



No. 08-002354-00005-0000

Fecha: 2009-07-01 16:39:16 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 50

FORMULARIO UNICO DE OPOSICIÓN

①

OPOSICION 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

Numero del expediente: 08.002.354

Solicitante: WYETH

SOLICITUD
PUBLICADA

Apoderado: ALVARO CORREA ORDÓÑEZ

Titulo de la nueva creación o denominación del signo: FORMAS DE DOSIFICACIÓN DE
IBERACIÓN RETARDADA ORALES ALTAMENTE BIODISPONIBLES DE SUCCINATO DE O-DESMETILVENLAFAXINA

Gaceta: 602

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: GYNOPHARM S.A.	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Numero: 802,006,279-4
	Dirección: Carrera 14 N° 94-44 Piso 7 Torre b Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA Telefono: 2 36 84 95 Fax: _____ E-mail: _____	
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Numero: 51.975.664 TP 83823
	Dirección: CARRERA 13 No. 119-95 Telefono: (571)213 12 13 Fax: (571)612 19 79 E-mail: negocios@optimum-co.com	

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 _____

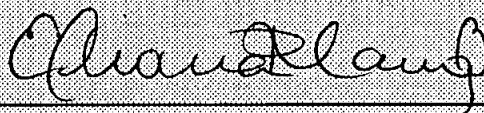
⑥ ANEXOS

- ☒ 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: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA:



C.C. 51.975.664

TP. 83823

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 082354

Asunto : Oposición a la solicitud de patente de Invención titulada
**"FORMAS DE DOSIFICACIÓN DE LIBERACIÓN
RETARDADA ORALES ALTAMENTE
BIODISPONIBLES DE SUCCINATO DE O-
DESMETILVENLAFAXINA"**

Solicitante : WYETH

Opositora : GYNOPHARM S.A.

Publicada en la *Gaceta de la Propiedad Industrial*
N° 602 del 31 de Marzo 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 **"FORMAS DE DOSIFICACIÓN DE LIBERACIÓN RETARDADA ORALES ALTAMENTE BIODISPONIBLES DE SUCCINATO DE O-**

DESMETILVENLAFAXINA", 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 succinato de **O-desmetilvenlafaxina**. 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 11 de enero de 2008 reivindicando prioridad bajo la solicitud US20050699623P del 2005-07-15; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° **602 del 31 de Marzo de 2009**, cuya publicación internacional corresponde a la WO2007011619 del 2007-01-25.

2.2. La solicitud colombiana **082354** objeto de la presente oposición, se refiere a una forma de dosificación unitaria altamente biodisponible, oral, de succinato de **O-desmetilvenlafaxina (DVS)** que tiene una liberación retardada de por lo menos



aproximadamente una hora y una liberación sostenida durante múltiples horas para proporcionar una liberación total de más de aproximadamente 85% dentro de aproximadamente 12 a aproximadamente 14 horas. En una modalidad, la composición DVS superbiodisponible tiene una liberación retardada de aproximadamente dos horas y una liberación total de más de aproximadamente 95% dentro de aproximadamente 12 a aproximadamente 14 horas. También se describe el uso de la formulación en el tratamiento de la depresión y la reducción de los efectos colaterales gastrointestinales de la O-desmetilvenlafaxina (ODV). La invención reivindica una composición de liberación sostenida de DVS (suscinato de O-desmetilvenlafaxina) superbiodisponible que comprende un núcleo que contiene por lo menos DVS y un relleno insoluble en agua en una unidad de dosificación oral que tiene una liberación retardada de por lo menos aproximadamente una hora y una liberación sostenida durante múltiples horas para proporcionar una liberación total de más de aproximadamente 85% dentro de aproximadamente 12 a aproximadamente 14 horas; donde tiene una liberación retardada de aproximadamente dos horas y una liberación total de más de aproximadamente 95% dentro de aproximadamente 12 a aproximadamente 14 horas; en donde dicha unidad de dosificación oral comprende adicionalmente un recubrimiento de liberación controlada que comprende etilcelulosa; en donde dicho recubrimiento de liberación controlada comprende aproximadamente 10% en peso de hipomelosa, con base en el peso de el recubrimiento de liberación controlada; en donde dicho recubrimiento de liberación controlada comprende aproximadamente 90% en peso de una dispersión de etilcelulosa, con base en el peso de el recubrimiento de liberación controlada; y en donde dicho recubrimiento de liberación controlada consiste de aproximadamente 5 a 20% en peso de la unidad de dosificación oral.

2.3. En primera instancia, se debe advertir que las reivindicaciones también se refieren al uso y a un método de tratamiento 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 y a un método de tratamiento no sería patentable.

2.4. 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: WO2004096186 publicada el 11 de noviembre de 2004.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela una formulación en comprimidos recubiertos de liberación prolongada para venlafaxina, que comprende: (a) un núcleo que comprende una cantidad farmacéuticamente eficaz de venlafaxina o de una sal farmacéuticamente aceptable de la misma, estando dicho núcleo en forma de comprimido y comprendiendo dicho núcleo adicionalmente: (i) al menos el 40% en peso de una carga, por peso

de la formulación total; (ii) al menos el 5% en peso de un polímero celulósico soluble en agua seleccionado entre hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa, hidroxietilcelulosa, metilcelulosa, carboximetilcelulosa, por peso de la formulación total; (iii) al menos el 5% en peso de etilcelulosa, por peso de la formulación total; (b) un recubrimiento para dicho núcleo, comprendiendo dicho recubrimiento: (i) un polímero celulósico soluble en agua seleccionado entre hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa, hidroxietilcelulosa, metilcelulosa, carboximetilcelulosa; y (ii) un polímero celulósico insoluble en agua seleccionado entre etilcelulosa y acetato de celulosa. Particularmente en las tablas 5 y 6 revelan una composición de superbiodisponibilidad de venlafaxina de entrega sostenida que comprende un núcleo que contiene al menos venlafaxina HCL, un relleno insoluble en medio acuoso tal como celulosa microcristalina PH 101 y una cubierta de controlador de entrega que comprende etilcelulosa, entre otros. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 082354 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.

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

2.8.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización,*

comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”. A la fecha de prioridad, 15 de julio de 2005 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, una composición de superbiodisponibilidad de venlafaxina de entrega sostenida que comprende una núcleo que contiene al menos venlafaxina HCL, un relleno insoluble en medio acuoso tal como celulosa microcristalina PH 101 y una cubierta de controlador de entrega que comprende etilcelulosa, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. **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, algunas cláusulas reclaman el método terapéutico y esos no son aplicables 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 y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

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 dos de 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 **FORMAS DE DOSIFICACIÓN DE LIBERACIÓN RETARDADA ORALES ALTAMENTE BIODISPONIBLES DE SUCCINATO DE O-DESMETILVENLAFAXINA**”, cuyo titular es **WYETH**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 602 del 31 de Marzo 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: WO2004096186 publicada el 11 de noviembre 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:

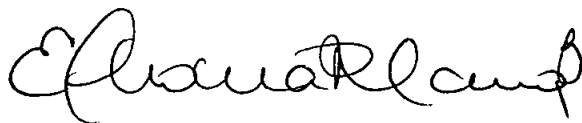
1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **GYNOPHARM S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- DI: WO2004096186 publicada el 11 de noviembre 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

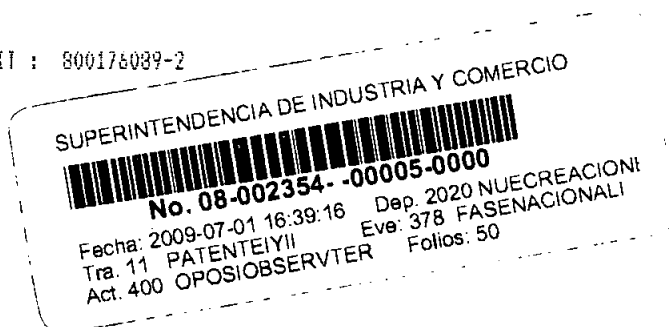
C.C. 51'975.664 de Bogotá

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

IBO OFICIAL DE CAJA : 09 - 47,647
HA : JULIO 1 DE 2009



***** CONSIGNACION *****

USITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
DPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	114281053	18/06/2009	4,305,000.00
DPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	114645996	27/03/2009	1,722,000.00

***** CONCEPTO *****

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

: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

IBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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. 08 2354, titulada "**FORMAS DE DOSIFICACION DE LIBERACION RETARDADA ORALES ALTAMENTE BIODISPONIBLES DE SUCCINATO DE O-DESMETILVENLAFAXINA**", cuyo titular es **WYETH**, publicada en la gaceta No. 602 del 31 de marzo 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 ____ días del mes de ____ 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 Circuito de Bogotá (E),
comparece WIS Alberto Palacios

Aragon

identificado con cédula de ciudadanía

CC 39788

y declara que la firma puesta en el presente
instrumento privado es suya y que el contenido
del mismo es cierto
Bogotá D.C.

