



No. 07-136799- -00004-0000

Fecha: 2009-04-29 11:25:44 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 31

FORMULARIO ÚNICO DE OPOSICIÓN

OPPOSICIÓN 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. | |

Número del expediente: 07-136799

Solicitante: **WYETH**

**SOLICITUD
PUBLICADA**

Apoderado: **ALVARO CORREA ORDONEZ**

Título de la nueva creación o denominación del signo: **"FORMULACIONES DE ESTRÓGENOS CONJUGADOS Y BAZEDOXIFENO"**

García	600
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③ OPOSICION PRESENTADA POR:

SOLICITANTE	Nombre: GYNOPHARM S.A Dirección: CALLE 80 No. 78B -201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>802.006.279-4</u>
	Teléfono: (571)3719900 Fax: (571)3730818 E-mail: negocios@optimum-co.com	
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ Dirección: CARRERA 13 No. 119-95 104 Teléfono: (571) 2131213 Fax: (571) 6121979 E-mail: <u>negocios@optimum-co.com</u>	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>51'975.664 TP.83823</u>

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.
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Signo opositor:

Justificación:

Justificación: La presente solicitud no cumple con los requisitos 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".

202
2
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: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: *Eliana Bohorquez*

C.C. 51.975.664

TP. 83823

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 07 136799 ✓
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIONES DE ESTRÓGENOS CONJUGADOS
Y BAZEDOXIFENO"
Solicitante : WYETH
Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 600 del 30 de Enero de 2009

Yo, **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 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 **"FORMULACIONES DE ESTROGENOS CONJUGADOS Y BAZEDOXIFENO"**, cuyo titular es **WYETH**, 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 ESTROGENOS. 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 27 de diciembre de 2007 reivindicando prioridad bajo la solicitud US20050694889P del 2005-06-29; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 600 del 30 de Enero de 2009, cuya publicación internacional corresponde a la WO2007002823 del 2007-01-04.

2.2. La solicitud colombiana 07 136799 objeto de la presente oposición, tiene relación con formulaciones de dosificación sólidas conteniendo estrógenos conjugados y bazedoxifeno, o una sal de ellos. En algunas modalidades las composiciones incluyen un núcleo comprende estrógenos conjugados y a lo menos una cobertura que comprende bazedoxifeno o una sal de ellos. Particularmente, se refiere a una composición farmacéutica comprende un núcleo y a lo menos una cobertura,



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

donde el núcleo comprende estrógenos conjugados y la cobertura comprende bazedoxifeno o una sal farmacéuticamente aceptable de estos; donde la composición farmacéutica es una tableta, donde los estrógenos conjugados están presentes en una cantidad cerca desde 0,10 a cerca de 1,0 mg, donde los estrógenos conjugados están presentes en una cantidad cerca desde 0,3 a cerca de 0,8 mg, donde los estrógenos conjugados están presentes en una cantidad cerca de 0,4 a cerca de 0,5 mg, donde los estrógenos conjugados están presentes en una cantidad cerca de 0,5 a cerca de 0,7 mg, donde el bazedoxifeno esta presente en una cantidad desde cerca de 1 a cerca de 50 mg, basado en el peso del bazedoxifeno de base libre, y donde el bazedoxifeno esta presente en una cantidad desde cerca de 5 a cerca de 25 mg, basado en el peso del bazedoxifeno de base libre.

2.3. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra 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"*. Así las cosas, 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 afecta la patentabilidad de la presente solicitud:

- D1: EP0803250 publicada el 29 de Octubre de 1997.
- D2: US2004063692 publicada el 1 de abril de 2004.

2.4. Ahora bien, el documento D1 revela sistemas de administración orales que comprende una pastilla comprimida medicinal que comprende un núcleo y una capa de azúcar, donde la capa de azúcar contiene una dosis de un esteroide hormonal. Particularmente, en los ejemplos 4 y 9 así como en la reivindicación 1 define que la pastilla farmacéutica comprende un núcleo interno comprimido y



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

una capa externa, en el que el núcleo comprimido y donde el ejemplo 4 define que la cubierta comprende Medroxiprogesterona Acetato, USP al 10% y el ejemplo 9 define que la cubierta comprende 5 mg de medrogestona. Ahora bien, el documento D2 se refiere a regímenes de medicación ampliados para el modulador de receptor de estrógeno selectivo bazedoxefino (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1 H-indol-5-ol). En el ejemplo 1 y 3 se define una formulación que incluye bazedoxifeno acetato para rápida disolución en regímenes o tratamientos en seres humanos.

2.5. Por lo tanto, visto dicho documento D2 en combinación con el documento D1, es evidente el conocimiento y la preexistencia del uso de formulaciones de dosificación sólidas conteniendo estrógenos conjugados y bazedoxifeno para rápida disolución así como el conocimiento de núcleos revestidos con cubiertas, sobre los cuales, a partir de lo revelado en los mismos es posible deducir y llegar de manera evidente a composiciones que incluyen un núcleo que comprende estrógenos conjugados y a lo menos una cobertura que comprende bazedoxifeno, de necesaria rápida disolución, de manera que la presente solicitud carece evidentemente de altura inventiva. Es evidente que un forma farmacéutica para un régimen de este tipo requiere una rápida disolución de bazedoxifeno y que al conjugarlo con otros estrógenos se hace necesario que su presencia no sea en el núcleo sino en la cubierta, cuando la técnica ya lo prevé como se ilustra en el documento D1, con el objeto del mismo y se ilustra ampliamente desde el resumen y se amplía en la descripción. Dicho documento D1 revela técnicas de elaboración de tabletas comprimidas con un núcleo revestido para dosificar esteroides hormonales a una rata de entrega, demostrando que es ampliamente conocido el método, que combinado con lo que ejemplifica el documento D2, respecto a la necesidad de suministrar una forma farmacéutica que incluye bazedoxifeno de rápida disolución, es posible evidentemente llegar a conformar una formulación que incluyen un



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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

núcleo que comprende estrógenos conjugados y a lo menos una cobertura que comprende bazedoxifeno.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 y con base en el documento D2, carece de ALTURA INVENTIVA.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07 136799 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.8.1. **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, 29 de junio de 2005, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a conformar una formulación que incluyen un núcleo que comprende estrógenos conjugados y a lo menos una cobertura que comprende bazedoxifeno, sobre el cual busca protección en el capítulo reivindicatorio.

2.9. 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 los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"FORMULACIONES DE ESTROGENOS CONJUGADOS Y BAZEDOXIFENO"**, cuyo titular es **WYETH**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 600 del 30 de Enero 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: EP0803250 publicada el 29 de Octubre de 1997.
- D2: US2004063692 publicada el 1 de abril de 2004.

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: EP0803250 publicada el 29 de Octubre de 1997.
- D2: US2004063692 publicada el 1 de abril de 2004.

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,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 400 OPOSIOBSERVTER Folios: 31

NIT : 8001

RECIBO OFICIAL DE CAJA : 09 - 32,047
FECHA : ABRIL 29 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
GYNOFARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	14074841	14/11/2008	1,064,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	287,000.00
		12 MARCAS Y LEMAS COMERCIALES	287,000.00
		TOTAL :	\$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



Gynopharm

The primary support
for the woman's health specialist

212. 12

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 **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **07 136.799**, titulada "**FORMULACIONES DE ESTRÓGENOS CONJUGADOS Y BAZEDOXIFENO**", cuyo titular es **WYETH**, publicada en la gaceta No. 600 del 30 de enero de 2009.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, 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 y judicialmente 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 Barranquilla (Colombia) a los 17 días del mes de Abril de 2009.

