Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-037959- -00003-0000
Fol: 05 2008-10-28 12:35:10 Dep: 2020 NUEVAS SOLICITUDES
Cla: 11 PATENTES Exp: 378 PASE NACIONAL
Ref: 000 OPOSICIONES Folios: 42

FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A :

- [x] Patente de Invención.
- [ ] Patente de Modelo de Utilidad.
- [ ] Diseño Industrial.
- [ ] Esquema de Trazado para Circuitos Integrados.
- [ ] Marcas de Productos o Servicios.
- [ ] Marca Colectiva.
- [ ] Marca de Certificación.
- [ ] Lema Comercial.

② SOLICITUD PUBLICADA

Numero del expediente: **07-037959**
Solicitante: BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Apoderado: EMILIO FERRERO
Titulo de la nueva creación o denominación del signo: "COMPRIMIDO BICAPA QUE COMPRENDE TELMISARTAN Y AMLODIPINO ".
Gaceta: **594**

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: **GYNOPHARM S.A** Dirección: **CALLE 80 No. 78B -201** Nacionalidad o Domicilio: Lugar de Constitución: **COLOMBIA BARRANQUILLA** Teléfono: **(571)3719900** Fax: **(571)3730818** E-mail:	**IDENTIFICACION** C.C. [ ] NIT [x] C.E. [ ] Otro [ ] Cual ____ Numero **802.006.279-4**
REPRESENTANTE O APODERADO	Nombre: **ELIANA ISAURA MORENO BOHORQUEZ** Dirección: **CARRERA 13 No. 119-95 104** Teléfono: **(571) 2131213** Fax: **(571) 6121979** E-mail: **negocios@optimum-co.com**	**IDENTIFICACIÓN** C.C. [x] NIT [ ] C.E. [ ] Otro [ ] Cual ____ Número **51`975.664** TP **83823**

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: **Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN**
Signo opositor: **No cumple con los requisitos de patentabilidad.**
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**

- [x] Comprobante de pago de la tasa.
- [x] Poderes, si fuere el caso.
- [x] Pruebas de los fundamentos de la oposicion.
- [ ] Documentos que acrediten el legítimo interés, si fuere el caso.
- [x] Documento que acredita la existencia y representacion legal de las partes, cuando sean personas juridicas.

⑦

NOMBRE: **ELIANA ISAURA MORENO BOHORQUEZ**

FIRMA: _____

C.C. 51.975.664 **TP.** 83823

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

Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 07 037.959
Asunto	: Oposición a la solicitud de patente de Invención titulada "COMPRIMIDO BICAPA QUE COMPRENDE TELMISARTAN Y AMLODIPINO"
Solicitante	: BOEHRINGER INGELHEIM INTERNATIONAL GMBH.
Opositora	: GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 594 del 31 de julio de 2008

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 "COMPRIMIDO BICAPA QUE COMPRENDE TELMISARTAN Y AMLODIPINO", cuyo titular es BOEHRINGER INGELHEIM INTERNATIONAL GMBH, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

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 legitimo 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 TELMISARTAN y AMLODIPINO. 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 17 de abril de 2007, reivindicando prioridad bajo la solicitud EP20040026234 del 2004-11-05; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **N° 594 del 31 de julio de 2008**, cuya publicación internacional corresponde a la WO2006048208 del 2006-05-11.

2.2. La solicitud colombiana **07 037.959** objeto de la presente oposición, se refiere a un comprimido bicapa que comprende una primera capa formulada para la liberación inmediata del antagonista del receptor de angiotensina II telmisartán desde una matriz de disolución de comprimido y una segunda capa formulada para la liberación inmediata del bloqueante de la cadena del calcio amlodipino desde

una matriz de desintegración o erosión de comprimido; donde una primera capa de telmisartán en una matriz de disolución de comprimido y una segunda capa de amlodipino en una matriz de desintegración o erosión de comprimido; en el que el telmisartán está en una forma sustancialmente amorfa; en el que la matriz de disolución de comprimido tiene características de liberación inmediata; en el que la matriz de disolución de comprimido comprende un agente básico, un diluyente soluble en agua y, opcionalmente, otros excipientes y adyuvantes; en el que el agente básico se selecciona entre hidróxidos de metal alcalino, aminoácidos básicos y meglumina; en el que el diluyente soluble en agua se selecciona entre monosacáridos tales como glucosa; oligosacáridos tales como sacarosa y lactosa; y alcoholes de azúcar tales como sorbitol, manitol y xilitol; en el que los demás excipientes y adyuvantes se seleccionan entre aglutinantes, vehículos, cargas, lubricantes, agentes de control de la fluidez, agentes para retrasar la cristalización, solubilizantes, agentes colorantes, agentes de control del pH, tensioactivos y emulsionantes; y, en el que la composición de telmisartán de la primera capa del comprimido se produce secando por pulverización una solución acuosa que comprende telmisartán y un agente básico para obtener un granulado secado por pulverización, mezclando dicho granulado secado por pulverización con un diluyente soluble en agua para obtener una premezcla y mezclando dicha premezcla con un lubricante para obtener una mezcla final.

