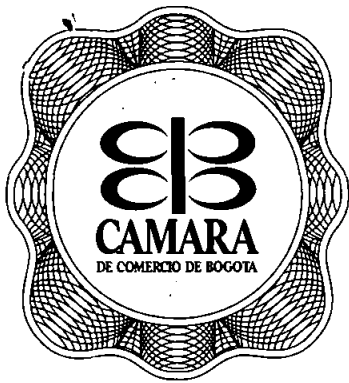
***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	295,000.00
		TOTAL :	\$ 295,000.00

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



01

* 8 8 4 0 5 0 0 6 *

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/01/07

HORA: 09:27:26

OPERATION: 03ERP0107026

PAGINA: 1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON
FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Dirección para notificaciones judiciales:

CR 49 C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2047.

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/01/07

HORA: 09:27:26

OPERACION: 03ERP0107026

PAGINA: 2

uso y consumo humano y veterinario. b) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal. c) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo, empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto; comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior, y, en

*** CONTINUA ***



01

* 8 8 4 0 5 0 0 7 *

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/01/07

HORA: 09:27:26

OPERACION: 03ERP0107026

PAGTNA: 3

 general, realizar cualquier acto o negocio que sea necesario o con-
 veniente para el desarrollo de su objeto social y para la mejor pro-
 teccion de sus intereses corporativos o lo de sus socios.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****4,000,000,000	*****4,000,000	*****1,000
Suscrito		
\$*****2,672,646,000	*****2,672,646	*****1,000
Pagado		
\$*****2,672,646,000	*****2,672,646	*****1,000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravámenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le corres-

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/01/07

HORA: 09:27:26

OPERACION: 03ERP0107026

PAGINA: 4

pondan como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva. El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente accidentales, sin que sea necesario para ello acreditar la ausencia del principal.-----

C E R T I F I C A

Que según Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:

GYNOPHARM S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

- | | |
|---|--------------------|
| 1. Llobet Poal Manuel | CC.*****14,670,196 |
| 2. Zanatta Reheman Leonardo Andres | CC.*****2,760,271 |
| 3. Munoz Marroquin Diego | CC.*****7,688,292 |
| 4. Montealegre Gonzalez Andres Leonardo | CC.*****79,950,262 |

Suplentes

- | | |
|-----------------------------------|--------------------|
| 1. Agudelo Pelaez Luis Hernando | CC.*****14,238,997 |
| 2. Aroca Almanza Arleth Ayelina | CC.*****36,718,415 |
| 3. Penaranda Urbina Adriana Paola | CC.*****53,120,683 |
| 4. tovar Vasquez Ruth | CC.*****52,175,756 |

C E R T I F I C A

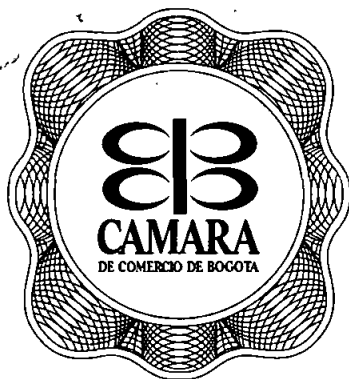
Que según Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Palacios Aragon Luis Alberto	CE.*****319,788

C E R T I F I C A

Que según Acta No. 49 del 03 de Marzo de 2008 correspondiente a la

*** CONTINUA ***



01



* 8 8 4 0 5 0 0 8 *

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/01/07

HORA: 09:27:26

OPERACION: 03ERP0107026

PAGINA: 5

Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*****351,283

C E R T I F I C A

Que según Acta No. 19 del 30 de Abril de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el No. 149,314 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal.	
PENALOSA AUDITORES & ASOCIADOS S.A.	Ni.*****830,095,635

C E R T I F I C A

Que por Documento Privado del 11 de Mayo de 2009, otorgado en Bogota por Peñalosa Auditores & Asociados S.A. inscrito en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el Nro 149,315 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Designado: Revisor Fiscal Ppal	
Padilla Romero Ivan Dario	CC.*****80,025,798
Designado: Revisor Fiscal Suplente	
Gomez Preciado Clara Judith	CC.*****52,544,226

C E R T I F I C A

Que según Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el señor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representación de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/01/07

HORA: 09:27:26

OPERACION: 03ERP0107026

PAGINA: 6

S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el señor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadanía No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOPHARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que por Escritura Pública No. 2,404 del 28 de Mayo de 2009, otorgada en la Notaria la. de Bogota cuya parte pertinente se inscribió en esta Cámara de Comercio, el 02 de Julio de 2009 bajo el No. 3,948 del libro respectivo,-----
consta que el señor LUIS ALBERTO PALACIOS ARAGON con CE No.319788, en su calidad de Representante Legal de GYNOPHARM S.A., manifesto que confiere poder general, amplio y suficiente a la Doctora -----
CAROLINA MARIA ROMERO CERON, identificada con cedula de ciudadanía numero 52.352.190, para que en nombre de la sociedad GYNOPHARM -----
S.A., promueva y defienda los intereses de la sociedad judicial y extrajudicialmente, en toda especie de gestiones y actuaciones ante las autooridades administrativas o jurisdiccionales en especial ----
para: a) Recibir notificaciones de cualesquiera tipo de actos -----
emanados de las autoridades administrativas o judiciales. b) -----
Presentar recursos por la via administrativa o judicial, renunciar a terminos, desistir, conciliar, transigir y modificar. c) Elevar peticiones y solicitar informacion a las autoridades -----
administrativas y jurisdiccionales. d) Presentar demandas ante las autoridades administrativas y judiciales.-----

C E R T I F I C A

*** CONTINUA ***



CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/01/07

HORA: 09:27:26

OPERACION: 03ERP0107026

PAGINA: 7

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 31 de Marzo de 2009.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles después de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

16

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para presentar ante ese Despacho una remisión de información a la solicitud de patente No. 08 067103, titulada "COMPOSICIONES FARMACEUTICAS QUE COMPRENDEN DERIVADOS DE ESTEROIDES SINTETICOS, MINERALES Y METABOLITO ACTIVO DE LA VITAMINA D, 1,25(OH)2D3 (CALCITRIOL) PARA LA PREVENCIÓN Y TRATAMIENTO DE LA OSTEOPOROSIS Y EL CONTROL DE LOS SÍNTOMAS DE LA MENOPAUSIA", cuyo titular es **WORLD-TRADE IMPORT-EXPORT, WTIE, AG**, publicada en la gaceta No. 610 del 30 de noviembre de 2009.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de dicha remisión, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

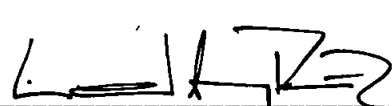
De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en _____ (Colombia) a los ____ días del mes de ____ de 2010.

GYNOPHARM S.A.

Cédula de Extranjería No. 319788.
NIT: 802.006.279-4
Representante Legal

Acepto:


CIELO ANGELA PEÑA RODRIGUEZ
C.C. 51'940.252 de Bogotá
T.P.A. 82701 del C.S. de la J.



DILIGENCIA DE PRESENTACION

El Notario Dieciocho del Circulo de Bogotá,

D C , hace constar que el presente documento

fue presentado personalmente por:

DAVID ALONSO

quien exhibio la C.E. *319788*

de *88m* y Tarjeta Profesional

No *...* C.S.J., y declaró que

la firma y la huella que aparecen en el

presente documento son suyas.

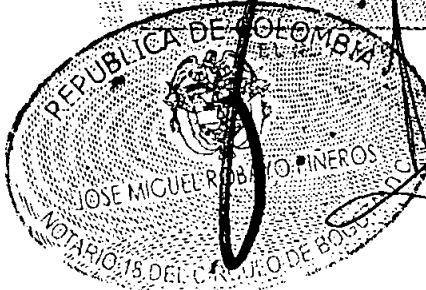
17 FEB 2010

BOGOTÁ, D.C.

FIRMA



HUELLA DEL
INDICE DERECHO





US 20040229854A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0229854 A1**

Haan De

(43) **Pub. Date: Nov. 18, 2004**

(54) **IMMEDIATE RELEASE DOSAGE FORM
FOR HRT**

Related U.S. Application Data

(62) Division of application No. 09/723,412, filed on Nov. 28, 2000, now abandoned.

(76) **Inventor: Pieter Haan De, Amsteleindstraat (NL)**

Publication Classification

Correspondence Address:

WILLIAM M. BLACKSTONE

AKZO NOBEL

1300 PICCARD DRIVE #206

ROCKVILLE, MD 20850-4373 (US)

(51) **Int. Cl.⁷ A61K 31/57**

(52) **U.S. Cl. 514/178**

(57) **ABSTRACT**

It has been recognized that tibolone, which is an agent in the treatment of menopausal complaints and osteoporosis, if formulated with a particle size in a defined range, displays an unexpectedly high bioavailability of one of its estrogenic metabolites, Org A.