GYNOPHARM S.A.

Cédula de Extranjería: No. 319788.

NIT: 802.006.279-4

Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHÓRQUEZ

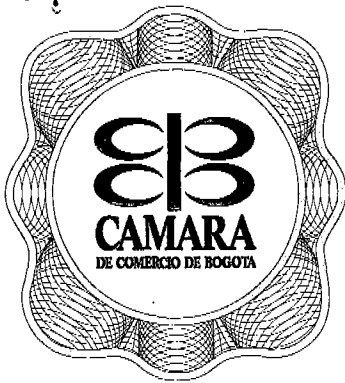
C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

RECONOCIMIENTO DE DOCUMENTO PRIVADO
 Ante mí, LILIANA CONSTANZA BARBOSA PLATA,
 Notaria Veinticinco del Circulo de Bogotá (E),
 comparece [Firma]
 identificado con cédula de ciudadanía
3197288
 y declara que la firma puesta en el presente
 instrumento privado es suya y que el contenido
 del mismo es cierto. **17 ABR. 2009**
 FIRMA [Firma]
 LILIANA CONSTANZA BARBOSA PLATA
 NOTARIA VEINTICINCO

NOTARIA PRIMERA DE CHIA
PRESENTACION PERSONAL
 Este memorial dirigido a Superintendencia de Industria y Comercio
 fué presentado personalmente ante el suscrito notario por Eliana Isaura Moreno Bohorquez
 Identificado C.C. 31.975.664 B10
 T.P. de Abogado No. 83873 C.S.
 Chía. 28 ABR 2009

[Firma]

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/04/20

HORA: 16:06:25

OPERACION: 02C030420146

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

Direccion 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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/04/20

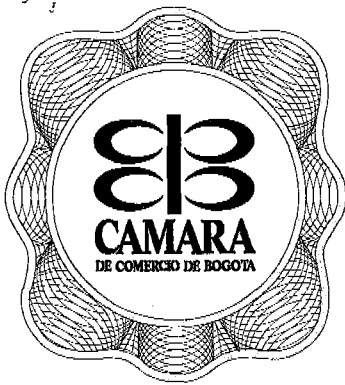
HORA: 16:06:25

OPERACION: 02C030420146

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 ***



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* 8 0 5 3 1 9 8 0 *

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/04/20

HORA: 16:06:25

OPERACION: 02C030420146

PAGINA: 3

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

C E R T I F I C A

CAPITAL

Nro Acciones

Valor Acci3n

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 gravamenes 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: 2009/04/20

HORA: 16:06:25

OPERACION: 02C030420146

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.

CERTIFICA

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

CERTIFICA

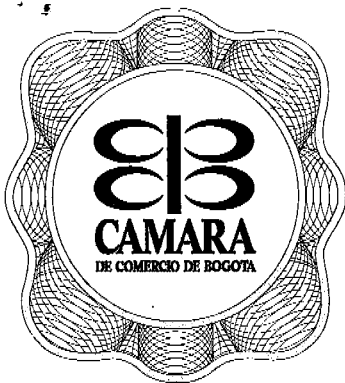
Que según Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

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

CERTIFICA

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

*** CONTINUA ***

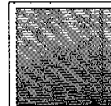


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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/04/20

HORA: 16:06:25

OPERACION: 02C030420146

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. 16 del 08 de Mayo de 2008 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 22 de Mayo de 2008 bajo el No. 140,053 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal	
Marroquin Sepulveda Edgar	CC.*****17,147,542

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 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el senor 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 representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM 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 senor 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 ciudadania No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comer-

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/04/20

HORA: 16:06:25

OPERACION: 02C030420146

PAGINA: 6

cio de Barranquilla bajo el No.1.872 del Libro respectivo, para
que en representacion de GYNOFARM S.A, suscriba las declaracio-
nes cambiarias a los que esta obligada GYNOFARM S.A. en el giro
ordinario de sus negocios y operaciones sociales.-----

CERTIFICA

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.

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.

CERTIFICA

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.

m. r. j. a.

ANEXO 1



(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 803 250 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
29.10.1997 Bulletin 1997/44

(51) Int. Cl.⁶: **A61K 9/20**

(21) Application number: 96308424.9

(22) Date of filing: 21.11.1996

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Designated Extension States:
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(30) Priority: 24.04.1996 US 637139

(71) Applicant:
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Madison, New Jersey 07940-0874 (US)

(54) **Controlled release of steroids from sugar coatings**

(57) A compressed medicinal tablet comprising a tablet core and a sugar coating, said sugar coating containing a dose of a hormonal steroid and a steroid release rate controlling amount of microcrystalline cellulose.

EP 0 803 250 A1

Description**BACKGROUND OF THE INVENTION**

5 In the past three decades, substantial effort has gone into the identification of methods for controlling the rate of release of drug from pharmaceutical tablets. Excipients have been incorporated into tablet cores to control dissolution, and hence absorption, of drugs. Tablets and spheroids have been coated with polymers to provide slow, diffusion - controlled release or site-specific release of drugs.

10 Tablets and encapsulated spheroid dosage forms have also been prepared containing multiple drugs, either in admixture or as separate tablet layers or spheroids. The drugs are provided to perform multiple functions or to provide synergism. Such tablets are especially useful in those circumstances where conventional therapy dictates the use of more than one drug possessing different but compatible activities. For example, diuretic agents are frequently administered with antihypertensive agents, and progestational agents in conjunction with estrogens.

Brief Description of the Invention

15 In accordance with this invention, there is provided a pharmaceutical tablet comprising an internal compressed core and an external sugar coating, wherein said compressed core optionally contains no pharmacologically-active agent or one or more non-steroidal, pharmacologically-active agents that are conventionally administered in conjunction with a hormonal steroid, the improvement which comprises the incorporation of a hormonal steroid and a hormonal steroid release rate controlling amount of micro-crystalline cellulose in said sugar coating. The compressed tablet core may be devoid of any medicament or it may contain a pharmaceutical agent other than a steroid, that is compatible with the steroid and any other therapeutic agent in the sugar coating. Thus, the sugar coated tablets of this invention may contain one or more pharmacologically-active agents, where the improvement in prior sugar coated tablets comprises 25 the incorporation of a hormonal steroid release rate controlling amount of microcrystalline cellulose in conjunction with a hormonal steroid in said sugar coating. The sugar-coated tablet may be finished with color coatings and polished as is common in coated tablets.

30 The contents of the tablet core are quite independent from the sugar coating in the sense that the sugar coating and the hormonal steroid contained in it are dissolved before disintegration of the compressed tablet core and dissolution of any drug component present in the core. The excipient components employed in formulation of the core tablet may include pharmaceutically-acceptable water-soluble and/or insoluble substances such as lactose, calcium phosphate, starch, calcium carbonate, dextrose, sorbitol, mannitol, microcrystalline cellulose, sucrose, polyvinylpyrrolidone, methylcellulose, carboxymethylcellulose, alginates, hydroxypropylcellulose, hydroxypropylmethyl-cellulose, ethylcellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, stearic acid, polyethylene glycol, sodium 35 lauryl sulfate, fumed silica, talc and the like.