2.3. En primera instancia, se debe advertir que las reivindicaciones 14 y 15 se refieren al 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 seria 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: WO03059327 publicada el 24 de julio de 2003.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela una pastilla farmacéutica bicapa que comprende una primera capa formulada para liberación inmediata de un receptor antagonista de angiotensina II de telmisartan en forma amorfa, y una segunda capa formulada para la liberación inmediata de un diurético tal como hidroclorotiazida HCTZ. Dicha anterioridad D1 también revela el método para producir dicha pastilla bicapa. Particularmente en las páginas 2, línea 6 a pagina 3 línea 27, página 6 línea 5 a 23, página 9 línea 1 a 23, y ejemplos 3 y 4, así como reivindicaciones 1 a 19, define que primera capa de dicha pastilla contiene telmisartan en la forma considerablemente amorfa dispersada en una matriz que se disuelve inmediatamente, donde dicha matriz puede tener propiedades ácidas, neutras o básicas y la matriz que se disuelve comprende un agente básico, un diluyente soluble en agua y, opcionalmente excipientes y adyuvantes. Según dicha anterioridad D1, los ejemplos específicos de agentes

convenientes básicos son alquil hidróxidos metálicos tales como NaOH y KOH; aminoácidos básicos como arginina y lisina; meglumina (Nmetil-D-glucamina), y NaOH y meglumina. En los ejemplos se ilustran varias alternativas de dicha forma farmacéutica. Los ejemplos específicos de diluyentes convenientes solubles en agua son hidratos de carbono como monosacáridos tal como la glucosa; oligosacaridos tal como sacarosa, anhidro lactosa y lactosa monohidrato; alcoholes de azúcar tales como sorbitol, manitol, dulcitol, ribitol y xilitol. Otros excipientes y/o adyuvantes, por ejemplo, son seleccionados entre aglutinantes, vehículos, cargas, lubricantes, agentes de control de la fluidez, agentes para retrasar la cristalización, solubilizantes, agentes colorantes, agentes de control del pH, tensioactivos y emulsionantes. Por lo tanto además que la presente solicitud comprende un método terapéutico no patentable a luz de la norma colombiana, también revela una forma farmacéutica que no es novedosa como lo indica esta solicitud anterior D1 de 2003 que revela con anterioridad tal forma bicapa. 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 **07 037.959** 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, 5 de noviembre de 2004 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, un comprimido bicapa que comprende una primera capa formulada para la liberación inmediata del antagonista del receptor de angiotensina II telmisartán desde una matriz de disolución de comprimido y una segunda capa formulada para la liberación inmediata un segundo activo, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. <u>CARENCIA DE APLICACIÓN INDUSTRIAL</u> 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 estos 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 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 "COMPRIMIDO BICAPA QUE COMPRENDE TELMISARTAN Y AMLODIPINO", cuyo titular es BOEHRINGER INGELHEIM INTERNATIONAL GMBH, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial **N° 594 del 31 de julio de 2008**

3. PRUEBAS

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

- D1: WO03059327 publicada el 24 de julio de 2003.

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: WO03059327 publicada el 24 de julio de 2003.

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 Nº 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.

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. **07 037.959,** titulada **"COMPRIMIDO BICAPA QUE COMPRENDE TELMISARTAN Y AMLODIPINO",** cuyo titular es **BOEHRINGER INGELHEIM INTERNATIONAL GMBH,** publicada en la gaceta No. 594 del 31 de Julio de 2008.

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 14 días del mes de 10 de 2008.

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 el Notario AGUSTIN FUERTES MORALES,
del Veintiuno (21) Circuito de Bogotá (E),
Compareció Luis Palacios
identificado con cédula de ciudadanía
y declara que la firma puesta en el presente
instrumento privado es suya y que el contenido
del mismo es cierto. 14 OCT. 2008
Bogotá D.C.
FIRMA

AGUSTIN FUERTES MORALES
NOTARIO VEINTICINCO(E)

COMPARECENCIA PERSONAL Y AUTENTICACION

El Notario Treinta y Nueve (39) de Bogotá, D.C. hace constar que el escrito dirigido al ... fué presentado personalmente por ... identificado con C.C. No. ... y T.P. No. ... y manifestó que lo firma ... aparecen en el presente documento son suyas y que el contenido del mismo es cierto.