(21) **Appl. No.: 10/781,493**

(22) **Filed: Feb. 18, 2004**

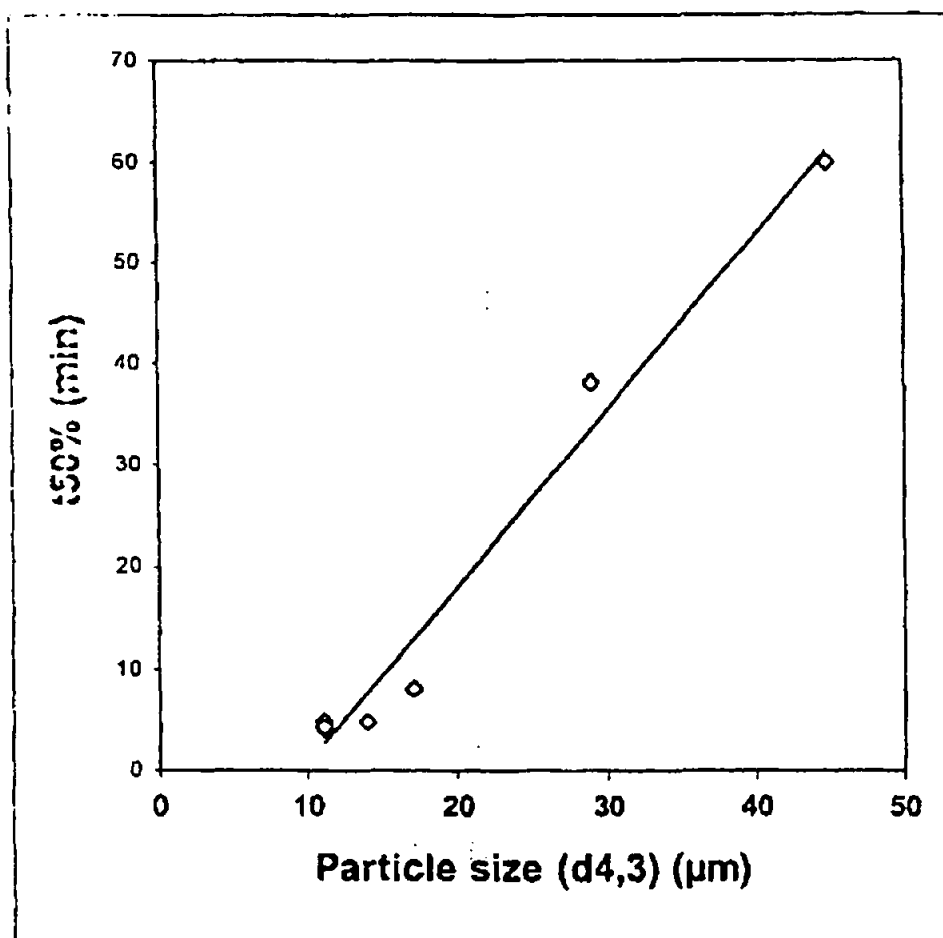


FIG.1

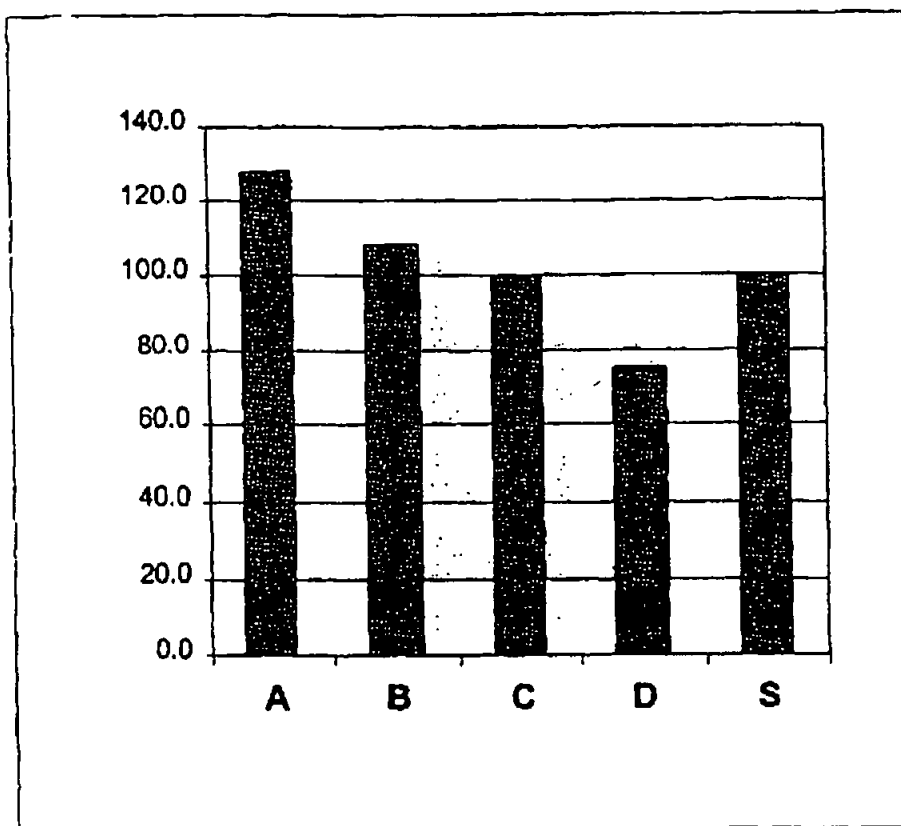


FIG. 2

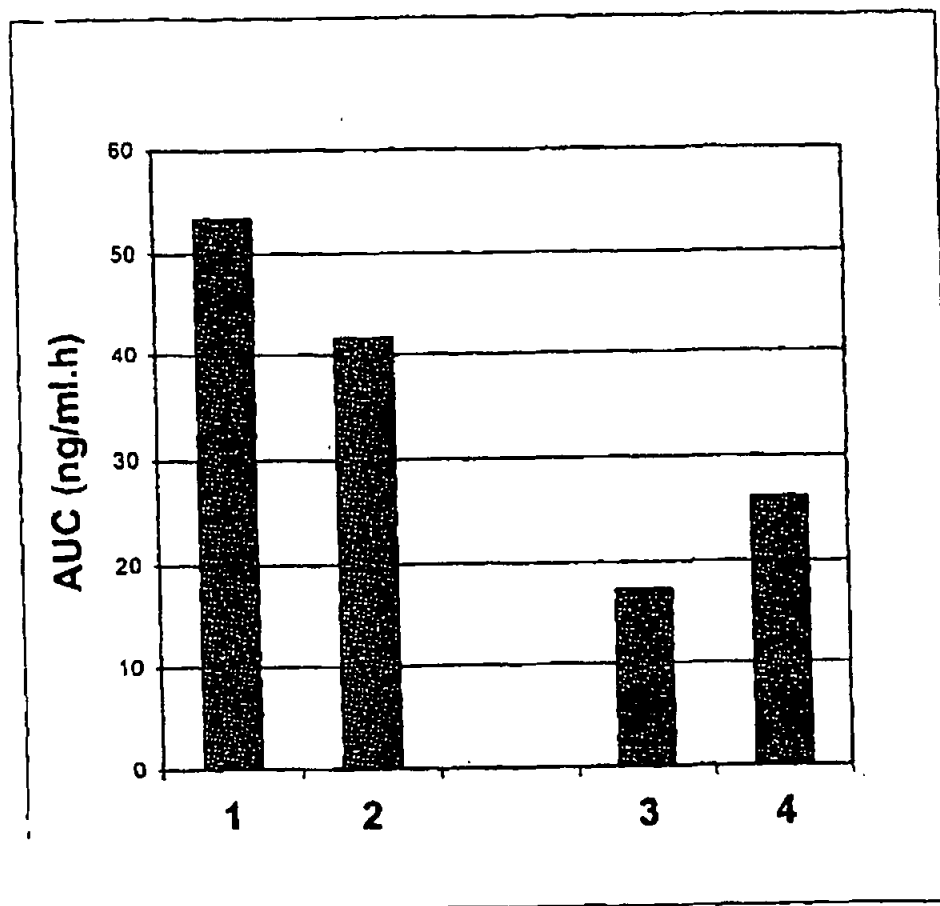


FIG. 3

IMMEDIATE RELEASE DOSAGE FORM FOR HRT

FIELD OF THE INVENTION

[0001] The invention pertains to a pharmaceutical formulation comprising, as the active substance, (7 α , 17 α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (tibolone), wherein the formulation is a solid, peroral dosage form of the immediate-release type.