The sugar coat containing the hormonal steroid also contains a steroid release rate-controlling amount of microcrystalline cellulose and, in certain circumstances, polyvinylpyrrolidone to aid in application of the sugar coat.

40 The tablet core is produced by compression of an admixture, which has preferably, been granulated, of the pharmaceutically-acceptable excipients, and, if desired, a therapeutic agent compatible with the steroid to be incorporated with the release rate controlling amount of microcrystalline cellulose in the sugar coating. The tablet core may have an unplasticized or plasticized seal coat designed to modify the drug release characteristics of any drug(s) contained within the core, or to protect them against moisture and/or oxygen. The non-medicated cores are those conventionally employed as placebo tablets in pharmacological studies.

Detailed Description of the Invention

45 This invention provides an improved compressed tablet in which, in addition to a conventional internal tablet core optionally containing no drug or one or more drugs that are pharmacologically compatible with a steroid in the external sugar coating, a sugar coating is present which comprises a hormonal steroid in an amount of about 0.1 to about 20 percent by weight of the sugar coating; microcrystalline cellulose in an amount from about 0.1 to about 3 percent by weight of the sugar coating; polyvinylpyrrolidone in from about 0 to about 5 percent by weight of the sugar coating; and sugar. On a unit dose basis, the tablet contains about 0.01 to about 50 milligrams, preferably about 0.015 to about 40 milligrams and more preferably about 0.02 to 30 milligrams, of total hormonal steroid load in the loaded sugar coating layer. If desired, an undercoat of inert filled sugar may be applied over a seal coat prior to the steroid loaded sugar coat layer. The inert filler-containing sub-layer sugar coating may be made up with sucrose containing about 7.5 to about 15 percent microcrystalline cellulose. The outer sugar coating may contain a coloring agent such as titanium dioxide or a primary, secondary or grayed tint as is customary in the tableting art. If desired, the coloring agent may be applied as a separate coating layer over the outer sugar layer. A final polish may be used to further finish and complete the tablet.

The sugar used in production of the sugar coatings referred to throughout this specification is a sugar product, such

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as sucrose, derived from beet or cane sources or starch, saccharide or polysaccharide converted sources, which are considered suitable for tablet coating purposes. The currently preferred sugar is sucrose.

It has been discovered that the release of a hormonal steroid from the sugar coating can be controlled by limiting the quantity of microcrystalline cellulose to from about 0.1 to about 3 percent by weight of the sugar coating. This use of a small quantity of microcrystalline cellulose in the sugar coat is unlike the use of this excipient as a compression aid or to assist disintegration of a tablet core. In the latter case, the concentration of microcrystalline cellulose may rise to as high as 15 to 30 percent of weight.

Examples of hormonal steroids suitable for incorporation into the sugar coating formulations of this invention include, for instance, one or more of the following steroids; medroxyprogesterone acetate, levonorgestrel, gestodene, medrogestone, estradiol, estriol, ethinylestradiol, mestranol, estrone, dienestrol, hexestrol, diethylstilbestrol, progesterone, desogestrel, norgestimate, hydroxyprogesterone, norethindrone, norethindrone acetate, norgestrel, megestrol acetate, methyltestosterone, ethylestrenol, methandienone, oxandrolone, trimegestone, dienogest, and the like. Additionally, the tissue selective progesterones and/or progesterone antagonists which may or may not have the typical steroidal functionality may be formulated into this technology. These include, but are not limited to: RU-486, onapristone, ZK-137316, ORG-31730, and HRP-2000. Where desired, estrogenic steroids and progestogenic steroids may be used in combination in the sugar coatings.

To illustrate *in vitro* dissolution rate control of steroid in the absence and presence of microcrystalline cellulose, the following illustrative examples are presented, without limitation:

20 **EXAMPLE 1**

A sugar coating consisting of the following solids was applied over a tablet core using either a non-perforated or perforated coating pan:

Sucrose, NF	87%
Polyvinylpyrrolidone	3%
Medroxyprogesterone Acetate, USP	10%

The rate of dissolution of the steroid was determined in accordance with 711 of USP XX, p.959 (1980), employing Apparatus 2, operating at 50 rpm by dissolving in 0.54% sodium lauryl sulfate in water at 37°C in six repeated trials (Method A). CV represents the coefficient of variation between these trials expressed as a percentage.

Time (min.)	Percent Steroid Released (CV%)
5	93 (5.2)
10	94 (5.3)
30	95 (5.3)
60	95 (5.4)
120	95 (5.4)

50 **EXAMPLE 2**

Tablets coated in the same manner with the same sugar coating as above were dissolved in 0.13% sodium lauryl sulfate in 0.1N HCl at 37°C using USP Apparatus 1 at 100 rpm, in six trials (method B). The results of this study were:

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EXAMPLE 3

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Additional tablets coated in the same manner with the same sugar composition were subjected to a flow-through dissolution test procedure in 0.12% sodium lauryl sulfate in 0.1N HCl at 37°C using a SOTAX Dissotest Apparatus at 5.7 mL/min. flow rate (Method C). The results of three separate runs were as follows:

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Time (min.)	Percent Steroid Released (CV%)
5	83 (6.0)
10	85 (5.8)
30	85 (6.2)
60	85 (6.1)
120	85 (6.2)

From these in vitro studies it is clear that medroxyprogesterone acetate, used here as a typical hormonal steroid, is released from the sugar coating extremely rapidly.

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EXAMPLE 4

For comparison purposes, and to illustrate the unexpected properties of the sugar coatings of this invention, a sugar coating consisting of the following solids was applied over a tablet core:

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Sucrose, NF	86.5%
Microcrystalline Cellulose	0.5%
PVP	3.0%
Medroxyprogesterone Acetate, USP	10.0%

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Employing the microcrystalline cellulose - containing sugar coated tablets and following Method A, the following in vitro dissolution data were obtained from three runs:

Time (min.)	Percent Steroid Released (CV%)
5	19.5 (49.5)
10	29.9 (32.8)
30	50.0 (23.0)
60	61.6 (19.5)
120	74.2 (19.2)

EXAMPLE 5

With additional microcrystalline cellulose - containing sugar coated tablets prepared in the same manner as above, following Method B in six runs, the following data were obtained:

Time (min.)	Percent Steroid Released (CV%)
5	2.3 (34.4)
10	8.2 (27.0)
30	17.9 (16.1)
60	26.5 (13.6)
120	32.7 (16.6)

EXAMPLE 6

And, following method C, with the tablets containing microcrystalline cellulose in the sugar coating, in three runs, the following data were obtained:

Time (min.)	Percent Steroid Released (CV%)
30	2.8 (34.4)
60	4.1 (24.8)
90	5.1 (22.3)
120	6.4 (22.3)
210	11.0 (19.4)
300	14.3 (11.0)

From these data it is apparent that a small amount of microcrystalline cellulose in the sugar coating (in this case 0.5% by weight of the sugar coating solids) has markedly retarded the release rate of hormonal steroid.