16 JUN. 2009

FIRMA

LILIANA CONSTANZA B.
NOTARIA VEINTICINCO

NOTARIA PRIMERA DE CHIA PRESENTACION PERSONAL

este memorial dirigido a Super Intendencia de Industria y Comercio

é presentado personalmente ante el suscrito notario por Elenco Isaura

Mejano Bohorquez

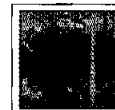
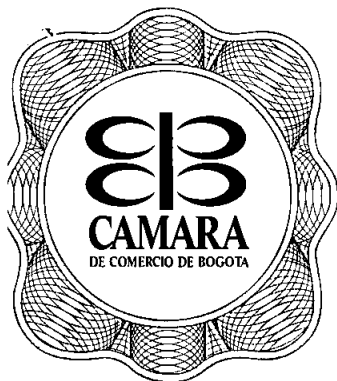
Identificado C.C. 51975664 Bogotá

P. de Abogado No. 83823

Chía. 01 JUL. 2009

Quintanilla





14

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/06/19

HORA: 13:11:00

OPERACION: 10ERP0619107

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

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/06/19

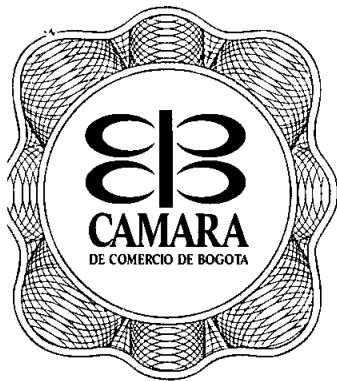
HORA: 13:11:00

OPERACION: 10ERP0619107

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

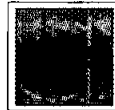
*** CONTINUA ***



01



* 8 2 6 9 2 6 4 5 *



25

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/06/19

HORA: 13:11:00

OPERACION: 10ERP0619107

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 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-

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CAMARA DE COMERCIO DE BARRANQUILLA

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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.-----

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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 |
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| 3. Penaranda Urbina Adriana Paola | CC.*****53,120,683 |
| 4. tovar Vasquez Ruth | CC.*****52,175,756 |

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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 Aragón 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

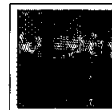
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FECHA: 2009/06/19

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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 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

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/06/19

HORA: 13:11:00

OPERACION: 10ERP0619107.

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 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 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 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 despues 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. k. j. a.

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- (74) Agent: **G. E. EHRLICH (1995) LTD.**; 11 Menachem Begin Street, 52 521 Ramat Gan (IL).
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(54) Title: EXTENDED RELEASE VENLAFAXINE TABLET FORMULATION

(57) Abstract: An extended release formulation for administration of venlafaxine in an oral tablet dosage form. The formulation preferably features a core, over which an outer coating is layered. The core preferably contains venlafaxine, a filler, and a water soluble cellulosic polymer, optionally and more preferably with a water insoluble cellulosic polymer. The core is preferably coated with a coating material. The coating preferably contains a mixture of water soluble cellulosic polymer and a water insoluble cellulosic polymer. According to a first embodiment of the present invention, the filler is preferably present in an amount of at least about 40% weight per weight of the total formulation. More preferably, the filler comprises microcrystalline cellulose. Most preferably, the filler solely comprises microcrystalline cellulose. Also most preferably, microcrystalline cellulose is present in the core in a range of from about 45% to about 65% weight per weight of the total formulation.



WO 2004/096186 A1

EXTENDED RELEASE VENLAFAXINE TABLET FORMULATION

FIELD OF THE INVENTION

The present invention is of a formulation for the extended release of venlafaxine.

5

BACKGROUND OF THE INVENTION

Extended release formulations for oral administration of drugs are preferred for a number of reasons. For example, they enable the patient to ingest the formulation less frequently, which may lead to increased patient compliance with the dosing regimen.

10 They may also result in fewer side effects, as peaks and troughs of the level of the drug in the bloodstream of the patient may both be decreased, leading to a more even drug level in the blood over a period of time. Such formulations may also provide a longer plateau concentration of the drug in the blood.

Many different types of extended release formulations are known in the art.
15 Currently, sustained and controlled release drug delivery systems administered by the oral route are usually based on either a gel forming matrix or coated formulations, or the combination thereof. The selection of the proper type of such an extended release formulation is crucial for effective drug delivery which minimizes side effects, and hence for patient compliance.

20 Venlafaxine, 1-[(2-dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol, is an important drug in the neuropharmacological arsenal, used for the treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Patent No. 4,535,186, which is hereby incorporated by reference as if fully set forth herein.

Venlafaxine hydrochloride may be administered to adults in compressed tablet form in
25 doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. It has been found that in therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma
30 levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

US Patent No. 6,274,171, issued on August 14, 2001, describes one attempted solution to the problem of frequent administration of venlafaxine. The disclosure teaches an extended release formulation of spheroids, which feature an outer film coating over spheroids containing venlafaxine, and which are placed in a hard gelatine capsule.

5 However, spheroids are a more costly and less efficient solid dosage form to produce, and also require the additional procedural step of being placed in a hard gelatin capsule.

Tablets are a less costly and a more efficient solid dosage form to manufacture, but as taught by US Patent No. 6,274,171, the production of tablets for an extended release formulation of venlafaxine does not provide satisfactory results (see column 4
10 lines 60-67, for example), both in terms of physical instability and too rapid dissolution.

Thus, US Patent No. 6,274,171 teaches that a formulation for venlafaxine of encapsulated spheroids is the only feasible solution for extended release.

Extended release tablet formulations are known in the art. Many of these formulations use combinations of polymers such as HPMC (hydroxypropyl
15 methylcellulose) and ethyl cellulose. For example, US Patent No. 4,657,757 teaches the use of either HPMC alone, or a combination of HPMC and ethyl cellulose. However, the use of a filler, or of a special release controlling coating, are not taught or suggested.

US Patent No. 6,274,171 clearly teaches that an extended release formulation of venlafaxine ameliorates sharp peaks in the blood levels, which are not desired, and that in
20 order to avoid side effects and sharp peaks in blood levels, an extended release formulation is required. However, US Patent No. 6,274,171 teaches that a tablet formulation for extended release of venlafaxine is not feasible.

US Patent No. 4,601,894 teaches that HPMC is preferably used in combination with a filler. However, it does not teach the combination of a water soluble cellulosic
25 polymer, such as HPMC, with a water insoluble cellulosic polymer, such as ethyl cellulose. It also does not teach the use of a special release controlling coating.

US Patent No. 5,451,409 teaches that a combination of HPMC and HEC (hydroxyethyl cellulose) may be used in a sustained release formulation, but teaches that a filler, such as microcrystalline cellulose, is not suitable in combination with cellulosic
30 polymers for a sustained release formulation. It also does not teach the use of a special release controlling coating.