BACKGROUND OF THE INVENTION

[0002] Tibolone is known as a tissue-specific and effective agent that can be used in hormone replacement therapy (HRT) in (post)menopausal women, for the treatment of menopausal and postmenopausal disorders, including climacteric complaints, vasomotor symptoms, osteoporosis, and vaginal atrophy. See, *int. al.*, U.S. Pat. No. 5,037,817 and WO 98/47517.

[0003] Throughout the past years, it has become known that tibolone displays a relatively complex metabolic pattern. Several compounds different from tibolone itself play a role as active metabolites. This makes it difficult to predict whether two different tibolone products are bioequivalent with each other. Even if it is known practice in the field that bioequivalence in the case of a compound which exerts its activity through a metabolite is to be measured, *in vivo*, by analysing plasma levels of the metabolite, this is a much more complex matter in the case of a compound as tibolone, which has more than one metabolite.

[0004] In order to set a standard for analysing the relative bioavailability of a drug substance upon oral administration, a customary method is to choose a model in which, for a dosage amount well within the therapeutic window, a maximum exposure to the drug is given. One generally viable way to achieve such maximum exposure is to provide the drug in the form of a solution. The normal expectation is that the bioavailability of the drug in solid form will be lower than that in the case of the solution. See, *int. al.*, Robert E. Notari, *Biopharmaceutics and Clinical Pharmacokinetics*, 4th edition (1987) p140.

[0005] In the case of tibolone, this experiment led to an unexpected result, on the basis of which the present invention was made.

[0006] For different solid formulations, an analysis was made of two of the main metabolite compounds, *viz.* 3 α -OH tibolone (hereinafter referred to as "Org A"), and 3 β -OH tibolone (hereinafter referred to as "Org B"). The finding is that one of these, Org A, turned out to become better available as compared to the solution, dependent on the particle size of tibolone. As this increase of bioavailability does not hold for the other above-mentioned metabolite, Org B, obvious explanations could not be given.

[0007] Besides being an unexpected result *per se*, this is an improvement of the solid pharmaceutical product as compared to the solution, since Org A is responsible for an important part of the estrogenic effect of tibolone (which, naturally, plays a role in its significant utility as an HRT agent for menopausal patients).

SUMMARY OF THE INVENTION

[0008] The invention thus resides in drug products of the immediate-release type, of the active substance tibolone

which show an improvement of Org A availability as compared to a reference situation with maximum exposure, *viz.* a solution. These drug products are characterized by comprising solid tibolone in a mean particle-size below 22.8 μ m as measured by the technique described below. Preferably, the mean particle size is below 20 μ m.

[0009] Incidentally, with the benefit of hindsight, one can assess that the product as produced in Example 1 of U.S. Pat. No. 5,037,817 satisfies these same criteria. This, however, is to be regarded as truly accidental, since a teaching on the bioavailability of Org A, let alone of the influence of particle size thereupon, cannot be derived from U.S. Pat. No. 5,037,817.

[0010] In addition to the above, it was realized that any assessment of bioequivalence of two tibolone products will fail if not Org A is measured. This leads to another aspect of the present invention, which is a method of examining whether one tibolone product is bio-equivalent with another tibolone product, and which resides therein that bio-equivalency is determined *in vivo* by analysing plasma levels of one or more metabolites of tibolone, one of which being Org A.

DETAILED DESCRIPTION OF THE INVENTION

[0011] The main requirements for the present invention include that a solid pharmaceutical composition of tibolone is provided, and that tibolone, when contained in the dosage form, has a particle size as defined above.

[0012] Tibolone being a known substance, it can be prepared in a known manner. In this respect reference is made to U.S. Pat. Nos. 3,340,279, 4,701,450, and 5,037,817.

[0013] Once the person skilled in the art appreciates that tibolone is to be provided in a certain particle size, he or she knows the general measures that can be taken to achieve this. A simple, though laborious and not economical method is to just produce tibolone in any solid form and screen the obtained particles using adequate mesh sizes so as to shift out the particles that are too large. An alternative method is to first dilute the active substance with a pharmaceutically acceptable carrier (e.g. a base granulate normally used for tableting or filling of capsules), and then screen the product. In that case the carrier materials effectively work as a processing aid in reducing the size of the active substance (the final maximum particle size of the active substance remains to be determined by the mesh-size of the screen). The necessary equipment as well as these screening methods are known to the skilled man. Another method, also known in general to the skilled person, is to again just produce tibolone in any solid form, and then subject it to a milling step wherein the required particle size is obtained. Suitable milling equipment is known to the skilled person. Instead of first producing tibolone and then rendering it into the right particle size, one can also take measures during synthesis and, particularly, crystallisation, to actually obtain tibolone in the desired particle size. The exact conditions required for this, will depend on the equipment and reaction circumstances used. As a general textbook reference on providing particles of a desired size, it is referred to Gennaro *et al.*, *Remington's Pharmaceutical Sciences*, (18th ed., Mack Publishing Company, 1990, pages 1436-1437 and 1615-1632.

[0014] In order to avoid undue experimentation, one can conduct a relatively simple test as to whether the particle size of tibolone, once incorporated into the solid, peroral, immediate-release dosage form (be it a compressed tablet, a capsule, or else), is adequate. This is a dissolution test, standardized to a dosage of 2.5 mg tibolone. The dosage form to be tested is put into a dissolution medium (aqueous sodium lauryl sulphate solution 0.25%). By means of a suitable technique, such as HPLC, it is measured at fixed points in time how much tibolone has been dissolved in the medium. This enables determining the dissolution rate of tibolone, given by the $t_{50\%}$ value, i.e. the point in time at which 50% of the tibolone, i.e. 1.25 mg, has been dissolved. A $t_{50\%}$ value of below 23.1 minutes correlates with a particle size of tibolone in compliance with the invention. It is imperative that the test be standardized to a dosage of 2.5 mg. This means that in the case of, e.g., a 5 mg tibolone tablet, one has to break it into two parts before conducting the test. Or, e.g., in the case of 1.25 mg or 0.625 mg tibolone dosage units, one has to take two, respectively 4, of such dosage units in the (also standardized) dissolution medium. FIG. 1 provides the correlation between tibolone particle size and the dissolution-rate ($t_{50\%}$) of a solid, immediate-release peroral dosage unit (a tablet) comprising tibolone. Such a correlation is generally valid in the case of immediate-release dosage forms. As indicated above, $t_{50\%}$ is the time needed for 50% of the drug to dissolve in vitro. The $t_{50\%}$ was calculated by means of linear interpolation between the first point >50% of the drug dissolved, and the previous point, sampling points being 5, 10, 15, 30, and 45 minutes after start.

[0015] If the tibolone has been provided in the adequate particle size before mixing with excipients, it can thereafter be mixed with excipients. Eventually, the mixture of tibolone and excipients (how ever obtained) can be incorporated into solid pharmaceutical dosage units in known manner. The dosage amount of tibolone therein will usually be of the order of 0.3 to 5.0 mg per dosage, more particularly 0.625, 1.25 or 2.5 mg.

[0016] The pharmaceutical dosage units of the present invention will generally take the form of tablets or capsules, but other solid or dry pharmaceutical preparations are included.

[0017] Methods for making such dosage units are well known. For example in the above-mentioned standard English language text Gennaro et al., Remington's Pharmaceutical Sciences, reference is made especially Part 8: Pharmaceutical Preparations and Their Manufacture), methods of making tablets, capsules and pills and their respective components are described.

[0018] Three methods of making tablets and capsules include the wet-granulation, dry-granulation, and direct compression methods.

[0019] Wet-granulation methods involve weighing out ingredients (actives and excipients, including a solvent), mixing the ingredients, granulating them, screening them damp, drying them, dry screening, lubrication, and compressing the resultant admixture into tablets or filling capsules with it. Such procedures result in tablets or capsules having at least adequate homogeneity and stability.

[0020] Direct compression methods involve weighing out direct-compression vehicles (including carriers) and active

ingredients, mixing of the ingredients, lubrication, and compressing the resulting admixture into tablets, or filling capsules with it.

[0021] Carriers for active substances in pharmaceutical dosage units are generally known to the skilled man, and do not require separate elucidation here.

[0022] Wet granulation distinguishes from dry granulation and dry-mixing in that a liquid (such as water, preferably containing a binder) is applied in wet granulation to produce agglomeration or granules.