FIRMA

28 OCT. 2008

MIGUEL ARTURO LINERO DE CANCIL
NOTARIO

DE PAPELERIA POR SOLICITUD DEL INTERESADO

100 13

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 85,189
FECHA : OCTUBRE 28 DE 2008

No 07 017059 00003 0000

***** C O N S I G N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
SYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754397	398101	10/07/2008	780,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754397	82359771	16/09/2008	1,084,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES		264,000.00
		TOTAL :	$	264,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

01

7480311 1

CAMARA
DE COMERCIO DE BOGOTA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20081014 Hora Certificado 15:57:26

Operacion : 02CP21014048 PAGINA No. 1

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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 P?blica No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta C?mara 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.
Correo electr?nico:

C E R T I F I C A

DURACION: El t?rmino de duraci?n de la sociedad se fij? 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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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 meterias 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 operacioes; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravamenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en 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 Acci?n
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

*** CONTINUA ***

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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.oo), 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.oo), 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 correspondan 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 acciedentales, sin que sea necesario para ello acreditar la ausencia del principal.----------

C E R T I F I C A

Que seg?n 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 inscribi? en esta C?mara 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 Reherman Leonardo Andres	CC.*******2,760,271
3. Munoz Marroquin Diego	CC.*******7,688,292

*** CONTINUA ***

****

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2. Aroca Almanza Arleth Ayelina CC.******36,718,415
3. Penaranda Urbina Adriana Paola CC.******53,120,683
4. tovar Vasquez Ruth CC.******52,175,756

C E R T I F I C A

Que seg?n 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 inscribi? en esta C?mara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Gerente General.	
Palacios Aragon Luis Alberto	CE.*********319,788

C E R T I F I C A

Que seg?n Acta No. 49 del 03 de Marzo de 2008 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

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

C E R T I F I C A

Que seg?n 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 inscribi? en esta C?mara de Comercio, el 22 de Mayo de 2008 bajo el No. 140,053 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
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,

*** CONTINUA ***

01

74803113

CAMARA
DE COMERCIO DE BOGOTA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20081014 Hora Certificado 15:57:26

Operacion : 02CP21014048 PAGINA No. 5

****

Amplio y Suficienta 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 Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOFARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOFARM S.A. en el giro ordinario de sus negocios y operaciones sociales.----------

C E R T I F I C A

Que en esta C?mara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disoluci?n, liquidaci?n o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su ?ltima Renovaci?n fue el: 23 de Abril de 2008.

La informaci?n sobre embargos de establecimiento se suministra en Certificados de Matr?cula, la de contratos sujetos a registro, en Certificados Especiales.

ANEXO 1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 July 2003 (24.07.2003)

PCT

(10) International Publication Number
WO 03/059327 A1

(51) International Patent Classification[7]: A61K 9/20, 31/635, 31/54, 31/495, 31/415

(21) International Application Number: PCT/EP02/00395

(22) International Filing Date: 16 January 2002 (16.01.2002)

(25) Filing Language: English

(26) Publication Language: English

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FRIEDL, Thomas** [DE/DE]; Dr. Hans-Liebherr-Strasse 48/4, 88416 Ochsenhausen (DE). **SCHEPKY, Gottfried** [DE/DE]; Händelstrasse 26, 79312 Emmendingen (DE).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/059327 A1

(54) Title: BILAYER PHARMACEUTICAL TABLET COMPRISING TELMISARTAN AND A DIURETIC AND PREPARATION THEREOF

(57) Abstract: A bilayer pharmaceutical tablet comprises a first layer formulated for immediate release of the angiotensin II receptor antagonist telmisartan from a dissolving tablet matrix which contains telmisartan in substantially amorphous form, and a second layer formulated for immediate release of a diuretic like hydrochlorothiazide from a fast disintegrating tablet matrix. A method of producing the bilayer tablet is also disclosed.

BILAYER PHARMACEUTICAL TABLET COMPRISING TELMISARTAN AND A DIURETIC AND PREPARATION THEREOF

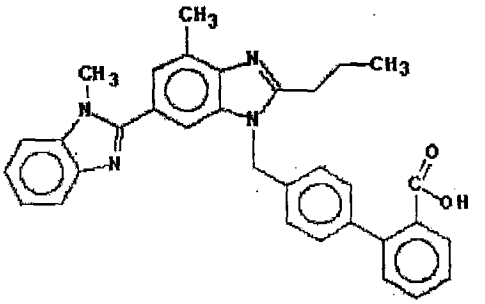
Field of invention

The present invention relates to a bilayer pharmaceutical tablet formulation comprising the angiotensin II receptor antagonist telmisartan in combination with a diuretic such as hydrochlorothiazide (HCTZ). The present invention also provides a method of producing said bilayer tablet.

Background of the invention

INN Telmisartan is an angiotensin II receptor antagonist developed for the treatment of hypertension and other medical indications as disclosed in EP-A-502314.