US Patent No. 6,217,903 teaches the combination of two or more cellulosic polymers, but specifically teaches away from the combination of HPMC and ethyl cellulose. Also, it teaches the use of relatively low amounts of fillers, such as

microcrystalline cellulose for example, of less than 30%, and typically only about 20% or less as a weight percent of the total formulation. It also does not teach the use of a special release controlling coating.

5 US Patent No. 6,350,471 teaches the combination of a water insoluble but water-permeable film forming polymer and a water soluble polymer, with a plasticizer, for forming a delayed release coating. However, the taught cores are immediate-release cores, or at least do not control the release characteristics of the formulation. Furthermore, it does not teach that a controlled release core would be suitable for use with the taught coating, as various deleterious effects (such as capping for example)
10 might be expected to result.

SUMMARY OF THE INVENTION

The background art does not teach or suggest a tablet formulation for the extended release of venlafaxine.

15 The present invention overcomes this deficiency of the background art by providing an extended release formulation for administration of venlafaxine in a tablet form.

The formulation preferably features a core, over which an outer coating is layered. The term "core" is hereinafter defined as an uncoated tablet.

20 The core comprises venlafaxine, preferably with a filler, and a water soluble cellulosic polymer and more preferably with a water insoluble cellulosic polymer. The core is coated with a coating material. The coating preferably comprises a mixture of water soluble cellulosic polymer and a water insoluble cellulosic polymer.

According to a first embodiment of the present invention, the filler is preferably
25 present in an amount of at least about 40% weight per weight of the total formulation. Unless otherwise noted, all percentages are given as percent weight per weight. By "total formulation", it is meant the core and coating together; if no coating is used, then the term refers to the core alone. More preferably, the filler comprises microcrystalline cellulose. Most preferably, the filler solely comprises microcrystalline cellulose. Also
30 most preferably, microcrystalline cellulose is present in the core in a range of from about 45% to about 65% weight per weight of the total formulation.

Preferably, the water soluble cellulosic polymer in the core is present in an amount of at least about 5% weight per weight of the total formulation. Optionally and preferably, the water soluble cellulosic polymer in the core is present in an amount of

21

from about 5 to about 20%, weight per weight of the total formulation. More preferably, the water soluble cellulosic polymer comprises HPMC (hydroxypropyl methylcellulose). Optionally and more preferably, HPMC comprises a high molecular weight form of this polymer. By "high molecular weight", it is meant a form of HPMC having a viscosity of
5 at least about 100 cps, and/or a form of HPMC having a molecular weight of at least about 1,000,000 g/mol. One non-limiting example of such a high molecular form of HPMC is Methocel K100M™ (Colorcon Inc., USA).

The viscosity of HPMC is proportional to molecular weight or chain length, and to concentration. A decrease in viscosity occurs with increasing temperature until the
10 temperature has been reached where gelation takes place. Commercial designation of these products may optionally be determined by viscosity values for 2% aqueous solutions at 20°C, using a viscometer according to A.S.T.M Standards 1347-72 and D 2363-72 (American Society for Testing and Materials, Philadelphia). This method involves the use of Ubbelohde tubes, which require only a small test sample, one type for
15 low viscosity and one for high viscosity. The viscometer is placed in a water bath at 20°C ± 0.1°C and the length of time required to deliver a given volume between index marks through a tube of specified capillary size is measured. The time in seconds is then converted to centipoise.

Solutions of HPMC are not strictly Newtonian. The shear-stress/rate-of-shear
20 relationship is usually not linear and the viscosity behaviour is pseudoplastic with increasing shear stress i.e. their viscosity decreases with increased shear. When the viscosity of a solution is less than 500cP, the viscosity is independent of shear and the solution may be regarded as Newtonian.

Most preferably, the water soluble cellulosic polymer in the core is present in an
25 amount of from about 8% to about 16 %, weight per weight of the total formulation.

Alternatively or additionally, the water soluble cellulosic polymer may comprise one or more of HPMC (hydroxypropyl methylcellulose), hydroxypropyl cellulose (more preferably of the high viscosity type), hydroxyethyl cellulose, polyethylene oxide, methyl cellulose, various water-soluble polysaccharides and carboxymethyl cellulose, including
30 sodium salts thereof.

Preferably, the water insoluble cellulosic polymer in the core is present in an amount of at least about 5% weight per weight of the total formulation. More preferably, the water insoluble cellulosic polymer comprises ethyl cellulose. Most preferably, the

water insoluble cellulosic polymer in the core is present in an amount of from about 5% to about 10 %, weight per weight of the total formulation.

Alternatively or additionally, the water insoluble cellulosic polymer may comprise one or more of cellulose acetate and ethyl cellulose. The water insoluble
5 cellulosic polymer, such as ethyl cellulose for example, may optionally be dry blended, or alternatively may be wet granulated with a solvent such as ethanol for example.

According to preferred embodiments of the present invention, the water soluble cellulosic polymer in the coating is present in an amount of up to about 5% weight per weight of the total formulation. More preferably, the water soluble cellulosic polymer
10 comprises HPMC (hydroxypropyl methylcellulose). Optionally and more preferably, HPMC comprises a low molecular weight form of this polymer. By "low molecular weight" form of HPMC, it is meant a polymer preferably having a viscosity of less than about 10 cps, and more preferably less than about 5 cps, and/or a polymer having a molecular weight of less than about 10,000 g/mol. One non-limiting example of such a
15 low molecular form of HPMC is Methocel E5™ (Colorcon Inc., USA). More preferably, the water soluble cellulosic polymer in the coating is present in an amount of from about 0.1% to about 3 %, weight per weight of the total formulation, and most preferably from about 0.3% to about 1 %, weight per weight of the total formulation.

Preferably, the water insoluble cellulosic polymer in the coating is present in an
20 amount of up to about 15% weight per weight of the total formulation. More preferably, the water insoluble cellulosic polymer comprises ethyl cellulose. Most preferably, the water insoluble cellulosic polymer in the coating is present in an amount of from about 2% to about 12 %, weight per weight of the total formulation. Also most preferably, ethyl cellulose in the coating is present in a range of from about 2 to about 12%, weight
25 per weight of the entire formulation.

According to still another embodiment of the present invention, there is provided a tablet which features a core containing venlafaxine and at least about 40% of a filler, upon which core is disposed a coating, the coating featuring a mixture of a water insoluble and a water soluble cellulosic polymer, wherein the coated tablet is
30 characterized as having a release profile of venlafaxine such that an extended release profile is obtained for venlafaxine *in vivo*. Surprisingly, the coated tablet provides a similar release profile to the background art encapsulated spheroid dosage form. The capability of the tablet dosage form to provide such a similar release profile is highly surprising.

Additionally, spheroids, as taught in the background art and especially as taught in US Patent No. 6,274,171, are essentially different from tablets.

The present invention preferably comprises a relatively high amount of the filler in the core. The combination of water soluble and water insoluble cellulosic polymers for both the core and the coating provides the desired bioavailability and extended release profile of the formulation according to the present invention. This combination is preferably used for a tablet dosage form, which the background art teaches is not feasible for use for an extended release formulation of venlafaxine (see for example US Patent No. 6,274,171, which clearly teaches away from such a combination in the tablet dosage form).

According to yet another embodiment of the present invention, there is provided a method for treating a subject by administering venlafaxine to the subject in need thereof, comprising administering a tablet containing venlafaxine in a core, in which the core also preferably comprises at least about 40% of a filler. The tablet also features a coating on the core, which preferably features a mixture of a water insoluble cellulosic polymer and a water soluble cellulosic polymer, wherein the tablet is characterized as having a prolonged release profile of venlafaxine *in vivo*.

According to another embodiment of the present invention, there is provided a coated tablet formulation, comprising: (a) a tablet core, comprising: (i) a therapeutically effective amount of venlafaxine or a pharmaceutically acceptable salt thereof; (ii) microcrystalline cellulose; (iii) HPMC (hydroxypropylmethyl cellulose) in a high molecular weight form; and (iv) ethyl cellulose; and (b) a tablet coating on the core, the coating comprising: (i) ethyl cellulose; and (ii) HPMC in a low molecular weight form.