[0023] The most widely used granulation methods in the pharmaceutical industry are the fluidized bed granulation and the Net-massing method in which a liquid is added to a powder or granulate in a vessel equipped with any type of agitation that will provide granules or agglomerates. Various operations can be recognised in the wet (massing) granulation, including milling of excipients, mixing of milled powders, preparation of binder solution, mixing the binder solution with the powder mixture to form the wet mass, granulation of the mass, coarse screening of wet mass, drying moist granules, and screening dry granules. It is obvious that, depending on the selected excipients and the size of the batch and the selected equipment, some of the operations can be combined or are not required or particular operations can be included. General methods of preparing granules are for instance described in *Pharmaceutical Dosage Forms: Tablets* (Volume I). Ed. H. A. Lieberman, L. Lachman, J. B. Schwartz (1989), Marcel Dekker Inc. New York and Basel pp. 131-190.

[0024] Advantages of wet granulation include improvement of the cohesiveness and compressibility of powders, a good particle size distribution, reduction of a great deal of dust and airborne contamination, prevention of segregation of components.

[0025] Small-scale production can be achieved by mixing and wetting the mass in mortars or stainless steel bowls, whereas for larger quantities twin-shell blenders, double-cone blenders, planetary mixers, rotary granulators, high shear mixers and fluid-bed granulation equipment can be applied. General mixing methods are disclosed in *Pharmaceutical Dosage Forms* (Volume 2). Ed. H. A. Lieberman, L. Lachman, J. B. Schwartz (1990), Marcel Dekker Inc. New York and Basel pp. 1-71. The dry excipients and, optionally, active ingredients are mixed in a suitable mixer, preferably a mixer in which both mixing and granulating can be performed, for instance a Gral high shear mixer, after which an aqueous binder solution is added. Another preferred method is suspending the active ingredients into the aqueous binder solution, which suspension is added to the dry mixture of excipients and granulated.

[0026] Granulates, tablets, and capsules prepared by wet-granulation or direct compression consist of several inert materials that can be found in conventional solid oral dosage forms in general. The ingredients can be classified in excipients which help to impart satisfactory processing and compression characteristics to the formulation like diluents, stabilising agents, binders, glidants and lubricants and in excipients to give the desirable physical characteristics to the finished tablet like disintegrants and colours. If required the tablets can be provided with a film coat, for instance as disclosed in *Pharmaceutical Dosage Forms* (Volume 3). Ed.

H. A. Lieberman, L. Lachman, J. B. Schwartz (1990), Marcel Dekker Inc. New York and Basel pp. 93-125.

[0027] Diluents ("filling excipients") usually make up the major portion of the carrier. Direct compression carriers are described in the same textbook, Volume I, second edition, Chapter 4, pages 195-246. The direct compression carriers can be classified into groups including water soluble polyalcohols such as lactose (including spray-dried lactose and anhydrous lactose), and polysaccharides such as the group of celluloses (e.g. Avicel® PH 101, PH 102, and PH 200, purified wood cellulose), and the group of water-insoluble starch products according to the invention (e.g. Starch 1500, potato starch, corn starch, wheat starch, including modified starches, agglomerated starches, granulated starches).

[0028] Binding agents or adhesives are used as substances that bind powders together and provide cohesiveness to the granulates and tablet formulation. Binders can be added dry and blended with the diluents and, optionally, the drug. In this case binders are activated by addition of water or other solvents. In other manufacturing procedures, the adhesives are dissolved or slurried in a liquid and, in this form, added to the mixed powders. Conventional binders include gelatine, water soluble modified starch, and sugars as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic gums which have been used include tragacanth, magnesium aluminium silicate, acacia, ammonium calcium alginate, sodium alginate, carboxymethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, polyethylene glycol and clays like Veegum.

[0029] Depending on for example the solubility of the binders in the various liquids, the binder can be added to the powder mix as a solution in water, or a water-solvent mixture.

[0030] In addition to the stabilising effect of the present invention, stabilising agents can be added to further reduce decomposition of tibolone if desired. Examples of such stabilising agents are of the group of antioxidants (such as ascorbyl palmitate and ascorbyl stearate) and the group of water soluble chelating agents (such as sodium EDTA and sodium ascorbate).

[0031] Materials to improve the flow characteristics are referred to as glidants. As an example, silicon dioxide, magnesium lauryl sulfate, magnesium aluminium silicate, magnesium oxide, talc or clays can be incorporated into the formulation to reduce interparticulate friction and to eliminate the problems associated with the flow of materials from larger to smaller apertures in the tablet presses.

[0032] Disintegrants (commonly used in immediate-release dosage forms, and known to the skilled person) can also be used in the dosage forms of the invention.

[0033] Before filling capsules or sachets, or compressing tablets, lubricants are mostly added to prevent friction and wear during processing. Some of the lubricants also demonstrate anti-adherent properties that can be relevant in case of sticking of tablet granulations to the faces of the punches and the die walls. Examples of the group of lubricants are the metallic stearates (magnesium stearate), talcum, stearic acid, sodium stearyl fumarate, hydrogenated vegetable oil, and high melting point waxes.

[0034] As indicated above, the invention also pertains to a method of examining whether one tibolone product is bioequivalent with another tibolone product. Described more fully, this is a method of determining by means of an in vivo bioequivalence study whether a drug product comprising solid tibolone is bioequivalent with another drug product comprising tibolone which is used as a standard tibolone product, the method comprising the steps of administering to a suitable test panel in a comparative trial the tibolone product of which the bioequivalence is to be determined and the standard tibolone product conducting an in vivo bioequivalence study, and measuring plasma levels of a measurable active substance, characterized in that the active substance is Org A. This method finds utility in the marketing approval of copies of existing market products comprising tibolone. In this respect, one can also view this as a "method of doing business." It is known in the pharmaceutical arts to try and obtain regulatory approval for a drug product through the filing of an ANDA (Abbreviated New Drug Application), referring to an original (standard) drug product on the basis of the same active substance. Thereby it is shown try means of a comparative trial that the ANDA drug product is bio-equivalent with the standard drug product by analysing and comparing plasma levels of an active compound present in the blood. It is known that, if the compound itself is not suitable for analysis (either because it cannot be determined per se, or because it is metabolized), another compound should be found for analysis (e.g. the active metabolite). The problem with doing this for tibolone, is that the metabolic pattern is too complicated to simply select which compound to analyse. By virtue of the present invention, it has now been found that the relevant analysis is that of Org A.

[0035] Assays

[0036] From the above, it is clear that several assays are used in describing the present invention. These are, in arbitrary order, the measurement of mean particle-size, the dissolution test referred to above, the assessment of bioequivalence. These will be described hereinbelow:

[0037] Particle Size Measurement

[0038] Principle:

[0039] The particle size distribution is determined by Laser Diffraction Spectroscopy.

[0040] Equipment:

[0041] Laser diffraction particle sizer equipped with a sample dispersion unit.

[0042] Reagents

[0043] 1. Polysorbate 80, analytical grade.

[0044] 2. Water, purified quality (concentration of particles $>10 \mu\text{m}$ is <1 per mL).

[0045] 3. Polysorbate solution 0.05%.

[0046] Dissolve 0.5 gram of polysorbate 80 (1) in 1.0 liter of water (2).

[0047] 4. Suspension liquid.

[0048] Add 50 mg of tibolone sample to 500 mL of polysorbate solution (3) and saturate by stirring for at least 60 minutes.