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EXAMPLE 7

Sugar coated tablets were prepared in which the sugar coat contained 0.0%, 0.5% or 2% microcrystalline cellulose in combination with 3.0% polyvinyl pyrrolidone, 10.0% medroxyprogesterone acetate and sucrose. These tablets were fed to four beagle dogs under fasting conditions and the blood plasma levels of steroid were determined at 0, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, and 24 hours. The resulting data were plotted, the area under the curve (AUC) calculated for a twenty four hour period and the time at which the maximum plasma concentration occurred was determined to be as follows:

Microcrystalline Cellulose %	AUC(0-24 Hrs) ngxhr/mL	tmax (Hr)	Cmax (ng/mL)
0.0	345	0.6	37.8
0.5	294	1.0	36.9
2.0	294	1.1	24.6

From these *in vivo* dog data, it is obvious that a marked change in bioavailability of a hormonal steroid occurs as the concentration of microcrystalline cellulose in the sugar coating increases from 0.0 to one containing 0.5 to 2.0% microcrystalline cellulose. Thus, the rate of release of hormonal steroid incorporated in a sugar coating may be controlled by incorporation of very small amounts of microcrystalline cellulose into sugar coating.

EXAMPLE 8

Sugar coated tablets were prepared in which the sugar coat contained 0.25%, 0.5% or 0.8% microcrystalline cellulose in combination with 0.5% polyvinyl pyrrolidone, 5.0% medroxyprogesterone acetate and sucrose. These tablets were subjected to an *in vitro* dissolution test employing the USP Disintegration Apparatus (USP XX, 201) p958) (1980) with a 0.54% sodium lauryl sulfate dissolution medium at 37°C. The following test data were obtained:

Percentage Medroxyprogesterone Acetate Dissolved (CV%)			
Time (Minutes)	0.25% Microcrystalline Cellulose	0.5% Microcrystalline Cellulose	0.8% Microcrystalline Cellulose
15	97.8 (5.2)	72.6 (9.5)	32.4 (15.2)
30	98.8 (5.3)	89.9 (6.3)	62.8 (8.2)
45	99.3 (5.2)	95.2 (5.6)	76.6 (6.9)
60	99.1 (5.2)	98.3 (5.7)	84.8 (6.6)
90	99.9 (5.3)	100.9 (6.0)	94.4 (6.9)
120	100.3 (5.6)	102.4 (5.3)	98.0 (7.1)

These dosage forms were also evaluated in a human bioavailability study. The dosage forms were administered in a cross-over design to twelve healthy female subjects. Blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4.5, 6, 8, and 12 hours and the plasma assayed for medroxyprogesterone acetate. The following data were obtained:

Microcrystalline Cellulose	AUC (0-12 h)	tmax (hr)	Cmax (ng/mL)
0.25%	26.0 ± 14.3*	2.9 ± 1.3	4.24 ± 3.0
0.5%	25.8 ± 10.5	3.2 ± 1.2	3.88 ± 1.87
0.8%	13.2 ± 4.0	3.9 ± 1.6	1.99 ± 0.73

*Mean values ± 1 Standard Deviation

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From the in vitro dissolution and in vivo human bioavailability data, it is clear that the drug release characteristics and bioavailability of the hormonal steroid, are controlled by the concentration of microcrystalline cellulose in the sugar coating.

EXAMPLE 9

A sugar coating containing 5 mg of medrogestone in a matrix of sucrose with 0.4% microcrystalline cellulose and 0.5% polyvinyl pyrrolidone was applied to a sealed and sugar-coated tablet core. The in vitro dissolution profile of this dosage form was compared to that of a rapidly-disintegrating compressed tablet containing 5 mg of medrogestone using the dissolution test described in 711 of USP XX, p. 959 (1980) employing Apparatus 2 operating at 50 r.p.m., with 900 mL of 0.54% sodium lauryl sulfate at 37°C. The following data were obtained:

Mean Percentage Medrogestone Released (CV%)		
Time (Minutes)	Conventional Rapidly Disintegrating Tablet	Sugar Coated Tablet Containing Medrogestone in Sugar Coat
15	95 (2.0)	6 (11.2)
30	95 (2.9)	11 (6.9)
45	97 (1.6)	15 (6.4)
60	97 (1.9)	18 (6.6)
120	98 (1.9)	25 (6.2)

The dramatic effect of reduced dissolution of medrogestone when the hormone is incorporated in a sugar coat containing 0.4% microcrystalline cellulose is clearly demonstrated.

One preferred embodiment of this invention is a compressed tablet in which the tablet core contains a unit dose of an estrogenic compound or a mixture thereof in an amount of from about 0.1 to about 5.0 milligrams, or more preferably from about 0.3 to about 2.5 milligrams, in combination with standard excipient compression aids and fillers. Most desirably, the conjugated estrogens found in the tablet core comprise the naturally occurring conjugated estrogen product known as Premarin®. Over a sugar coat on the compressed tablet is applied an additional sugar coat containing about 1 to about 50 milligrams and preferably about 1.5 to about 30 milligrams, of medroxyprogesterone acetate, a color coat, and finally, a polish coat. In other applications, it is preferable to employ a non-medicated core with a sugar coating containing a steroid such as trimegestone and more preferably, a sugar coating containing a mixture of steroids such as trimegestone and a conjugated estrogen.

Claims

1. A pharmaceutical tablet comprising an internal compressed core and an external sugar coating, wherein said compressed core contains either
 - i) no pharmacologically-active agent
 - or ii) one or more non-steroidal, pharmacologically-active agents that are conventionally administered in conjunction with a hormonal steroid, characterised in that the sugar coating comprises a hormonal steroid and a hormonal steroid release rate controlling amount of microcrystalline cellulose.
2. A pharmaceutical tablet comprising a non-medicated, compressed core and a sugar coating characterised in that the sugar coating comprises a hormonal steroid and a hormonal steroid release rate controlling amount of microcrystalline cellulose.
3. A pharmaceutical tablet as claimed in Claim 1 or Claim 2, wherein the sugar present in the coating is sucrose.
4. A pharmaceutical tablet as claimed in any one of Claims 1 to 3 wherein the hormonal steroid present in the sugar

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coating is medroxyprogesterone acetate, levonorgestrel, gestodene, medrogestone, estradiol, estriol, ethinylestradiol, mestranol, estrone, dienestrol, hexestrol, diethylstilbestrol, progesterone, desogestrel, norgestimate, hydroxyprogesterone, norethindrone, norethindrone acetate, norgestrel, megestrol acetate, methyltestosterone, ethylestrenol, methandienone, oxandrolone, trimegestone or dienogest .

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5. A pharmaceutical tablet as claimed in any one of Claims 1 to 4 wherein the hormonal steroid present in the sugar coating is RU-486, onapristone, ZK-137316, ORG-31730 or HRP-2000.

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6. A pharmaceutical tablet as claimed in any one of Claims 1 to 5 wherein the sugar coating comprises from about 0.1% to about 3% microcrystalline cellulose, by weight.

7. A pharmaceutical tablet as claimed in any one of Claims 1 to 6 wherein the sugar coating comprises from about 0 to about 5% polyvinylpyrrolidone, by weight.

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8. A pharmaceutical tablet as claimed in any one of Claims 1 to 7 wherein the sugar coating comprises from about 0.1 to about 20% hormonal steroid, by weight.