According to still another embodiment of the present invention, there is provided a process for manufacturing a coated tablet containing venlafaxine, the process comprising: preparing a granulation of venlafaxine, HPMC, microcrystalline cellulose and ethyl cellulose, wherein an amount of the HPMC is greater than 8% weight per weight of the tablet, an amount of the microcrystalline cellulose is greater than about 40% weight per weight of the tablet, and an amount of the ethyl cellulose is greater than about 5% weight per weight of the tablet; compressing the granulation into cores; and coating the cores with a mixture of aqueous ethyl cellulose and HPMC to obtain the coated tablets.

Optionally, the process may comprise: preparing a granulation of venlafaxine, HPMC, microcrystalline cellulose and ethyl cellulose; adding a lubricant to the granulate;

compressing the granulation into cores; and coating the cores with a mixture of ethyl cellulose and HPMC to obtain the coated tablets.

Also optionally, the process may comprise: mixing venlafaxine, HPMC, microcrystalline cellulose and ethyl cellulose to form a mixture; adding a lubricant to the mixture; compressing the mixture into cores; and coating the cores with a mixture of ethyl cellulose and HPMC to form the tablets.

Venlafaxine is preferably administered as venlafaxine hydrochloride, although optionally any pharmaceutically suitable form, and optionally and more preferably any pharmaceutically suitable salt, may be used. Such pharmaceutically acceptable salts thereof are disclosed for example in U.S. Patent No. 4,535,186, which is hereby incorporated by reference as if fully set forth herein. Suitable dosage ranges are typically from about 75 mg to about 150 mg of venlafaxine base per day. All dosages given in this application, unless otherwise specified, are calculated according to the weight of venlafaxine base contained therein. For example, suitable dosage ranges of venlafaxine hydrochloride are typically from about 84.8mg to about 169.5mg venlafaxine hydrochloride per day, which corresponds to the dosage range given above for venlafaxine base. Preferably, the amount of venlafaxine hydrochloride, given as a percent weight per weight for the total formulation, is in a range of from about 5 % to about 40 %. More preferably, the amount of venlafaxine hydrochloride is in a range of from about 10 % to about 30 %, weight per weight. Most preferably, the amount of venlafaxine hydrochloride is about 22.5%, weight per weight.

Unless otherwise indicated, the term "venlafaxine" includes the base form and/or any pharmaceutically acceptable salt.

The tablet formulation of the present invention may optionally be used for any type of treatment for which venlafaxine and/or one of its pharmaceutically acceptable salts is recommended and/or is suitable. Uses which are known in the art include, but are not limited to, all forms of depression, either in hospital or in out-patient clinics, depressive illness with or without melancholy, depression accompanied by anxiety, depression related to aging, episodes of depression in a limited sense, especially an episode with vital symptoms, major depression, including severe episodes in hospitalized patients, new depressive episodes, panic disorder, generalized anxiety disorder- short or long-term treatment, and anxiety, including long-term treatment for melancholia.

Surprisingly, the tablet formulation of the present invention was quite effective with venlafaxine, given that the background art teaches away from the use of tablets, and

instead teaches that spheroids are a suitable solid dosage form. Spheroids and tablets are quite different as taught in the background art.

BRIEF DESCRIPTION OF THE DRAWINGS

5 The invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

FIGS. 1A-1C show *in vitro* dissolution profiles of venlafaxine from different exemplary formulations according to the present invention;

10 FIG. 2 shows an *in vitro* dissolution profile of venlafaxine from a tablet formulation that differs from the present invention;

FIG. 3 shows an *in vitro* dissolution profile of venlafaxine according to a preferred embodiment of the present invention; and

FIGS. 4-5 show *in vivo* release profiles of venlafaxine in the formulation according to the present invention.

15

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of an extended release formulation for administration of venlafaxine or a pharmaceutically acceptable salt as a tablet.

20 The formulation preferably features a core, over which an outer coating is layered.

The core contains venlafaxine or a pharmaceutically acceptable salt, preferably with a filler, and a water soluble cellulosic polymer, more preferably with a water insoluble cellulosic polymer. The core is preferably coated with a coating material. The coating preferably contains a mixture of water soluble cellulosic polymer and a water
25 insoluble cellulosic polymer.

According to a first embodiment of the present invention, the filler is preferably present in an amount of at least about 40% weight per weight of the total formulation. More preferably, the filler comprises microcrystalline cellulose. Most preferably, the filler solely comprises microcrystalline cellulose. Also most preferably, microcrystalline
30 cellulose is present in the core in a range of from about 45% to about 65% weight per weight of the total formulation.

Preferably, the water soluble cellulosic polymer in the core is present in an amount of at least about 5% weight per weight of the total formulation. More preferably, the water soluble cellulosic polymer comprises HPMC (hydroxypropyl methylcellulose).

Optionally and more preferably, HPMC comprises a high molecular weight form of this polymer as previously defined. More preferably, the water soluble cellulosic polymer in the core is present in an amount of from about 5% to about 20 %, weight per weight of the total formulation. Most preferably, the water soluble cellulosic polymer in the core is present in an amount of from about 8% to about 16 %, weight per weight of the total formulation.

Alternatively or additionally, the water soluble cellulosic polymer may comprise one or more of HPMC (hydroxypropyl methylcellulose) hydroxypropyl cellulose (more preferably of the high viscosity type), hydroxyethyl cellulose, and carboxymethyl cellulose, including sodium salts thereof.

Preferably, the water insoluble cellulosic polymer in the core is present in an amount of at least about 5% weight per weight of the total formulation. More preferably, the water insoluble cellulosic polymer comprises ethyl cellulose. Most preferably, the water insoluble cellulosic polymer in the core is present in an amount of from about 5% to about 10 %, weight per weight of the total formulation.

Alternatively or additionally, the water insoluble cellulosic polymer may comprise one or more of cellulose acetate, and ethyl cellulose.

According to preferred embodiments of the present invention, the water soluble cellulosic polymer in the coating is present in an amount of up to about 5% weight per weight of the total formulation. More preferably, the water soluble cellulosic polymer comprises HPMC (hydroxypropyl methylcellulose). Optionally and more preferably, HPMC comprises a low molecular weight form of this polymer as previously defined. More preferably, the water soluble cellulosic polymer in the coating is present in an amount of from about 0.1% to about 3 %, and most preferably from about 0.3% to about 1 %, weight per weight of the total formulation.

Preferably, the water insoluble cellulosic polymer in the coating is present in an amount of up to about 15% weight per weight of the total formulation. More preferably, the water insoluble cellulosic polymer comprises ethyl cellulose. Most preferably, the water insoluble cellulosic polymer in the coating is present in an amount of from about 2% to about 12 %, weight per weight of the total formulation.

According to still another embodiment of the present invention, the core is preferably in a form of a tablet, and the core preferably further comprises a lubricant. The lubricant more preferably comprises magnesium stearate, which most preferably is present in an amount of up to about 2% weight per weight of the core, although

optionally a concentration of from about 0.25% to about 5% weight per weight may be used. Alternatively or additionally, the lubricant may optionally be selected from the group consisting of stearate salts (magnesium, calcium, etc); stearic acid, talc, castor oil, hydrogenated palm oil, some type of starch, polyethylene glycol, sodium stearyl
5 fumarate, compritrol (glycerol behenate), waxes, or a combination thereof.

Optionally and more preferably, the core further comprises a flow regulating agent. Preferably, the flow regulating agent comprises colloidal silicon dioxide, most preferably in an amount of up to about 1%, weight per weight of the total formulation.