- [0049] Filtrate the supernatant liquid and use the filtered solution.
- [0050] Instrument Conditions:
- [0051] Particle sizer Malvern Mastersizer S or equivalent
- [0052] Lens type: 300RF (range 0.05 μm -900 μm)
- [0053] Active beam length: 2.4 mm
- [0054] Sample dispersion unit: Malvern MS1 or equivalent
- [0055] Sample flow rate: $\frac{3}{4}$ of maximum flow rate
- [0056] Sweeps
- [0057] sample number: 10000
- [0058] background number: 10000
- [0059] Presentation: Fraunhofer
- [0060] Analysis model: Polydisperse
- [0061] Sample Suspension:
- [0062] Homogenize the sample in the sample container.
- [0063] Transfer about 30 mg of the sample into a 10 mL glass container.
- [0064] Add about 2 mL of suspension liquid (4) and close the container.
- [0065] Suspend the sample in an ultrasonic bath to complete deagglomeration.
- [0066] Measurement:
- [0067] Fill the sample dispersion unit with suspension liquid (4) and measure the blank background.
- [0068] Add the required amount of the homogeneous sample suspension dropwise into the sample dispersion unit, and analyse.
- [0069] Calculation:
- [0070] Calculate the mean particle size in which the $d_{(4.3)}$ =volume-mean diameter of the particles in μm .
- [0071] Dissolution Rate of Tibolone.
- [0072] Principle:
- [0073] After dissolution, tibolone is determined by reversed phase liquid chromatography.
- [0074] Equipment:
- [0075] 1. Liquid chromatograph with temperature controlled column compartment and variable wavelength absorption detector.
- [0076] 2. Dissolution apparatus 2 according to USP-DIS-SOLUTION <711> (paddle).
- [0077] Reagents and Reference Standards:
- [0078] 1. Water, HPLC grade USP/ACS suitable for gradient elution analysis or equivalent (e.g. milli-Q).
- [0079] 2. Methanol, analytical reagent.
- [0080] 3. Sodium lauryl sulphate solution 99%, Merck or equivalent.
- [0081] 4. Dissolution medium: Sodium lauryl sulphate solution 0.25%.
- [0082] Remove dissolved air from water (1) by purging with helium or equivalent before adding sodium lauryl sulphate (3).
- [0083] Weigh 10 g of sodium lauryl sulphate (3) and dissolve in 2.0 liter of hot water (1).
- [0084] Cool to room temperature and dilute to 4.0 liter with water (1) at room temperature.
- [0085] Mix carefully, in order to prevent the formation of lather.
- [0086] 5. Tibolone, reference standard.
- [0087] 6. Suitable sinkers in the case of capsules
- [0088] Reference Solution (in Duplicate):
- [0089] Accurately weigh about 25 mg of tibolone (5) and transfer into a 50 mL volumetric flask.
- [0090] Dissolve in and dilute to volume with methanol (2).
- [0091] Transfer 1.0 mL of this solution into a 100 mL volumetric flask.
- [0092] Dilute to volume with dissolution medium (4).
- [0093] Mix carefully, in order to prevent the formation of lather.
- [0094] Sample Preparation:
- [0095] Drug substance:
- [0096] Accurately weigh about 2.5 mg of tibolone and transfer into a gelatine capsule. Add about 20 glass beads, close the capsule and mix gently.
- [0097] Bring the capsule into the dissolution medium using a pair of tweezers and open the capsule to start dissolution.
- [0098] For a pharmaceutical dosage form tested, the final amount of tibolone added to the dissolution medium must be 2.5 mg. If the dosage contains less than 2.5 mg tibolone per dosage unit extra dosage units should be added to the medium.
- [0099] Tablet:
- [0100] Add a tablet to the dissolution medium to start dissolution.
- [0101] Capsule:
- [0102] Place the capsule in a suitable sinker and add the sinker with capsule to the dissolution medium to start dissolution.
- [0103] Test Solution:
- [0104] Prepare the test solution according to USP-Dissolution <711>.
- [0105] Withdraw about 10 mL of the test solution using a glass syringe equipped with stainless steel cannula (or equivalent glass device).
- [0106] Immediately centrifuge the solution and use the clear supernatant.

- [0107] Dissolution Conditions:
- [0108] Apparatus: USP-Dissolution apparatus 2
- [0109] Dissolution medium: see reagents no. 4
- [0110] Volume of Dissolution medium: 500 ml
- [0111] Temperature: 37 $\pm$ 0.5° C.
- [0112] Speed: 0.83 Hz (50 r.p.m.)
- [0113] Sampling time: 5, 10, 15, 30, and 45 minutes after start.
- [0114] Chromatographic Conditions:
- [0115] Column: Hypersil ODS, 5 μ m, 100x4.6 mm or equivalent
- [0116] Column temperature: 40° C.
- [0117] Mobile phase: methanol+water (77+23 v/v)
- [0118] Flow rate: 0.5 ml/min
- [0119] Detector: variable wavelength absorption detector, 205 nm, abs. range about 0.1 AUFS
- [0120] Injection volume: 200 μ l
- [0121] Number of injections: reference solutions: 3
- [0122] test solutions: 2
- [0123] dissolution medium: 1
- [0124] System Suitability Test:
- [0125] Indicating retention time for tibolone is 5.0 minutes.
- [0126] Alter the water concentration of the mobile phase if any impurity coelutes with tibolone.
- [0127] Criteria:
- [0128] 1. Relative standard deviation of injections of the reference solutions: RSD 3%.
- [0129] 2. Ratio of the mean response factors of the 2 reference solutions: 0.97 $\pm$ 1.03.
- [0130] 3. Response of any peak in the chromatogram of the dissolution medium at the position of tibolone: <3% with respect to the response of the tibolone peak in the chromatogram of the reference solution.
- [0131] Calculation:
- [0132] Calculate the amount of tibolone dissolved in the sample.
- [0133] Bioequivalence
- [0134] Assay for Org A
- [0135] For the determination of Org A, deuterated Org A can be used as internal standard. Plasma samples can be extracted with solid-phase extraction, thereafter silylated and quantified with capillary gas chromatography with mass spectrometric detection in the CI-mode. The lower limit of quantification was 0.1 ng/ml.
- [0136] In Vivo Study
- [0137] To assess the bioequivalence between a tibolone product (indicated as test treatment) and a reference treatment (such as Livial™ or Xyvion™) a single-dose (2.5 mg)

2-way crossover study should be performed. The wash-out period between the two treatments should be at least seven days. The total number of subjects should be at least 22, i.e. 1 subjects per sequence. Subjects should be postmenopausal women, aged 55-65, and physically and mentally healthy. Following single-dose administration, blood samples should be taken at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20 and 24 hours post-dosing. The Org A concentrations should be determined in plasma according to the method described earlier. Based on the Org A plasma concentrations the peak concentrations (C_{max}) and the area under the plasma-concentration-versus-time curve from zero to the time point of the last measurable concentration ($AUC_{0-tlast}$) as well as the area under the plasma-concentration-versus-time curve from zero extrapolated to infinity ($AUC_{0-\infty}$) should be calculated. Bioequivalence should be assessed based on C_{max} , $AUC_{0-tlast}$ and $AUC_{0-\infty}$ using 90% confidence intervals for the ratio of the test and reference treatment derived from an Analysis of Variance on log_e-transformed parameter values. The formulations are considered to be bioequivalent if the 90% confidence intervals for the above mentioned ratios of C_{max} , $AUC_{0-tlast}$ and $AUC_{0-\infty}$ are fully contained within the acceptance range 0.80-1.25.

[0138] The invention will be illustrated hereinafter with reference to the following Examples and the Figures.

EXAMPLE 1

[0139] Solid dosage forms of tibolone are made by a process similar to that described in U.S. Pat. No. 5,037,817.

[0140] Composition of the Tablets:

Ingredient	Quantity
Tibolone	2.5 mg
Potato starch	10 mg
Ascorbyl palmitate	0.2 mg
Magnesium stearate	0.5 mg
Lactose	86.8 mg
Tablet mass	100 mg

[0141] A basic granulate is prepared by granulation of a mixture of lactose (diluent), potato starch (90% of the total amount; disintegrant) and potato starch mucilage (10% of the total amount; binder) in a fluid bed granulator. After granulation, the basic granulate is passed through a sieve. Part of the granulate (approx. 10% w/w of the final batch size) is mixed with tibolone and ascorbyl palmitate using a suitable blender and then passed through a premix sieve. The tibolone premix and the remainder of the basic granulate are mixed in a suitable blender. Magnesium stearate is added and mixed. The mixture is compressed into 100 mg tablets.

[0142] Thus four batches have been prepared, the only material difference between them being analysed as the particle size of tibolone. See the table below.

EXAMPLE 2

[0143] A solution of tibolone is made as follows. Tibolone is dissolved into Ethanol 96%. The final concentration of tibolone in solution is 1 mg/ml. The solution is mixed and filled in 5 ml vials; 2.5 ml/vial. Dilute instruction: The

content of the vial must be diluted with 2.5 ml of solvent (water for injection) up to a total volume of 5 ml before use.

Table of Tibolone Drug Product Batches

[0144]

Batch	Initial particle size tibolone D _(4,3) (μm)	Premix sieve (μm)	Mean particle size of tibolone in dosage form (μm)
A	14	250	14.4 μm
B	45	125	19.3 μm
C	102	125	22.8 μm
D	102	250	48.2 μm
S	Solution according to Example 2		

EXAMPLE 3

[0145] The tibolone batches of Examples 1 and 2 are tested for the relative bioavailability of Org A. This test is conducted in the form of the single-dose (2.5 mg) 2-way cross-over study as described hereinbefore, exactly complying with the requirements thereof. The results are depicted in the Figures.