9. A pharmaceutical tablet as claimed in any one of Claims 1 to 8 wherein the sugar coat contains an estrogenic steroid and a progestogenic steroid.

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10. A method for the preparation of a pharmaceutical tablet as claimed in any one of Claims 1 to 9 comprising applying a sugar coating comprising a hormonal steroid and a hormonal steroid release rate controlling amount of microcrystalline cellulose to a core containing either

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i) no pharmacologically-active agent
or ii) one or more non-steroidal, pharmacologically-active agents that are conventionally administered in conjunction with a hormonal steroid.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 8424

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
P,X	EP 0 722 720 A (AMERICAN HOME PROD) 24 July 1996 * see the whole document*	1,3,4,6-8,10	A61K9/20
Y	* " *	2,5	
Y	--- WO 94 09762 A (MERCK & CO INC ;DEMPSKI ROBERT E (US); OLIVERO ROBERT C (US); SCHO) 11 May 1994 * see claim 1, page 4 lines 5-19, and page 8 lines 26-34 *	2,5	
A	--- EP 0 009 410 A (LILLY CO ELI) 2 April 1980 * see claim 1 *	1,2,5	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			A61K
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 18 June 1997	Examiner Isert, B
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background D : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

EPO FORM 150 (04.96) (P04C01)

ANEXO 2



US 20040063692A1

22-25
227(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0063692 A1**
Komm et al. (43) **Pub. Date: Apr. 1, 2004**(54) **BAZEDOXIFENE TREATMENT REGIMENS**(22) **Filed: Jun. 13, 2003**(75) **Inventors: Barry Samuel Komm, Wayne, PA (US); Simon Nicholas Jenkins, Audubon, PA (US); James Charles Ermer, Eagleville, PA (US); Mark Andrew Collins, Schwenksville, PA (US); Geraldine Marie Ferron, Wayne, PA (US); Pol Boudes, Berwyn, PA (US); Wendy Ann Dulin, Tuxedo, NY (US)****Related U.S. Application Data**(60) **Provisional application No. 60/388,596, filed on Jun. 13, 2002.****Publication Classification**(51) **Int. Cl.⁷ A61K 31/55**
(52) **U.S. Cl. 514/217.09****Correspondence Address:****COZEN O' CONNOR, P. C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508 (US)**(57) **ABSTRACT**(73) **Assignee: Wyeth, Madison, NJ**(21) **Appl. No.: 10/460,843**

This invention relates to extended dosing regimens for the selective estrogen receptor modulator bazedoxefine (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1 H-indol-5-ol).

BAZEDOXIFENE TREATMENT REGIMENS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of U.S. Provisional Application Serial No. 60/388,596 filed Jun. 13, 2002, which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] This invention relates to extended dosing regimens for the selective estrogen receptor modulator bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol).

[0003] Classically, estrogens are known as sex steroids affecting the reproductive tract that are required for the development of secondary sexual characteristics. However, estrogens are no longer regarded as strictly reproductive hormones and the appreciation of their effect on many organ systems has grown considerably in recent years. For example, although hormone replacement therapy was first developed to relieve menopausal hot flushes, its indications have expanded to include the treatment of vaginal atrophy and prevention of osteoporosis. Partly because such large numbers of women have used replacement therapy, a sizable body of evidence has accumulated strongly suggesting that estrogens have beneficial effects on many other organs including the bladder (improving tone and reducing incontinence), colon (reduction of cancer risk), brain (improved cognition) and cardiovascular system (improved lipid profile, reduction of risk of disease).

[0004] Estrogens can exert their effects on cells in several ways, and the most well-characterized mechanism of action is via their interaction with receptors (ERs), leading to alterations in gene transcription. To date, two ERs have been discovered: ER α and ER β . ERs are ligand-activated transcription factors and belong to the nuclear hormone receptor superfamily. Other members of this family include the progesterone, androgen, glucocorticoid and mineralocorticoid receptors.

[0005] The development of therapeutically useful and selective ER ligands has become possible, not only because of our increased understanding of the complexities of estrogen biology, but also because a wide variety of ER ligands have been developed over the years, some of which exhibit unexpected activities. ERs have a relatively large and flexible binding pocket [Anstead, G. M., *Steroids* 1997, 62: 268-303], which can accommodate structurally diverse ligands. These ligands include steroids, (e.g. 17 β -estradiol, estrone), phytoestrogens (e.g. genistein, coumestrol), and xenobiotics (e.g. polychlorinated biphenols). Traditionally, compounds having roughly the same biological effects as 17 β -estradiol, the most potent endogenous estrogen, are referred to as "ER agonists". Those which, when given in combination with 17 β -estradiol, block its effects are called "ER antagonists".

[0006] It has been known for some time that estrogen receptors adopt different conformations when binding ligands. However, the consequence and subtlety of these changes has been only recently revealed. The three dimensional structures of ER α and ER β have been solved by

co-crystallization with various ligands and clearly show the repositioning of helix 12 in the presence of an estrogen receptor antagonist which sterically hinders the protein sequences required for receptor-coregulatory protein interaction [Pike, A. C. W., *EMBO* 1999, 18: 4608-4616; Shiau, A. K., *Cell* 1998, 95: 927-937].

[0007] As mentioned above, ER ligands have been historically classified as ER agonists or antagonists. In reality there is a continuum between these activities and indeed some compounds behave as estrogen receptor agonists in some tissues and estrogen receptor antagonists in others. The precise reason why the same compound can have cell-specific effects has not been elucidated, but the differences in receptor conformation and/or in the milieu of coregulatory proteins have been suggested.

[0008] Tamoxifen, a case in point, was initially developed as an ER antagonist for breast cancer treatment. It was subsequently discovered that, while an ER antagonist in the breast, it had ER agonist activity in the bone and uterus [Jordan, C. V., *Breast Cancer Res* 1987, 4: 31-35]. This unexpected finding of mixed ER agonist and antagonist activity within a single compound spawned efforts to develop other selective compounds with improved profiles, and now tamoxifen is referred to as a "first generation SERM" or "tissue selective estrogen" [McDonnell, D. P., *J Soc Gyn Invest* 2000, 7: S10-S15; Goldstein, S. R., *Human Reproduction Update* 2000, 6:212-224].

[0009] The development of raloxifene (a second generation SERM), originally aimed at the breast cancer treatment market to compete with tamoxifen, was redirected toward the treatment and prevention of osteoporosis in postmenopausal women. Preclinical data revealed that it spared bone, lowered LDL cholesterol, while demonstrating minimal estrogenic impact on the uterus and mammary gland. Other SERMs including bazedoxifene are currently in development.

DESCRIPTION OF THE INVENTION

[0010] This invention provides extended dosing regimens (less frequently than daily) for the SERM bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol), or a pharmaceutically acceptable salt or prodrug thereof, particularly bazedoxifene acetate, which range from administering bazedoxifene every second day to administering bazedoxifene once every week.

[0011] As used herein, the term "extended dosing regimen" means administration ranging from every second day to once weekly.

[0012] As used herein, unless otherwise modified by a specific salt or prodrug, the term "bazedoxifene" means bazedoxifene, its pharmaceutically acceptable salts and prodrugs.