According to other preferred embodiments of the present invention, the coating
10 preferably further comprises a plasticizer. More preferably, the plasticizer includes at least one of dibutyl sebacate, polyethylene glycol and polypropylene glycol, dibutyl phthalate, diethyl phthalate, triethyl citrate, tributyl citrate, acetylated monoglyceride, acetyl tributyl citrate, triacetin, dimethyl phthalate, benzyl benzoate, butyl and/or glycol esters of fatty acids, refined mineral oils, oleic acid, castor oil, corn oil, camphor,
15 glycerol and sorbitol or a combination thereof. More preferably, the plasticizer comprises dibutyl sebacate, particularly for combination or use with ethyl cellulose. Most preferably, the plasticizer also comprises polyethylene glycol, of which a non-limiting example is Macrogol 400™ (Uniqema, USA), particularly for use or combination with HPMC. Most preferably, the plasticizer is present in an amount of up
20 to about 5%, which is most preferably in a range of from about 0.01% to about 3% of the total formulation, percent weight per weight.

According to still another embodiment of the present invention, there is provided a tablet which features a core containing venlafaxine (base or a pharmaceutically acceptable salt thereof) and at least about 40% of a filler, upon which core is disposed a
25 coating, the coating featuring a mixture of a water insoluble and a water soluble cellulosic polymer, wherein the tablet is characterized as providing a release profile of venlafaxine such that a therapeutically effective blood plasma concentration of venlafaxine is provided over a twenty-four period, with peak blood plasma levels of venlafaxine of no more than about 150 ng/ml.

30 According to yet another embodiment of the present invention, there is provided a method for treating a subject by administering venlafaxine to the subject in need thereof, comprising administering a tablet containing venlafaxine (base or a pharmaceutically acceptable salt) in a core, in which the core also contains at least about 40% of a filler. The tablet also features a coating on the core, which preferably features a mixture of a

28

water insoluble and a water soluble cellulosic polymer. Preferably, the tablet is characterized as having the previously described release profile of venlafaxine.

The present invention is also preferably characterized according to a suitable dissolution profile. One non-limiting example of such a dissolution profile is as follows.

- 5 The dissolution profile is preferably determined in USP Apparatus 1 (basket) at 100 rpm in phosphate buffer at pH 6.8 as shown in the table below:

Table 1: Exemplary Dissolution Profile

Time (hours)	Average % Venlafaxine released
2	<30
4	25-45
8	55-75
12	75-95
24	>80

- 10 According to an exemplary, non-limiting embodiment of the present invention, the venlafaxine formulation may optionally be manufactured as follows. This process is for manufacture with the following ingredients: core - ethyl cellulose, venlafaxine hydrochloride, microcrystalline cellulose, HPMC, colloidal silicon dioxide, and magnesium stearate; coating - polyethylene glycol, HPMC, ethyl cellulose, and dibutyl
15 sebacate.

- For manufacture of the core, ethyl cellulose is dissolved in a suitable organic solvent such as ethyl alcohol for example, to form a granulation solution. Venlafaxine hydrochloride, HPMC and microcrystalline cellulose are then mixed. The dissolved ethyl cellulose is then added to the mixture to form a granulate. The granulate is dried,
20 for example with a fluid bed dryer. The dried granulate is then milled, and then optionally blended to form a blend.

Next, colloidal silicon dioxide and magnesium stearate are sieved. The sieved materials are preferably mixed with the previously prepared blend. The mixture is then compressed to form the tablets.

- 25 For the coating, PEG and HPMC are dissolved in water to form a solution. The solution is then added to the suspension of ethyl cellulose with dibutyl sebacate, and stirred for about 45 minutes to form the coating solution.

The previously prepared cores are then coated with the coating solution.

EXAMPLES

For the purposes of the examples below, and without any intention of being limiting, unless otherwise noted, the term "venlafaxine" refers to venlafaxine hydrochloride.

Example 1: Tests *in vitro*

These examples are of illustrative implementations of the method and formulation according to the present invention. It should be noted that all examples given herein use venlafaxine hydrochloride, referred to herein as "venlafaxine" for the purpose of brevity and without any intention of being limiting. Several formulations were tested *in vitro* to determine the release profile, as described in greater detail below.

Briefly, dissolution of the venlafaxine tablets was tested by using the *in vitro* basket method (USP), in which each tablet, containing 75 mg of venlafaxine hydrochloride (calculated relative to the weight of venlafaxine base), was placed in a vessel containing 900 ml of a suitable phosphate buffer, at pH 6.8. The basket was rotated at 100 rpm. Samples were taken at 2, 4, 8, 12 and 24 hours after the tablet was placed in the basket.

The formulations tested are given in Table 2.

Table 2: Different formulations of venlafaxine (75 mg of base)

Tablet content	A		B		C	
	mg/tab	%	mg/tab	%	mg/tab	%
Core:						
Venlafaxine HCl	84.85	22.3	84.85	18.6	84.85	21.9
Microcrystalline cellulose PH 101	214.15	56.4	244.15	53.7	207.15	53.4
Ethyl cellulose 100 CPS	20	5.3	25	5.5	20	5.15
HPMC 2208	30	7.9	60	13.2	37	9.5

Colloidal Silicon Dioxide	2.0	0.53	2.0	0.44	2.0	0.52
Magnesium Stearate	4.0	1.0	4.0	0.88	4.0	1.0
Total weight uncoated tablet	355	93	420	92	355	91
<u>Coating</u>						
Ethyl cellulose aqueous solution (as dried weight)	18	4.7	25	5.5	25	6.4
Dibutyl sebacate	4.3	1.1	6	1.3	5.5	1.4
HPMC 2910/5	2.9	0.76	4.0	0.88	1.9	0.5
Macrogol 400 (PEG)	0.09	0.02	0.12	0.03	0.6	0.15
Total weight of coating	25	6.6	35	7.7	33	8.5
Total weight of formulation	380	100	455	100	388	100

As shown in Figure 1A with regard to formulation "A", a suitable controlled release formulation was obtained, with a suitable dissolution profile. Similar results were obtained for formulations "B" and "C", as shown in Figures 1B and 1C. For each of Figures 1A-1C, the *in vitro* dissolution profile is shown in comparison with the reference formulation, Effexor™ XL 75 mg capsules of Wyeth (USA).

Table 3 shows the comparative dissolution in terms of the concentration of venlafaxine hydrochloride obtained at each time point, given as the percentage of the total concentration of venlafaxine hydrochloride in the formulation.

Table 3

Time (h)	Formulation A	Formulation B	Formulation C
2	21	7	10
4	42	27	32
8	74	56	65

12	94	78	86
24	100	100	100

By contrast, Figure 2 shows the results for a tablet formulation which features an uncoated core formulation according to Table 4 (uncoated tablet formulation).

5 Table 4

Tablet content	uncoated tablet formulation	
	mg/tab	%
Core:		
Venlafaxine HCl (75 mg of base)	84.85	23.5
Microcrystalline cellulose PH 101	244.15	58.1
Ethyl cellulose 100 CPS	60	14.2
HPMC 2208	25	6.0
Colloidal Silicon Dioxide	2.0	0.48
Magnesium Stearate	4.0	1.0
Total weight uncoated tablet	420	

The *in vitro* basket results for Figure 2 demonstrate that the dissolution profile of the uncoated tablet formulation is clearly too rapid to provide a suitable controlled release formulation, as 50% release of venlafaxine during dissolution occurs in 2 hours, while the coated tablet formulation according to the present invention preferably provides about 20% release in 2 hours, as shown in Figure 3. Thus, the combination of the coating and the core for the formulation of the present invention provides the desired dissolution profile and is therefore important.

1.5 Example 2: Tests *in vivo*

This example is of an illustrative implementation of a preferred embodiment of the formulation according to the present invention with venlafaxine. It should be noted

that this example given herein uses venlafaxine hydrochloride, referred to herein as "venlafaxine" for the purpose of brevity and without any intention of being limiting. It should be noted that the tested solid dosage form contained 75 mg of venlafaxine base. The formulation was tested *in vitro* to determine the dissolution profile. The *in vitro* dissolution profile was determined as for Example 1 above, according to the formulation shown in Table 5.