[0146] FIG. 1 provides the correlation between tibolone particles size and tablet-dissolution described hereinbefore.

[0147] In FIG. 2 the relative bioavailability of Org A is shown. On the Y-axis is depicted the relative Area Under the plasma-concentration versus time curve (AUC), with the solution (batch S) being the reference at 100%. From the picture it is clear that batches A, B and C show an unexpected bioavailability of Org A at least equal to that of the solution batch S.

[0148] In FIG. 3 the AUC of Org A and Org B is shown for batches A and S, as follows:

[0149] (1) is a bar indicating the AUC for Org A after the administration of batch A;

[0150] (2) is a bar indicating the AUC for Org A after the administration of batch S;

[0151] (3) is a bar indicating the AUC for Org B after the administration of batch A;

[0152] (4) is a bar indicating the AUC for Org B after the administration of batch S.

[0153] From the relative height of the bars, one can see that the effect of enhanced bioavailability of Org A resulting from the administration of solid tibolone having the appropriate particle size, is not observed for Org B.

1-12. (Cancelled, without prejudice or disclaimer)

13. A method of treatment or prevention of menopausal complaints, comprising administering to a patient in need thereof an effective amount of a pharmaceutical formulation in the form of an immediate-release peroral dosage unit, comprising tibolone, wherein the pharmaceutical formulation has a bioavailability, in vivo, of 3'-OH tibolone at a level above that provided by a solution of tibolone, wherein the amount of tibolone in the immediate-release peroral dosage unit and in the tibolone solution are substantially the same.

14. The method of claim 13, wherein the tibolone in the immediate-release peroral dosage unit has a mean particle size below about 22.8 μm.

15. The method of claim 14, wherein the tibolone in the immediate-release peroral dosage unit has a mean particle size below about 20 μm.

16. The method of claim 13, wherein the rate of dissolution of tibolone from the pharmaceutical formulation is such that when the pharmaceutical formulation is subjected to a dissolution-test, wherein a sample of said pharmaceutical formulation containing 2.5 mg of tibolone is exposed to a 0.25% sodium lauryl sulfate solution and the dissolution rate is measured, a t_{50%} value about 23.1 minutes is obtained.

17. The method of claim 16, wherein the tibolone in the immediate-release peroral dosage unit has a mean particle size below about 22.8 μm.

* * * * *

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/59, 33/06, 9/20, 47/10	A1	(11) International Publication Number: WO 99/06051 (43) International Publication Date: 11 February 1999 (11.02.99)
(21) International Application Number: PCT/EP98/04567 (22) International Filing Date: 21 July 1998 (21.07.98) (30) Priority Data: FI97A000184 30 July 1997 (30.07.97) IT (71) Applicant (for all designated States except US): A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L. [IT/IT]; Via Sette Santi, 3, I-50131 Firenze (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): VALLERI, Maurizio [IT/IT]; Via Galliano, 147, I-50144 Firenze (IT). TOSETTI, Alessandro [IT/IT]; Via F. Paoletti, 13, I-50132 Bagno a Ripoli (IT). (74) Agent: GERVASI, Gemma; Notarbartolo & Gervasi S.p.A., Corso di Porta Vittoria, 9, I-20122 Milan (IT).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D AND CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE		
(57) Abstract Described herein is a pharmaceutical composition containing Vitamin D and calcium, comprising a binding agent chosen from among the group consisting of: propylene glycol, a polyethylene glycol presenting a molecular weight comprised between 300 and 1500, liquid paraffin or silicone oil, useful for the treatment of nutritional deficiency of calcium and Vitamin D in the elderly.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D AND
CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE

Scope of the invention

The present invention refers to pharmaceutical compositions containing Vitamin D
5 and a calcium salt, the process for their preparation, and their use in the treatment
of pathological forms involving loss of bone tissue in the elderly, such as
osteoporosis, as well as in the prevention of illnesses linked to calcium
metabolism in the elderly, such as those leading to fractures of the proximal femur
or other non-vertebral fractures.

10 **State of the art**

The use of Vitamin D and calcium salts, either separately or in association, for
various illnesses, among which those concerning calcium metabolism in the
elderly, is already well documented in the state of the art. For example, in FR
2724844, the existence of a therapeutic association is claimed between Vitamin D
15 and calcium salts in combating osteoporosis.

However, the Vitamin D and calcium-based pharmaceutical formulations available
today still present a number of problems which render them not altogether
acceptable.

The problems that had to be faced for the pharmaceutical compositions that are
20 the subject of the present invention were in particular:

- a) the homogeneity of distribution of Vitamin D₃ in the final mixture;
- b) the properties of flow of the powder of the calcium salt used; and, when
present,
- c) the rate of reconstitution of the suspension to be prepared as and when
25 required.

In fact, for the preparation of these formulations, normally Vitamin D is used in the
so-called "coated" form, since it presents greater stability than the pure crystalline
form.

The "coated" form, however, presents the disadvantage of consisting of small
30 granules that are highly dense and smooth, which renders their distribution inside
the final mixture even more problematic, this distribution in itself already being
complex on account of the small amount of the vitamin involved in comparison

with the other constituents of the pharmaceutical compositions that are the subject of the present patent.

In addition, the calcium salt used for this type of preparations normally undergoes a granulation process (either damp or dry) to overcome the problems due to the poor characteristics of flow that it presents in its most widely used form, i.e., in the form of fine powder, which makes it unsuitable for processing using ordinary high output rate machines. However, the granules (including those obtained with specific excipients for favouring disgregation) present a poor disgregation rate, which is instead highly desirable for the pharmaceutical preparation in bags, both in order to guarantee a good level of bio-availability and to obtain a suspension to be prepared as and when required, in which the salt may be finely divided in order to reduce the rate of sedimentation of the suspension and eliminate the "sand" effect which is noted when granular suspensions of this type are taken.

There is therefore an evident need to have available new pharmaceutical formulations containing a Vitamin D-calcium association which may enable a high dosage of calcium mixed in a homogenous way with very low doses of Vitamin D (for example 1-2 g of calcium for 500 - 1000 I.U. of Vitamin D), may present a good stability, may have a high level of bio-availability, may be suited to being processed using high-speed production machines, and may be pleasant to take for the patient.

Detailed description of the invention

The pharmaceutical composition according to the invention makes it possible to overcome the aforesaid problems owing to a "granulation" of the calcium salt, at the rate of 1 - 2 g of calcium for 500 - 1000 I.U. of vitamin D, in the presence of propylene glycol or a polyethylene glycol presenting a molecular weight comprised between 300 and 1500 (for formulations that involve subsequent disgregation in water) or (in the case of pharmaceutical formulations that do not envisage subsequent disgregation) with liquid paraffin or silicone oil.

Surprisingly, the addition of the calcium salt to the above said glycols makes it possible to obtain, a triple advantageous effect::

a) The even and diffused distribution of the glycol over the calcium granules, as well as over the other components of the formulation, plays a "binding" effect on

the small granules of coated Vitamin D₃. In this way, there is an anchoring of the particles of the vitamin to the system, thus enabling its even distribution ;

b) The atypical granulation of the calcium salt, taking place with this agent, modifies the properties of flow just enough to obtain a mixture having
5 characteristics of smoothness such as to enable its processing with high output machines;

c) The aforesaid modification of the properties of flow of the calcium salt however is not an obstacle to its complete re-dispersion, where this is required, once the aqueous suspension has been reconstituted.

10 Moreover the moistening effect exerted by the propylene glycol on the calcium phosphate must be considered. This effect renders the operation of reconstitution of a dispersion faster than the one obtainable without its use.

According to the invention particularly preferred is propylene glycol. In this connection it is important to note that the well-known sour taste of propylene
15 glycol or somewhat bitter one of low-molecular-weight polyethylene glycols may be easily covered by the common excipients and sweeteners, without affecting the pleasantness of the resultant pharmaceutical composition.

As binding agents for pharmaceutical forms that do not have to be dispersed in water, the substances that have proved extremely useful, and hence constitute a
20 subject of the present invention, are liquid paraffin and silicone oil. These components in fact make it possible to obtain the same aggregating effect as the previous excipients and an equivalent distribution of the active principles.

Among the various forms of Vitamin D used for the formulations according to the invention, Vitamin D₃, Vitamin D₂ and their mixtures are preferred.

25 The calcium salt used for the present invention is, for example, chosen in the group consisting of: phosphate, glycerophosphate, carbonate, bicarbonate, lactate, citrate, tartrate, gluconate, and chloride.

Particularly preferred is calcium phosphate and, more particularly, tribasic phosphate.