[0013] The preparation of bazedoxifene and its pharmaceutically acceptable salts is described in U.S. Pat. No. 5,998,402, which is hereby incorporated by reference. Bazedoxifene acetate has been evaluated in clinical trials using dosages of 10, 20, and 40 mg/day. Based on the results of these trials, it is anticipated that doses between 5 and 80 mg/day will provide satisfactory results.

[0014] The ability of bazedoxifene to be successfully administered on an extended dosing regimen was estab-

lished in an in vivo standard pharmacological test procedure which evaluated bone mineral density (BMD), change in body weight, and uterine weight using bazedoxifene acetate as a representative compound of this invention. The following briefly describes the procedure used and results obtained in the standard pharmacological test procedure.

[0015] Female Sprague Dawley CD rats, ovariectomized (ovx) or sham ovx, were obtained 1 day after surgery from Taconic Farm (weight range 240-275 g). They were housed 3 or 4 rats/cage in a room on a 14/10 (light/dark) schedule

along the defined area above the subject. The data for BMD values (expressed in g/cm²) and individual scans were stored for statistical analysis.

[0017] One week after BMD evaluation the rats were euthanized by carbon dioxide suffocation. The uteri were removed and the weights taken. The following table summarizes the results that were obtained. The sham group was not ovariectomized; all other groups were ovariectomized. In the table below, bazedoxifene acetate is abbreviated as BZA.

Treatment	N	Total BMD ^a	Trabecular BMD ^a	Δ Body Weight ^b	Uterine Weight ^c
Sham	8	681.96 ± 10.5*	552.71 ± 16.8*	47.4 ± 4.6*	594.0 ± 73.0*
Vehicle	8	550.51 ± 20.8	359.93 ± 27.8	91.6 ± 9.3	99.7 ± 5.1
BZA 0.3 mg/kg 7x/week	8	604.33 ± 18.6*	425.90 ± 26.3*	60 ± 5.6*	140.3 ± 6.3
BZA 0.3 mg/kg 1x/week	8	556.56 ± 20.5	361.93 ± 34.5	80.5 ± 2.0	131.3 ± 7.0
BZA 1.0 mg/kg 1x/week	8	562.90 ± 7.7	353.03 ± 15.7	71.3 ± 4.8*	149.9 ± 5.0
BZA 3.0 mg/kg 1x/week	8	589.36 ± 10.9	427.00 ± 10.0*	59.3 ± 7.0*	127.3 ± 10.9

^aMean(mg/cm³) ± SEM

^bMean(g) ± SEM

^cMean(mg) ± SEM

*p < 0.05 vs. corresponding vehicle

and provided with food (Purina 500 rat chow) and water ad libitum. Treatment for all studies began 1 day after the animals arrival and dosed either daily or once weekly as indicated for 6 weeks. A group of age matched sham operated rats not receiving any treatment served as an intact, estrogen replete control group for each study. All treatments were prepared in 1% tween 80 in normal saline at defined concentrations so that the treatment volume was 0.1 mL/100 g body weight.

[0016] Five weeks after the initiation of treatment and one week prior to the termination of the study, each rat was evaluated for bone mineral density (BMD). The BMD's of the proximal tibiae (PT) and fourth lumbar vertebrae (L4) were measured in anesthetized rats using a dual energy X-ray absorptiometer (Eclipse XR-26, Norland Corp. Ft. Atkins, Wis.). The dual energy X-ray absorptiometer (DXA) measurements for each rat were performed as follows: Fifteen minutes prior to DXA measurements, the rat was anesthetized with an intraperitoneal injection of 100 mg/kg ketamine (Bristol Laboratories, Syracuse, N.Y.) and 0.75 mg/kg acepromazine (Aveco, Ft.Dodge, Iowa). The rat was placed on an acrylic table under the DXA scanner perpendicular to its path; the limbs were extended and secured with paper tape to the surface of the table. A preliminary scan was performed at a scan speed of 50 mm/second with a scan resolution of 1.5 mm×1.5 mm to determine the region of interest in PT and L4. Small subject software was employed at a scan speed of 10 mm/second with resolution of 0.5 mm X 0.5 mm for final BMD measurements. The software allows the operator to define a 1.5 cm wide area to cover the total length of L4. The BMDs for respective sites were computed by the software as a function of the attenuation of the dual beam (46.8 KeV and 80 KeV) X-ray generated by the source underneath the subject and the detector travelling

[0018] The results obtained in the standard pharmacological test procedure using bazedoxifene acetate as a representative compound, demonstrate that bazedoxifene can be administered on an extended dosing regimen, while retaining efficacious results. Based on the results shown above, bazedoxifene can be administered according to an extended dosing regimen ranging from once every two days, to once per week. The dosage for a given dosing regimen can be given all at once or given multiple times on the same day. Based on individual patient needs, bazedoxifene can be administered every second day, every third day, every fourth day, every fifth day, every sixth day, or every seventh day (once weekly). The administration period can also be adjusted depending on the needs of the patient, and still be considered to be administered according to an extended dosing regimen. For example, the dosage can be given once every other day, and then after medical follow-up be adjusted to be administered every third day, and eventually once weekly. When administered in this fashion, it is still considered to be administered according to an extended dosing regimen. It is preferred that the extended dosing regimen be administration once weekly, where the weekly dosage is given on one day, either as a single dose, or divided into two or more doses during the same day. It is preferred that the oral daily dosage in humans is between 5-80 mg. When bazedoxifene is administered once weekly, it is preferred that the once per week dosage will be from 3-15 times that of the daily dosage. Accordingly, it is preferred that the once weekly oral dosage be between 15 and 1200 mg given once per week; with the dosage being given in one or more doses during the administration day. When bazedoxifene is administered according to an every second day regimen, it is preferred that the daily dosage be from the daily dosage to 5 times that of the daily dosage. Accordingly, it is preferred

in the once every second day regimen, that the oral dosage be between 5 and 400 mg given once every second day, with the dosage being given in one or more doses during the administration day. It is preferred that the extended dosage period will be once weekly administration.

[0019] The uses of bazedoxifene are disclosed in U.S. Pat. No. 5,998,402, which is hereby incorporated by reference. Such uses include lowering cholesterol, triglycerides, Lp(a), or LDL levels; inhibiting or treating hypercholesterolemia; or hyperlipidemia. Bazedoxifene is useful in the treatment and inhibition of bone loss, which may result from an imbalance in an individual's formation of new bone tissues and the resorption of older tissues, leading to a net loss of bone. Such bone depletion results in a range of individuals, particularly in post-menopausal women, women who have undergone bilateral oophorectomy, those receiving or who have received extended corticosteroid therapies, those experiencing gonadal dysgenesis, and those suffering from Cushing's syndrome. Special needs for bone, including teeth and oral bone, replacement can also be addressed using these compounds in individuals with bone fractures, defective bone structures, and those receiving bone-related surgeries and/or the implantation of prosthesis. In addition to those problems described above, bazedoxifene can be used in treatments for osteoarthritis, hypocalcemia, hypercalcemia, Paget's disease, osteomalacia, osteomalacia, osteomalacia, multiple myeloma and other forms of cancer having deleterious effects on bone tissues.