Table 5

Tablet content	Formulation of the present invention	
	mg/tab	%
Core:		
Venlafaxine HCl	84.85	22.3
Microcrystalline cellulose PH 101	204.15	53.7
Ethyl cellulose 100 CPS	20	5.26
HPMC 2208	40	10.5
Colloidal Silicon Dioxide	2.0	0.52
Magnesium Stearate	4.0	1.04
Total weight uncoated tablet	355	93
<u>Coating</u>		
Ethyl cellulose aqueous solution (as dried weight)	18	4.73
Dibutyl sebacate	4.0	1.05
HPMC 2910/5	1.9	0.5
Macrogol 400 (PEG)	0.6	0.15
Total weight of coating	24.5	6.6

Total weight of formulation	379.5	100
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The *in vitro* dissolution profile is shown in Figure 3. The results are tabulated in Table 6. As can be seen, an appropriate dissolution profile was obtained, different from those obtained by the uncoated examples.

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Table 6

Time (h)	Formulation of the present invention
2	21
4	40
8	70
12	87
24	97

10 The *in vivo* release of venlafaxine from the above-referenced formulation was determined as follows. A bioequivalence study was performed in order to assess the relative bioavailability of the test product Venlafaxine 75 mg ER tablet of the present invention ("formulation of present invention"; see Table 5 above) in comparison to the reference product Effexor™ XL 75 mg capsules of Wyeth ("reference formulation"). The study was designed as a two-way randomized crossover study with a one week wash-out period. Thirty eight volunteers concluded the study. Due to a statistical outlier, one volunteer was removed from the statistical calculation for the $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$.

15 At the start of each period, one tablet/capsule of either formulation was administered to fasting volunteers and blood samples were withdrawn according to the following schedule: 0, 1, 2, 3, 4, 5, 6, 7, 7.5, 8, 8.5, 9, 10, 12, 15, 24, 36, 48 and 60 hours post dose.

20 Plasma concentrations of venlafaxine and of its main metabolite O-desmethylvenlafaxine (ODV) were determined using HPLC analytical method with UV

detection. The limit of quantitation (LOQ), defined as the lowest concentration determined with accuracy and run-to-run precision lower than 20% was 1.5 ng/ml.

All values below the limit of quantitation (BLQ) were set to zero for pharmacokinetic and statistical computations

5 A concentration-time curve was constructed for each volunteer for each period. The maximal concentration (C_{max}) and the time of its occurrence (T_{max}) were directly observed from the curves and the area under the curve (AUC) was computed for each volunteer.

10 For all parameters, the distributional properties of the residuals from the linear model were investigated directly, and after logarithmic transformation (multiplicative model). As recommended by Steinijans et al [Steinijans V.W., Hauschke D. An Update on the statistical analysis of bioequivalence studies. *Int. J. Clin. Pharmacol., Ther. and Toxicol.*, 1989, 28(3): 105-110.], for pharmacokinetic reasons, the results of the multiplicative model are presented even when both models were found adequate. Thus,
15 the presented ratios of AUC and C_{max} are geometric means of the individual ratios.

 The median values and differences between test and reference T_{max} were reported and a 90% non-parametric Confidence Interval was computed by the method proposed by Hauschke et al. which does not require the restrictive assumption of an equal period effect.

20

CONCLUSION:

 The extent of absorption, as reflected by the AUC_(0-∞) ratio of 1.06, supports the determination of bioequivalence between the two preparations, with a 90% ANOVA Confidence Interval of 0.97→1.15. The 90% ANOVA Confidence Interval after
25 logarithmic transformation is included in the 0.80-1.25 range.

 The extent of absorption, as reflected by the AUC_(0-t) ratio of 1.08, supports the determination of bioequivalence between the two preparations, with a 90% ANOVA Confidence Interval of 0.99→1.17. The 90% ANOVA Confidence Interval after logarithmic transformation is included in the 0.80-1.25 range.

30 The rate of absorption, as reflected by the C_{max} values, with a ratio of 0.99, supports the determination of bioequivalence between the two preparations, with a 90% ANOVA Confidence Interval of 0.91→1.07. The 90% ANOVA Confidence Interval after logarithmic transformation is included in the 0.80-1.25 range.

The difference in Time to Maximal concentration, as reflected by the T_{max} values, have the median difference estimate of 0.50 hours with a 90% nonparametric Confidence Interval of $-0.25 \rightarrow 1.25$. This indicates an equivalent rate of absorption.

5 **Conclusions for ODV metabolite:**

The extent of absorption, as reflected by the $AUC_{(0-\infty)}$ ratio of 1.08, supports the determination of bioequivalence between the two preparations, with a 90% ANOVA Confidence Interval of $1.01 \rightarrow 1.15$. The 90% ANOVA Confidence Interval after logarithmic transformation is included in the 0.80-1.25 range.

10

The extent of absorption, as reflected by the $AUC_{(0-1)}$ ratio of 1.09, supports the determination of bioequivalence between the two preparations, with a 90% ANOVA Confidence Interval of $1.02 \rightarrow 1.17$. The 90% ANOVA Confidence Interval after logarithmic transformation is included in the 0.80-1.25 range.

15

The rate of absorption, as reflected by the C_{max} values, with a ratio of 1.02, supports the determination of bioequivalence between the two preparations, with a 90% ANOVA Confidence Interval of $0.93 \rightarrow 1.13$. The 90% ANOVA Confidence Interval after logarithmic transformation is included in the 0.80-1.25 range.

20

The difference in Time to Maximal concentration, as reflected by the T_{max} values, have the median difference estimate of 1.50 hours with a 90% nonparametric Confidence Interval of $0.50 \rightarrow 2.50$. This indicates an equivalent rate of absorption.

Thus, the formulation of the present invention and the reference formulation exhibit very similar pharmacokinetic profiles and should be considered as bioequivalent.

25

The pharmacokinetic parameters obtained in this study are presented in the following tables and figures:

PHARMACOKINETIC PARAMETERS (Table 7):

	AUC _(0-∞) (ng x hour/ml) (n=37)	AUC _(0-t) (ng x hour/ml) (n=37)	Cmax (ng/ml) (n=38)	Tmax (hours) (n=38)
VENLAFAXINE 75mg (present invention)	677.56 ± 434.28 (160.10 ; 2085.51)	646.65 ± 434.39 (140.09 ; 2029.58)	37.80 ± 20.09 (11.11 ; 88.42)	7.74 ± 2.69 (5.00 ; 15.00)
REFERENCE FORMULATION XL 75mg (originator)	626.40 ± 378.36 (202.46 ; 1868.75)	589.23 ± 371.98 (143.71 ; 1785.91)	37.46 ± 17.42 (9.96 ; 75.19)	7.12 ± 1.95 (5.00 ; 12.00)
CV% (Coefficient of Variation)	22%	22%	21 %	
RATIO* (90% ANOVA C.I.)	1.06 (0.97 ; 1.15)	1.08 (0.99 ; 1.17)	0.99 (0.91 ; 1.07)	
DIFFERENCE ESTIMATE** (range) (90% non parametric C.I.)				0.50 (-7.00 ; 9.00) (-0.25 ; 1.25)

The presented values for all pharmacokinetic parameters are mean $\pm$ SD and (range).

* The presented ratios are the geometric means of the ratios between test
5 and the reference parameters. Parametric estimators and Parametric Confidence
Intervals, based on the linear model with logarithmic transformation (multiplicative
model), are given.

** The presented difference is the median difference with its corresponding
range. 90% non-parametric Confidence Intervals for the median difference with its
10 corresponding median estimate was computed by the method of Hauschke et al.
[Hauschke D, Steinijans V.W., Diletti E. A distribution free procedure for the statistical
analysis of bioequivalence studies. Int. J. Clin. Pharmacol., Ther. and Toxicol., 1990,
28(2): 72-78], which does not require the restrictive assumption of equal period effect as
previous methods.