30 Normally the quantity of calcium phosphate is comprised between 30 - 80% by weight calculated on the total composition.

The pharmaceutical compositions that form the subject of the present patent moreover comprise the usual moistening agents (e.g., sucrose palmitate); fluidifying agents (such as, colloidal silica); suspending agents (such as cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose); organoleptic correctors
5 (such as, flavouring substances, citric acid); sweeteners (such as mannitol, sorbitol, saccharin salts, aspartame, etc.); and colouring agents (such as E110).

It must be noted that the pharmaceutical compositions according to the present invention are not suitable for dermatology applications (for example in the form of creams).

- 10 According to a preferred formulation (bags) the pharmaceutical composition of the present application contains the propylene or the polyethylene glycol in a quantity comprised between 5 - 15% by weight calculated on the total weight of the formulation.

Non-limiting examples of the present invention are the following:

15 Example 1

Lot for 6000 bags

The sucrose palmitate, citric acid and sodium saccharin are sifted using a sieve with 0.5-mm mesh.

- 20 The propylene glycol is distributed over the calcium phosphate in a high speed granulator by setting the following process parameters:

2 minutes with impeller at 80 r.p.m. and chopper turned off, followed by 2 minutes with impeller at 160 r.p.m. and chopper at 1500 r.p.m.

The colloidal silica, 25% of the mannite required, the citric acid, and the sodium saccharin are added to the mixture.

- 25 The above is mixed for 6 minutes with impeller at 80 r.p.m. and chopper at 1500 r.p.m. until a homogeneous composition is obtained.

- Prepared separately, in a cube mixer at a rate of 25 r.p.m. for 15 minutes, is a premix consisting of sucrose palmitate, microcrystalline cellulose and carboxymethyl cellulose, lemon flavouring, E110, the remaining part of the
30 mannite, and the Vitamin D₃.

The mixture thus obtained is transferred into the granulator and mixed with the rest of the preparation, according to the following parameters:

1 minute with impeller at 140 r.p.m. and chopper at 1500 r.p.m., followed by 30 seconds with impeller at 140 r.p.m. and chopper turned off.

The granulate thus obtained is distributed in the bags, which thus contain a preparation having the following composition:

5	Tribasic calcium phosphate	3.100 g
	(corresponding to 1200 mg of Ca^{++})	
	Cholecalciferol (Vit. D ₃) 100 000 IU/g	0.008 g
	(corresponding to 800 IU)	
	Propylene glycol	0.800 g
10	E110	0.002 g
	Colloidal silica	0.120 g
	Lemon flavouring	0.100 g
	Microcrystalline cellulose - MCC	0.200 g
	Sodium saccharin	0.015 g
15	Anhydrous citric acid	0.165 g
	Sucrose monopalmitate	0.120 g
	Mannitol q.s. to	7.000 g

In a similar way, but using polyethylene glycol instead of propylene glycol, bags may be prepared containing a preparation having the following composition:

20	Tribasic calcium phosphate	3.100 g
	(corresponding to 1200 mg of Ca^{++})	
	Cholecalciferol (Vit. D ₃) 100 000 IU/g	0.008 g
	(corresponding to 800 IU)	
	Polyethylene glycol 400	0.800 g
25	E110	0.002 g
	Colloidal silica	0.120 g
	Lemon flavouring	0.100 g
	Microcrystalline cellulose - MCC	0.200 g
	Sodium saccharin	0.015 g
30	Anhydrous citric acid	0.165 g
	Sucrose monopalmitate	0.120 g
	Mannitol q.s. to	7.000 g

Example 2 (tablets)

Preparation for 20,000 tablets

The liquid paraffin is distributed over the calcium phosphate in a high speed granulator, setting the following process parameters:

- 5 2 minutes with impeller at 80 r.p.m. and chopper turned off, followed by 2 minutes with impeller at 160 r.p.m. and chopper at 1500 r.p.m.

The colloidal silica, the carboxymethyl cellulose, the sodium saccharin and the orange flavouring are sifted using a sieve with a 0.5-mm mesh.

- 10 Vitamin D₃ is added to the above-mentioned components and the product is mixed using a cube mixer at a rate of 25 r.p.m. for 5 minutes.

The sorbitol is then added, and everything is mixed in the cube mixer for 10 minutes at 25 r.p.m.

This premix is transferred into the granulator and is mixed with the rest of the preparation, by setting the following process parameters:

- 15 1 minute with impeller at 140 r.p.m. and chopper at 1500 r.p.m., followed by 30 seconds with impeller at 140 r.p.m. and chopper turned off.

The granulate is compressed to the required weight to obtain tablets having the following composition:

	Tribasic calcium phosphate	3.100 g
20	(corresponding to 1200 mg of Ca ⁺⁺)	
	Cholecalciferol (Vit. D ₃) 100 000 IU/g	0.008 g
	(corresponding to 800 IU)	
	Liquid paraffin	0.500 g
	Sodium carboxymethyl cellulose	0.050 g
25	Sodium saccharin	0.015 g
	Orange flavouring	0.100 g
	Sorbitol q.s. to	4.400 g

In the same way, using silicone oil instead of liquid paraffin, it is possible to obtain tablets having the following composition:

30	Tribasic calcium phosphate	3.100 g
	(corresponding to 1200 mg of Ca ⁺⁺)	
	Cholecalciferol (Vit. D ₃) 100 000 IU/g	0.008 g

(corresponding to 800 IU)

	Silicone oil	0.500 g
	Sodium carboxymethyl cellulose	0.050 g
	Sodium saccharin	0.015 g
5	Orange flavouring	0.100 g
	Sorbitol q.s. to	4.400 g

The pharmaceutical compositions that form the subject of the present invention were made for the purpose of being used in the treatment of nutritional deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone tissue linked to age and to prevent proximal femur fractures and other non-vertebral fractures. These pharmaceutical compositions may be used also to prevent osteoporosis induced by chronic treatment with corticosteroids.

I.U. as used in the present application means International Units and corresponds to the amount having the activity of 0.0025 γ of Vitamin D3.

CLAIMS

- 1 1. Pharmaceutical composition containing as active principles Vitamin D
2 associated to a calcium salt characterized in that it comprises a binding agent
3 chosen in the group consisting of: propylene glycol, a polyethylene glycol
4 presenting a molecular weight comprised between 300 and 1500, liquid paraffin or
5 silicone oil and that the Vitamin D is present at the rate of 1 - 2 g of calcium for
6 500 1000 I.U. of Vitamin D.
- 1 2. Pharmaceutical composition according to Claim 1, in which the calcium used
2 is in the form of a salt chosen in the group consisting of:
3 phosphate, glycerophosphate, carbonate, bicarbonate, lactate, citrate, tartrate,
4 gluconate, and chloride.
- 1 3. Pharmaceutical composition according to Claims 1 and 2, in which the calcium
2 salt is calcium phosphate.
- 1 4. Pharmaceutical composition according to Claim 3 wherein the calcium
2 phosphate is 30 - 80% by weight calculated on the total composition.
- 1 5. Pharmaceutical composition according to Claim 1, in which the Vitamin D
2 used is Vitamin D₂ (or ergocalciferol), Vitamin D₃ (or cholecalciferol), or one of
3 their mixtures.
- 1 6. Pharmaceutical composition according to Claim 5, in which the vitamin used is
2 Vitamin D₃.
- 1 7. Pharmaceutical composition (bag) according to Claim 1, containing the
2 propylene glycol or polyethylene glycol in a quantity comprised between 5-15%
3 by weight calculated on the total composition.
- 1 8. Pharmaceutical composition (tablet) according to Claim 1, containing liquid
2 paraffin or silicone oil.
- 1 9. Pharmaceutical composition according to Claim 7, characterized as follows:
- | | |
|---|---------|
| 2 Tribasic calcium phosphate | 3.100 g |
| 3 (corresponding to 1200 mg of Ca ⁺⁺) | |
| 4 Cholecalciferol (Vit. D ₃) 100 000 IU/g | 0.008 g |
| 5 (corresponding to 800 IU) | |
| 6 Propylene glycol | 0.800 g |
| 7 E110 | 0.002 g |

8	Colloidal silica	0.120 g
9	Lemon flavouring	0.100 g
10	Microcrystalline cellulose - MCC	0.200 g
11	Sodium saccharin	0.015 g
12	Anhydrous citric acid	0.165 g
13	Sucrose monopalmitate	0.120 g
14	Mannitol q.s. to	7.000 g

1 10. Pharmaceutical composition according to Claim 7, characterized as follows:

2	Tribasic calcium phosphate	3.100 g
3	(corresponding to 1200 mg of Ca^{++})	
4	Cholecalciferol (Vit. D ₃) 100 000 IU/g	0.008 g
5	(corresponding to 800 IU)	
6	Polyethylene glycol 400	0.800 g
7	E110	0.002 g
8	Colloidal silica	0.120 g
9	Lemon flavouring	0.100 g
10	Microcrystalline cellulose - MCC	0.200 g
11	Sodium saccharin	0.015 g
12	Anhydrous citric acid	0.165 g
13	Sucrose monopalmitate	0.120 g
14	Mannitol q.s. to	7.000 g

1 11. Pharmaceutical composition according to Claim 8, characterized as follows:

2	Tribasic calcium phosphate	3.100 g
3	(corresponding to 1200 mg of Ca^{++})	
4	Cholecalciferol (Vit. D ₃) 100 000 IU/g	0.008 g
5	(corresponding to 800 IU)	
6	Liquid paraffin	0.500 g
7	Sodium carboxymethyl cellulose	0.050 g
8	Sodium saccharin	0.015 g
9	Orange flavouring	0.100 g
10	Sorbitol q.s. to	4.400 g

1 12. Pharmaceutical composition according to Claim 8, characterized as follows:

2	Tribasic calcium phosphate	3.100 g
3	(corresponding to 1200 mg of Ca^{++})	
4	Cholecalciferol (Vit. D_3) 100 000 IU/g	0.008 g
5	(corresponding to 800 IU)	
6	Silicone oil	0.500 g
7	Sodium carboxymethyl cellulose	0.050 g
8	Sodium saccharin	0.015 g
9	Orange flavouring	0.100 g
10	Sorbitol q.s. to	4.400 g

1 13. Process for the preparation of a pharmaceutical composition according to
2 Claims 1 and 7, characterized by the following steps:

- 3 a) In a granulator turning at high speed, distribute the binding agent, consisting
4 of propylene glycol or low-molecular-weight polyethylene glycols over the calcium
5 salt.
- 6 b) Add the colloidal silica, approximately 25% of the mannite, the citric acid, and
7 the sodium saccharin, and mix for the time required and at the appropriate speed.
- 8 c) Add the mixture, prepared separately, consisting of sucrose palmitate, a
9 suspending agent, flavouring, colouring agent, the remaining part of the mannite,
10 and the Vitamin D_3 , and mix together with the rest of the preparation.
- 11 d) Distribute the granulate thus obtained into bags.

1 14. Process for the preparation of a pharmaceutical composition according to
2 Claims 1 and 8, characterized by the following steps:

- 3 a) In a granulator turning at high speed, distribute the binding agent, consisting of
4 liquid paraffin or silicone oil, over the calcium salt.
- 5 b) Add in order, to a mixture of colloidal silica, carboxymethyl cellulose and
6 sodium saccharin previously sifted, the Vitamin D_3 and the sorbitol, mixing
7 thoroughly every time before a new ingredient is added. Pour the mixture into the
8 rotating granulator and mix for the required time and at the appropriate speed.
- 9 c) Compress the granulate to the required weight to obtain the desired tablets.

1 15. Composition according to Claim 1, for use in the treatment of nutritional
2 deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone

3 tissue linked to age and to prevent femoral fractures and other non-vertebral
4 fractures.

1 16. Composition according to Claim 1, for use in the prevention of osteoporosis
2 induced by treatment with corticosteroids.

1 17. Method for the treatment of nutritional deficiency of calcium and Vitamin D in
2 the elderly, to reduce the loss of bone tissue linked to age and to prevent femoral
3 fractures and other non-vertebral fractures, in which therapeutically effective
4 quantities of a composition according to Claim 1 are administered to the patient.

1 18. Method according to Claim 16 for the prevention of osteoporosis induced by
2 treatment with corticosteroids.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/04567

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/59 A61K33/06 A61K9/20 A61K47/10

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 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 588 539 A (TEVA) 23 March 1994 see the whole document ---	1-7
X	FR 2 073 271 A (J. BOIVIN ET AL.) 1 October 1971 see the whole document ---	1, 2, 5, 6, 8
A	WO 96 09036 A (LABORATOIRE INNOTHERA) 28 March 1996 cited in the application see the whole document -----	1-17

☐ 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.
- "&" document member of the same patent family

Date of the actual completion of the international search

26 November 1998

Date of mailing of the international search report

09/12/1998

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) 340-3016

Authorized officer

Scarponi, U

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/04567

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 588539 A	23-03-1994	AT 148630 T	15-02-1997
		AU 667742 B	04-04-1996
		AU 4740893 A	24-03-1994
		CA 2106423 A	19-03-1994
		DE 69307977 D	20-03-1997
		DE 69307977 T	28-08-1997
		DK 588539 T	10-03-1997
		ES 2098672 T	01-05-1997
		GR 3023127 T	30-07-1997
		JP 6219952 A	09-08-1994
		US 5565442 A	15-10-1996
		US 5804573 A	08-09-1998
		ZA 9306835 A	14-04-1994
FR 2073271 A	01-10-1971	NONE	
WO 9609036 A	28-03-1996	FR 2724844 A	29-03-1996
		AU 3168395 A	09-04-1996
		CA 2200568 A	28-03-1996
		DE 29521515 U	05-06-1997
		EP 0785769 A	30-07-1997
		FI 971188 A	20-05-1997
		HU 77702 A	28-07-1998
		JP 10505850 T	09-06-1998
		NO 971356 A	21-03-1997
		PL 319585 A	18-08-1997



No. 08-067103- -00004-0000

Fecha: 2010-02-25 17:34:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 16

adicación

FORMULARIO UNICO DE OPOSICIÓN

1		OPOSICIÓN A SOLICITUD DE:	
☒ Patente de Invención		☐ Marca Colectiva	
☐ Patente de Modelo de Utilidad		☐ Marca de Certificación	
☐ Diseño Industrial		☐ Lema Comercial	
☐ Esquema de Trazado para Circuitos Integrados		☐ Marcas de Productos o Servicios	
		☐ Denominación de Origen	
2		SOLICITUD PUBLICADA	
Número del expediente: 08-067103		Solicitante: WORLD-TRADE IMPORT-EXPORT, WTIE, AG	
Apoderado: DILIA MARIA RODRIGUEZ D'ALEMAN		Título de la nueva creación o denominación del signo: COMPOSICIONES FARMACEUTICAS QUE COMPRENDEN DERIVADOS DE ESTEROIDES SINTETICOS MINERALES, Y METABOLITO ACTIVO DE LA VITAMINA D, 1:25:(OH)2D3 CALCITRIOL	
Gaceta: No. 610 DE 30/NOV/2009 N.P. 800			
3		OPOSICIÓN PRESENTADA POR:	
OPOSITOR	Nombre: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.	IDENTIFICACIÓN	
	Dirección: CRA. 1 # 46-84 Nacionalidad o Domicilio: COLOMBIA CALI - VALLE Lugar de Constitución: CALI- VALLE	☐ C.C. ☒ NIT ☒ C.E. ☐ Otro	
	Teléfono: 052 6877700 Fax: 052 6877790 E-mail:	Cual: Número 890.301.463-8	
REPRESENTANTE O APODERADO	Nombre: TITO NOE PARRA MURILLO	IDENTIFICACIÓN	
	Dirección: CALLE 108 # 51-45 BOGOTA Teléfono: 7422525 Fax: 7424092 E-mail:	☒ C.C. ☐ NIT ☐ C.E. ☐ Otro	
		Cual: Número 79.579.680 T.P. 71.168	
4		FUNDAMENTOS DE LA OPOSICIÓN	
Causal:		Signo fundamento de la oposición:	
Expediente y/o registro de la marca opositora (De ser marca el signo fundamento de la oposición):		Justificación: VER ANEXO	
5		PRÓROGA	
Comprobante de pago No. _____		☐ SI ☐ NO Fecha: _____	
6		INVOCACIÓN DE NOTORIEDAD	
Comprobante de pago No. _____		☐ SI ☐ NO Fecha: _____	
7		CONCEPTO DE OPOSICIÓN	
Comprobante de pago No. 10.15.102		☐ SI ☐ NO Fecha: 24/FEB/2010 24 FEB 09	

8 ANEXOS

☐ SI ☐ NO

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuera el caso.
- ☐ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés , si fuere el caso.
- ☒ Documento que acrediten la existencia y representación legal de las partes, cuando sean personas jurídicas.
- ☐ Tasa de próroga
- ☒ Copias para traslado.

9 Nombre y firma

Nombre: TITO NOE PARRA MURILLO

Firma

C.C.

79.579.680

T.P. 71.168

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