[0020] Bazedoxifene is also useful for treating many maladies which result from estrogen effects and estrogen excess or deficiency including osteoporosis, prostatic hypertrophy, male pattern baldness, vaginal and skin atrophy, acne, dysfunctional uterine bleeding, endometrial polyps, benign breast disease, uterine leiomyomas, adenomyosis, ovarian cancer, infertility, breast cancer, endometriosis, endometrial cancer, polycystic ovary syndrome, cardiovascular disease, contraception, Alzheimer's disease, cognitive decline and other CNS disorders, as well as certain cancers including melanoma, prostate cancer, cancers of the colon, CNS cancers, among others. Additionally, bazedoxifene can be used for contraception in pre-menopausal women, as well as hormone replacement therapy in post-menopausal women or in other estrogen deficiency states where estrogen supplementation would be beneficial. Bazedoxifene may also be used in disease states where amenorrhea is advantageous, such as leukemia, endometrial ablations, chronic renal or hepatic disease or coagulation diseases or disorders.

[0021] It is preferred that bazedoxifene is administered orally. Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

[0022] Solid oral formulations, preferably in the form of a film coated tablet or capsule, useful for this invention include the active pharmacological agents disclosed herein in combination with carrier or excipient systems having the components:

[0023] a) a filler and disintegrant component comprising from about 5% to about 82% by weight (wgt) of the total formulation, preferably between about 30% and about 80% of the formulation, of which from about 4% to about 40% by weight of the total formulation comprises one or more pharmaceutically acceptable disintegrants;

[0024] b) optionally, a wetting agent comprising from about 0.2 to about 5% of the composition (wgt), such as selected from the group of sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, sugar esters of fatty acids and glycerides of fatty acids;

[0025] c) a lubricant comprising from about 0.2% to about 10% of the composition (wgt), such as selected from the group of magnesium stearate or other metallic stearates (e.g. calcium stearate or zinc stearate), fatty acid esters (e.g. sodium stearyl fumarate), fatty acids (e.g. stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulfates and sodium chloride; and

[0026] d) optionally, a glidant comprising from about 0.1% to about 10% (wgt) of the composition, the glidant selected from those known in the art, including from the group of silicon dioxide, talc, metallic stearates, calcium silicate, or metallic lauryl sulfates.

[0027] While the formulations described herein may be used in an uncoated or non-encapsulated solid form, preferably the final compositions are coated or encapsulated. The pharmacological compositions may be optionally coated with a film coating, preferably comprising from about 0.3% to about 8% by weight of the overall composition. Film coatings useful with the present formulations are known in the art and generally consist of a polymer (usually a cellulosic type of polymer), a colorant and a plasticizer. Additional ingredients such as wetting agents, sugars, flavors, oils and lubricants may be included in film coating formulations to impart certain characteristics to the film

coat. The compositions and formulations herein may also be combined and processed as a solid, then placed in a capsule form, such as a gelatin capsule.

[0028] The filler component listed above may utilize the filler or binder components known in the art for solid oral formulations. Pharmaceutically acceptable fillers or binding agents selected from those known in the art including, but not limited to, lactose, microcrystalline cellulose, sucrose, mannitol, calcium phosphate, calcium carbonate, powdered cellulose, maltodextrin, sorbitol, starch, or xylitol.

[0029] In conjunction with or in place of the materials listed above for the filler component, the present formulations utilize disintegrant agents. These disintegrants may be selected from those known in the art, including pregelatinized starch and sodium starch glycolate. Other useful disintegrants include croscarmellose sodium, crospovidone, starch, alginic acid, sodium alginate, clays (e.g. veegum or xanthan gum), cellulose floc, ion exchange resins, or effervescent systems, such as those utilizing food acids (such as citric acid, tartaric acid, malic acid, fumaric acid, lactic acid, adipic acid, ascorbic acid, aspartic acid, erythorbic acid, glutamic acid, and succinic acid) and an alkaline carbonate component (such as sodium bicarbonate, calcium carbonate, magnesium carbonate, potassium carbonate, ammonium carbonate, etc.). The disintegrant(s) useful herein will comprise from about 4% to about 40% of the composition by weight, preferably from about 15% to about 35%, more preferably from about 20% to about 35%. Some components may have multiple functions in the formulations of this invention, acting e.g. as both a filler and a disintegrant, such a component may be referred to as a filler disintegrant and its function in a specific formulation may be singular even though its properties may allow multiple functionality.

[0030] The pharmaceutical formulations and carrier or excipient systems herein preferably also contain an antioxidant or a mixture of antioxidants, most preferably ascorbic acid. Other antioxidants which may be used include sodium ascorbate and ascorhyl palmitate, preferably in conjunction with an amount of ascorbic acid. A preferable range for the antioxidant(s) is from about 0.5% to about 15% by weight, most preferably from about 0.5% to about 5% by weight.

[0031] Among the formulations of this invention are pharmaceutical formulations containing a pharmaceutically effective amount of an active pharmacological agent and a carrier or excipient system comprising:

[0032] a) a filler and disintegrant component comprising between about 50% and about 87% of the formulation, with from about 4% to about 40% of the formulation comprising one or more disintegrant agents;

[0033] b) a wetting agent comprising between about 0.5% and about 2.7% of the formulation;

[0034] c) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and

[0035] d) a glidant comprising between about 0.1% and about 5.5% of the formulation.

[0036] The percentages listed in the formulations above indicate percentages by weight of the total weight of the components listed from a) to d). The formulations above also preferably contain an optional antioxidant component,

preferably ascorbic acid, at a concentration of from about 0.5% to about 5.5% by weight of the formulation. The formulations are also preferably contained within a pharmaceutically acceptable capsule, such as a gel capsule, or coated with a film coating comprising from about 0.3% to about 8% by weight of the formulation.

[0037] This invention also comprises a pharmaceutical carrier or excipient systems useful in pharmaceutical compositions utilizing as an active ingredient one or more of the compounds described herein, or a pharmaceutically acceptable salt thereof, as described herein. These pharmaceutical carrier or excipient systems comprise, by weight:

[0038] a) a filler and disintegrant component comprising between about 54% and about 80% of the formulation, with the disintegrant agent(s) therein comprising from about 4% to about 40% by weight of the overall formulation;

[0039] b) a wetting agent comprising between about 0.55% and about 2.5% of the formulation;

[0040] c) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and

[0041] d) a glidant comprising between about 0.1% and about 5.0% of the formulation.

[0042] The more preferred carrier or excipient systems above also optionally and preferably contain an antioxidant component, preferably ascorbic acid, at a concentration of from about 0.1% to about 5.0% by weight.

[0043] Among the carrier or excipient systems of this invention are those comprising:

[0044] a) a filler and disintegrant component, as described above, comprising between about 50% and about 87% of the formulation, the disintegrant(s) therein comprising from about 25% to about 35% of the formulation, by weight;

[0045] b) a wetting agent comprising between about 0.55% and about 2.7% of the formulation;

[0046] c) a lubricant comprising between about 0.2% and about 5.5% of the formulation;

[0047] d) a glidant comprising between about 0.1% and about 5.5% of the formulation; and

[0048] e) an antioxidant component, preferably ascorbic acid, at a concentration of from about 0.1% to about 5.5% by weight.