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PHARMACOKINETIC PARAMETERS FOR ODV (metabolite; Table 8)

	AUC _(0-∞) (ng x hour/ml) (n=37)	AUC _(0-t) (ng x hour/ml) (n=37)	C _{max} (ng/ml) (n=38)	T _{max} (hours) (n=38)
VENLAFAXINE 75mg (present invention)	2626.94 $\pm$ 927.52 (722.99 ; 4554.44)	2521.34 $\pm$ 890.38 (695.76 ; 4255.25)	92.49 $\pm$ 31.43 (30.79 ; 153.00)	11.74 $\pm$ 4.05 (5.00 ; 24.00)

REFERENCE FORMULATION XL 75mg (originator)	2399.42 ± 745.34 (539.99 ; 4002.54)	2266.02 ± 715.75 (511.43 ; 3702.41)	90.62 ± 30.18 (24.63 ; 157.78)	10.14 ± 2.45 (5.00 ; 15.00)
CV% (Coefficient of Variation)	16%	17%	25 %	
RATIO* (90% ANOVA C.I.)	1.08 (1.01 ; 1.15)	1.09 (1.02 ; 1.17)	1.02 (0.93 ; 1.13)	
DIFFERENCE ESTIMATE** (range) (90% non parametric C.I.)				0.50 (-6.00 ; 12.00) (1.50 ; 2.50)

The presented values for all pharmacokinetic parameters are mean $\pm$ SD and (range).

- 5 * The presented ratios are the geometric means of the ratios between test and the reference parameters. Parametric estimators and Parametric Confidence Intervals, based on the linear model with logarithmic transformation (multiplicative model), are given.

- 10 ** The presented difference is the median difference with its corresponding range. 90% non-parametric Confidence Intervals for the median difference with its

corresponding median estimate was computed by the method of Hauschke et al., which does not require the restrictive assumption of equal period effect as previous methods.

- 5 Figures 4 and 5 show the blood concentration values for the venlafaxine formulation according to the present invention after administration, for the formulation according to the present invention. As can be seen, the *in vivo* release profiles for the formulation according to the present invention and for the reference are highly similar.

WHAT IS CLAIMED IS:

1. An extended release coated tablet formulation for venlafaxine, comprising:
 - (a) a core comprising a pharmaceutically effective amount of venlafaxine or a pharmaceutically acceptable salt thereof, said core being in a form of a tablet and said core further comprising:
 - (i) at least 40% of a filler, weight per weight of the entire formulation;
 - (ii) at least 5% of a water soluble cellulosic polymer, weight per weight of the entire formulation;
 - (iii) at least 5% of ethyl cellulose, weight per weight of the entire formulation;
 - (b) a coating for said core, said coating comprising:
 - (i) a water soluble cellulosic polymer; and
 - (ii) a water insoluble cellulosic polymer.
2. The coated tablet of claim 1, wherein said filler is present in an amount of from about 45 to about 65%, weight per weight of the entire formulation.
3. The coated tablet of claim 2, wherein said filler comprises microcrystalline cellulose.
4. The coated tablet of claim 2, wherein said filler comprises solely microcrystalline cellulose.
5. The coated tablet of any of claims 1-4, wherein said water soluble cellulosic polymer in said core is present in a range of from about 5% to about 20%, weight per weight of the entire formulation.
6. The coated tablet of any of claims 1-5, wherein said water soluble cellulosic polymer in said core comprises HPMC (hydroxypropyl methylcellulose).
7. The coated tablet of any of claims 1-5, wherein said water soluble cellulosic polymer in said core comprises hydroxypropyl cellulose (HPC).

8. The coated tablet of any of claims 1-5, wherein said water soluble cellulosic polymer in said core comprises hydroxyethyl cellulose.
9. The coated tablet of any of claims 1-5, wherein said water soluble cellulosic polymer in said core comprises polyethylene oxide.
10. The coated tablet of any of claims 1-5, wherein said water soluble cellulosic polymer in said core comprises methyl cellulose.
11. The coated tablet of any of claims 1-5, wherein said water soluble cellulosic polymer in said core comprises water soluble polysaccharide.
12. The coated tablet of any of claims 1-5, wherein said water soluble cellulosic polymer in said core comprises carboxymethyl cellulose.
13. The coated tablet of claim 6, wherein said HPMC in said core is present in a range of from about 8 to about 16%, weight per weight of the entire formulation.
14. The coated tablet of any of claims 4 or 13, wherein said HPMC in said core comprises a high molecular weight form of HPMC.
15. The coated tablet of claim 14, wherein said high molecular weight form of HPMC has a viscosity of at least about 100 cps.
16. The coated tablet of any of claims 1-15, wherein said water insoluble cellulosic polymer in said coating is present in an amount of up to about 15%.
17. The coated tablet of any of claims 1-16, wherein said water insoluble cellulosic polymer in said coating comprises ethyl cellulose.
18. The coated tablet of claim 17, wherein said ethyl cellulose is present in a range of from about 2 to about 12%, weight per weight of the entire formulation.

19. The coated tablet of any of claims 1-18, wherein said water soluble cellulosic polymer in said coating comprises HPMC.
20. The coated tablet of claim 19, wherein said HPMC is present in a range of from about 0.1 to about 3%, weight per weight of the entire formulation.
21. The coated tablet of claim 20, wherein said HPMC is present in a range of from about 0.3 to about 1%, weight per weight of the entire formulation.
22. The coated tablet of any of claims 19-21, wherein said HPMC comprises a low molecular weight form of HPMC.
23. The coated tablet of claim 22, wherein said low molecular form of HPMC is characterized in that said HPMC has a viscosity of less than about 10 cps.
24. The tablet of claim 23, wherein said HPMC has a viscosity of less than about 5 cps.
25. The coated tablet of any of claims 1-24, wherein said core further comprises a flow regulating agent.
26. The coated tablet of claim 25, wherein said flow regulating agent comprises colloidal silicon dioxide.
27. The coated tablet of claim 26, wherein said colloidal silicon dioxide is present in an amount of up to about 1% weight per weight of said core.
28. The coated tablet of any of claims 1-27, wherein said core further comprises a lubricant.
29. The coated tablet of claim 28, wherein said lubricant comprises magnesium stearate.

30. The coated tablet of claim 29, wherein said magnesium stearate is present in a concentration of from about 0.25% to about 5%, weight per weight of the core.

31. The coated tablet of claim 30, wherein said magnesium stearate is present in an amount of up to about 2%, weight per weight of the core.

32. The coated tablet of claim 28, wherein said lubricant is selected from the group consisting of stearate salts; stearic acid, talc, sodium stearyl fumarate, and compritol (glycerol behenate), or a combination thereof.

33. The coated tablet of any of claims 1-32, wherein said coating further comprises a plasticizer.

34. The coated tablet of claim 33, wherein said plasticizer comprises at least one of dibutyl sebacate, polyethylene glycol, polypropylene glycol, dibutyl phthalate, diethyl phthalate, triethyl citrate, tributyl citrate, acetylated monoglyceride, acetyl tributyl citrate, triacetin, dimethyl phthalate, benzyl benzoate, butyl and/or glycol esters of fatty acids, refined mineral oils, oleic acid, castor oil, corn oil, camphor, glycerol and sorbitol or a combination thereof.

35. The coated tablet of claim 34, wherein said plasticizer is present in an amount of up to about 5%.

36. The coated tablet of claim 35, wherein said plasticizer is present in a range of from about 0.01% to about 3% of the total formulation, percent weight per weight.

37. The coated tablet of any of claims 33-36, wherein said plasticizer comprises dibutyl sebacate.

38. The coated tablet of claim 37, wherein said plasticizer further comprises PEG (polyethylene glycol).

39. The coated tablet of any of claims 1-38, wherein the formulation provides a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period,

said blood plasma concentration of venlafaxine having a peak level of not more than about 150 ng/ml.