EXAMPLE 1

Bazedoxifene Acetate-Rapid Dissolution Formulations

[0049]

Ingredient	without Ascorbic Acid	With Ascorbic Acid
Bazedoxifene acetate, micronized*	10.00	10.00

-continued

Ingredient	without Ascorbic Acid	With Ascorbic Acid
Lactose NF fast flow	33.10	31.60
Microcrystalline Cellulose, NF (Avicel PH101)	25.00	25.00
Starch 1500	20.00	20.00
Sodium Lauryl Sulfate NF	1.50	1.50
Sodium Starch Glycolate	10.00	10.00
Ascorbic Acid USP	—	1.5
Syloid 244 FP	0.15	0.15
Magnesium Stearate	0.25	0.25

*Amount in formula is adjusted for actual potency of bazedoxifene as free base. Corresponding adjustment made with lactose.

[0050] The formulations given above in Table 1 were prepared by incorporating a portion of the excipients in the granulation and a portion is also added in the final blending steps as dry powders. A dissolution profile generated for the formulations demonstrated almost 90% release of the drug in 30 minutes. Thus, the unique combination of disintegrants and soluble diluents plus the incorporation of both granulated and powdered solids into the composition ensures the fastest release of drug.

[0051] Wet granulation of the formulations as described in Table 1 may be carried out by mixing the drug and ascorbic acid with a portion of the lactose, microcrystalline cellulose, pregelatinized starch and sodium starch glycolate. The sodium lauryl sulfate is dissolved in the water and used to granulate the mixture of powders in a high shear mixer. The granulation is dried in a fluid bed dryer to a moisture of 2-3%. The particle size of the dried granulation is controlled by passing through a mill equipped with knife-edged blades and using a 20- or 30-mesh screen. The silicon dioxide and remaining lactose, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate are mixed with the milled granulation in a tumble-type mixer. The final blend is prepared by adding magnesium stearate to the tumble-type mixer and mixing. Compression is carried out on a rotary tablet press using appropriate size tooling. Coating is performed in conventional coating pans and applying the coating suspension to achieve a suitable film coat.

EXAMPLE 2

Modified Bazedoxifene Acetate Formulation % w/w

[0052]

Ingredient	5% granulation
Bazedoxifene acetate, micronized ^a	5.00
Lactose NF	41.00
Microcrystalline Cellulose, NF	35.00
Pregelatinized Starch NF	10.00
Sodium Lauryl Sulfate NF	1.50
L-Ascorbic Acid USP	1.50
Sodium Starch Glycolate NF	5.50

-continued

Ingredient	5% granulation
Magnesium Stearate NF ^c	0.50
Pur. Water USP ^b	qs

^aAmount in formula is adjusted for actual potency of bazedoxifene acetate as free base. Corresponding adjustment made with Lactose.

^bUsed in process but does not appear in the final product.

EXAMPLE 3

Bazedoxifene Acetate at 5% Granulation

[0053] A preferred carrier or excipient system for formulating a granulation of from about 2 to about 8% by weight of one of the active pharmacological agents of this invention, preferably about 5%, may be produced utilizing the carrier or excipient components on a weight percentage; lactose from about 32% to about 38%, microcrystalline cellulose from about 32% to about 38%, pregelatinized starch from about 12% to about 16%, ascorbic acid from about 1% to about 2%, sodium lauryl sulfate from about 1% to about 2%, sodium starch glycolate from about 4% to about 8%, silicon dioxide from about 0.1% to about 0.2% and magnesium stearate from about 0.3% to about 0.7%.

[0054] A formulation of this invention utilizing bazedoxifene as the active ingredient at a 5% granulation was prepared utilizing the components listed below in a granulation part of components and a dry part.

Item No.	Ingredients	Mg/Unit
Granulation Part:		
1	Bazedoxifene acetate	5.00
2	Lactose NF	26.60
3	Microcrystalline Cellulose NF	25.00
4	Pregelatinized Starch NF	10.00
5	Ascorbic Acid USP	1.50
6	Sodium Lauryl Sulfate NF	1.50
7	Sodium Starch Glycolate NF	4.00
8	Water, Purified USP	Q.S.
		73.60
Dry Part:		
12	Lactose NF (fast flo)	9.75
10	Microcrystalline Cellulose NF	10.00
11	Pregelatinized Starch NF	4.00
12	Sodium Starch Glycolate NF	2.00
13	Silicon Dioxide NF	0.15
14	Magnesium Stearate NF	0.50
		100.00

[0055] A film coat of White Opadry I (YS-1-18027-A) was applied to the tablets, which were compressed as follows:

Dose of Bazedoxifene	tablet weight, mg	mg of film coat applied/tablet
5 mg	100	6.0
10 mg	200	8.0
20 mg	400	13.0

[0056] It is intended that each of the patents, applications, and printed publications including books mentioned in this patent document be hereby incorporated by reference in their entirety.

[0057] As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

What is claimed is:

1. A method of treating or inhibiting bone loss in a mammal in need thereof, which comprises administering an effective amount of bazedoxifene according to an extended dosing regimen.

2. The method according to claim 1, wherein the bazedoxifene is bazedoxifene acetate.

3. The method according to claim 2, wherein the bazedoxifene is administered once weekly

4. The method according to claim 2, wherein the bazedoxifene is administered every second day.

5. A method of lowering cholesterol, triglycerides, Lp(a), or LDL levels; inhibiting or treating hypercholesterolemia; or hyperlipidemia; in a mammal in need thereof, which comprises administering an effective amount of bazedoxifene according to an extended dosing regimen.

6. The method according to claim 5, wherein the bazedoxifene is bazedoxifene acetate.

7. The method according to claim 6, wherein the bazedoxifene is administered once weekly

8. The method according to claim 6, wherein the bazedoxifene is administered every second day.

9. A method of treating or inhibiting cardiovascular disease in a mammal in need thereof, which comprises admin-

istering an effective amount of bazedoxifene according to an extended dosing regimen.

10. The method according to claim 9, wherein the bazedoxifene is bazedoxifene acetate.

11. The method according to claim 10, wherein the bazedoxifene is administered once weekly

12. The method according to claim 10, wherein the bazedoxifene is administered every second day.

13. A method of treating or inhibiting dementias, neurodegenerative disorders, and Alzheimer's disease; providing neuroprotection or cognition enhancement in a mammal in need thereof, which comprises administering an effective amount of bazedoxifene according to an extended dosing regimen.

14. The method according to claim 13, wherein the bazedoxifene is bazedoxifene acetate.

15. The method according to claim 14, wherein the bazedoxifene is administered once weekly

16. The method according to claim 14, wherein the bazedoxifene is administered every second day.

17. A method of treating or inhibiting osteoporosis in a mammal in need thereof, which comprises administering an effective amount of bazedoxifene according to an extended dosing regimen.

18. The method according to claim 17, wherein the bazedoxifene is bazedoxifene acetate.

19. The method according to claim 18, wherein the bazedoxifene is administered once weekly

20. The method according to claim 18, wherein the bazedoxifene is administered every second day.

* * * * *



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2020
Bogotá, D.C.,

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234

Doctor:
Álvaro Correa Ordóñez
Apoderado

Oficio N°: 9867

ASUNTO:

Radicación PCT N°	07-136799
Trámite	011
Evento	379
Actuación	440
Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Gynopharm S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

28 AGO. 2009

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021