40. The coated tablet of any of claims 1-39, wherein the venlafaxine comprises venlafaxine hydrochloride.

41. The coated tablet of any of claims 1-40, having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in phosphate buffer at pH 6.8 according to a table:

Time (hours)	Average % Venlafaxine released
2	<30
4	25-45
8	55-75
12	75-95
24	>80

42. Use of a therapeutic dosage of a coated tablet formulation according to any of claims 1-41 for providing a therapeutic blood plasma concentration of venlafaxine or a pharmaceutically acceptable salt thereof in a subject over a twenty four hour period, said blood plasma concentration of venlafaxine or a pharmaceutically acceptable salt thereof having a peak level of not more than about 150 ng/ml.

43. The use of claim 42, wherein said venlafaxine comprises venlafaxine hydrochloride.

44. Use of a therapeutic dosage of a coated tablet formulation according to any of claims 1-41 for treating a subject by administering to the subject in need of treatment thereof.

45. The use according to claim 44, wherein said coated tablet formulation provides a therapeutic blood plasma concentration of venlafaxine or a pharmaceutically acceptable salt thereof over a twenty four hour period, said blood plasma concentration

of venlafaxine or a pharmaceutically acceptable salt thereof having a peak level of not more than about 150 ng/ml.

46. The use according to claims 44 or 45, wherein said venlafaxine comprises venlafaxine hydrochloride.

47. A method for administering venlafaxine to a subject in need thereof, the method comprising the step of administering a therapeutic dosage of the coated tablet formulation of any of claims 1-41 to the subject.

48. The method of claim 47, wherein said venlafaxine is administered as a salt.

49. The method of claim 48, wherein said venlafaxine salt comprises venlafaxine hydrochloride.

50. The method of claim 48, wherein said venlafaxine salt is administered in the dosage range of about 75 mg to about 150 mg venlafaxine (weight determined as per venlafaxine base) per day.

51. An extended release formulation of venlafaxine in the form of a coated tablet, comprising:

- (a) a tablet core comprising:
 - (i) a therapeutically effective amount of venlafaxine or a pharmaceutically acceptable salt thereof;
 - (ii) microcrystalline cellulose in an amount in a range of from about 45% to about 65% weight per weight of the entire formulation;
 - (iii) a water soluble cellulosic polymer, said polymer being present in a range of from about 5% to about 20% weight per weight of the entire formulation; and
 - (iv) a water insoluble cellulosic polymer being present in a range of from about 5% to about 10% weight per weight of the entire formulation; and
- (b) a coating surrounding said core, said coating comprising:
 - (i) a water insoluble cellulosic polymer, said polymer being present in a range of from about 2% to about 12% weight per weight of the entire formulation; and

46

- (ii) a water soluble cellulosic polymer.

52. A formulation for extended release of venlafaxine, comprising:

- (a) a core for containing the venlafaxine, said core comprising:

- (i) microcrystalline cellulose, in a range of from about 45 to about 65%, weight per weight of the entire formulation;

- (ii) HPMC (hydroxypropyl methylcellulose), in a range of from about 8 to about 16%, weight per weight of the entire formulation; and

- (iii) ethyl cellulose, in a range of from about 5 to about 10%, weight per weight of the entire formulation; and

- (b) a coating for coating said core, said coating comprising:

- (i) ethyl cellulose, in a range of from about 2 to about 12%, weight per weight of the entire formulation; and

- (ii) HPMC, in a range of from about 0.3 to about 1%, weight per weight of the entire formulation.

53. The formulation of claim 52, wherein said core further comprises colloidal silicon dioxide.

54. The formulation of claim 53, wherein said colloidal silicon dioxide is present in an amount of up to about 1% weight per weight of said core.

55. The formulation of any of claims 52-54, wherein said core further comprises a lubricant.

56. The formulation of claim 55, wherein said lubricant comprises magnesium stearate.

57. The formulation of claim 56, wherein said magnesium stearate is present in an amount of up to about 2%, weight per weight of the core.

58. The formulation of claim 55, wherein said lubricant is selected from the group consisting of stearate salts; stearic acid, talc, sodium stearyl fumarate, and compritol (glycerol behenate), or a combination thereof.

59. The formulation of any of claims 52-58, wherein said core further comprises a flow regulating agent.

60. The formulation of claim 59, wherein said flow regulating agent comprises colloidal silicon dioxide.

61. The formulation of claim 60, wherein said flow regulating agent comprises colloidal silicon dioxide in an amount of up to about 1%, weight per weight of the total formulation.

62. The formulation of any of claims 52-61, wherein said coating further comprises a plasticizer.

63. The formulation of claim 62, wherein said plasticizer comprises at least one of dibutyl sebacate, polyethylene glycol and polypropylene glycol, dibutyl phthalate, diethyl phthalate, triethyl citrate, tributyl citrate, acetylated monoglyceride, acetyl tributyl citrate, triacetin, dimethyl phthalate, benzyl benzoate, butyl and/or glycol esters of fatty acids, refined mineral oils, oleic acid, castor oil, corn oil, camphor, glycerol and sorbitol or a combination thereof.

64. The formulation of claim 63, wherein said plasticizer is present in an amount of up to about 5%.

65. The formulation of claim 64, wherein said plasticizer is present in a range of from about 0.5% to about 3% of the total formulation, percent weight per weight.

66. The formulation of any of claims 62-65, wherein said plasticizer comprises dibutyl sebacate.

67. The formulation of claim 66, wherein said plasticizer further comprises PEG (polyethylene glycol).

48

68. The formulation of any of claims 52-67, wherein said coating and said core form a coated tablet.

69. The formulation of any of claims 52-68, wherein said HPMC in said core comprises a high molecular weight form of HPMC.

70. The formulation of any of claims 52-69, wherein said HPMC in said coating comprises a low molecular weight form of HPMC.

71. The formulation of any of claims 52-70, having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in phosphate buffer at pH 6.8 according to a table:

Time (hours)	Average % Venlafaxine released
2	<30
4	25-45
8	55-75
12	75-95
24	>80

72. A process for manufacturing a coated tablet containing venlafaxine, the process comprising:

preparing a granulation of venlafaxine, HPMC, microcrystalline cellulose and ethyl cellulose, wherein an amount of said HPMC is greater than 8% weight per weight of the tablet, an amount of said microcrystalline cellulose is greater than about 40% weight per weight of the tablet, and an amount of said ethyl cellulose is greater than about 5% weight per weight of the tablet;

compressing said granulation into cores; and

coating said cores with a mixture of aqueous solution of ethyl cellulose and HPMC to obtain the coated tablets.

73. A process for manufacturing a coated tablet containing venlafaxine, the process comprising:

preparing a granulation of venlafaxine, HPMC, microcrystalline cellulose and ethyl cellulose;

adding a flow regulating agent and a lubricant to said granulate;

compressing said granulation into cores;

and

coating said cores with a mixture of ethyl cellulose and HPMC to obtain the coated tablets.

74. A process for manufacturing a tablet containing venlafaxine, the process comprising:

mixing venlafaxine, HPMC, microcrystalline cellulose and ethyl cellulose to form a mixture;

adding a flow regulating agent and a lubricant to said mixture;

compressing said mixture into cores;

and

coating said cores with a mixture of ethyl cellulose and HPMC to form the tablets.

75. A coated tablet formulation, comprising:

(a) a tablet core, comprising:

(i) a therapeutically effective amount of venlafaxine or a pharmaceutically acceptable salt thereof;

(ii) microcrystalline cellulose;

(iii) HPMC (hydroxypropylmethyl cellulose) in a high molecular weight form; and

(iv) ethyl cellulose; and

(b) a tablet coating on said core, said coating comprising:

(i) ethyl cellulose; and

(ii) HPMC in a low molecular weight form.

76. An extended release coated tablet formulation for venlafaxine, substantially as described in the specification.

77. A process for manufacturing a tablet containing venlafaxine, substantially as described in the specification.

11

51

2020
Bogotá, D.C.,

Doctor:
Álvaro Correa Ordóñez
Apoderado

Oficio N°: 9863

ASUNTO:	Radicación PCT N°	08-2354
	Trámite	011
	Evento	379
	Actuación	440
	Folios	010

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, _____.

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