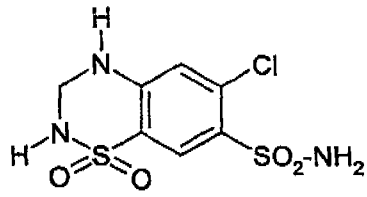
Its chemical name is 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-ylmethyl]-biphenyl-2-carboxylic acid having the following structure:



Telmisartan is generally manufactured and supplied in the free acid form. It is characterized by its very poor solubility in aqueous systems at the physiological pH range of the gastro-intestinal tract of between pH 1 to 7. As disclosed in WO 00/43370, crystalline telmisartan exists in two polymorphic forms having different melting points. Under the influence of heat and humidity, the lower melting polymorph B transforms irreversibly into the higher melting polymorph A.

Hydrochlorothiazide (HCTZ) is a thiazide diuretic which is orally administered in the treatment of edema and hypertension.

The chemical name of HCTZ is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide having the following structure



Objects of the invention

Combination therapy of telmisartan with a diuretic like HCTZ is expected to show synergistic therapeutic efficacy in the treatment of hypertension.

It was therefore an object of the present invention to provide a fixed dose combination drug comprising telmisartan and a diuretic such as HCTC, said combination drug displaying the required fast dissolution and immediate drug release profile combined with adequate stability.

Generally, a fixed-dose combination of drugs intended for immediate release is prepared by either making a powder mixture or a co-granulate of the two active ingredients with the necessary excipients, normally keeping the basic formulation of the corresponding mono-drug preparation and simply adding the second drug component.

With a combination of telmisartan and HCTZ, this approach was not feasible due to the incompatibility of HCTZ with basic compounds such as, e.g., meglumine (N-methyl-D-glucamine) which is a component of conventional telmisartan formulations, and the reduced dissolution rate of HCTZ from a dissolving matrix as compared with dissolution from a disintegrating tablet.

Several galenical approaches to overcome the incompatibility problem have been investigated. A classical approach is to coat the HCTZ particles in a fluidized-bed granulator with a polymer solution containing water soluble polymers like hydroxypropylcellulose, hydroxypropylmethylcellulose or polyvinylpyrrolidone, thereby

during mixing and compressing. Yet, by these means it was not possible to reduce the contact area of HCTZ with the telmisartan formulation in a compressed tablet to a degree sufficient to achieve the desired prolonged shelf life.

Furthermore, the dissolution rate of HCTZ from tablets comprising coated HCTZ in a telmisartan formulation was further reduced due to the gel-forming properties of the polymer.

Another approach was to produce separate film-coated tablets for telmisartan and HCTZ in such a size and shape that these could be filled into a capsule. By dividing the doses into two to four single small tablets for telmisartan and into one or two small tablets for HCTZ, a capsule of size 1 to 0 long could be filled. Yet, with this approach the drug dissolution rate of telmisartan was reduced compared to the single entities due to a lag-time effect of the large capsule shells. Furthermore, with regard to patient compliance a zero long capsule is not deemed reliable.

Summary of the invention

In accordance with the present invention, is has now been found that the above-described problems associated with conventional approaches in the preparation of a fixed dose combination drug comprising telmisartan and a diuretic could be overcome by means of a bilayer pharmaceutical tablet comprising a first layer containing telmisartan in substantially amorphous form in a dissolving tablet matrix, and a second layer containing a diuretic in a disintregrating tablet matrix.

The bilayer tablet according to the present invention provides a largely pH-independent dissolution of the poorly water-soluble telmisartan, thereby facilitating dissolution of the drug at a physiological pH level, and also provides for immediate release of the diuretic from the fast disintegrating matrix. At the same time, the bilayer tablet structure overcomes the stability problem caused by the incompatibility of diuretics like HCTZ with basic constitutents of the telmisartan formulation.

In a further aspect, the present invention relates to an improvement in bilayer tableting technology and provides a method of producing a bilayer pharmaceutical tablet comprising the steps of:

(i) providing a first tablet layer composition by

a) preparing an aqueous solution of telmisartan, at least one basic agent and, optionally, a solubilizer and/or a crystallization retarder;

b) spray-drying said aqueous solution to obtain a spray-dried granulate;

c) mixing said spray-dried granulate with a water-soluble diluent to obtain a premix;

d) mixing said premix with a lubricant to obtain a final blend for the first tablet layer;

e) optionally, adding other excipients and/or adjuvants in any of steps a) to d);

(ii) providing a second tablet layer composition by

f) mixing and/or granulating a diuretic with the constituents of a disintegrating tablet matrix and, optionally, further excipients and/or adjuvants;

g) admixing a lubricant to obtain a final blend for the second tablet layer;

(iii) introducing the first or the second tablet layer composition in a tablet press;

(iv) compressing said tablet layer composition to form a tablet layer;

(v) introducing the other tablet layer composition into the tablet press; and

(vi) compressing both tablet layer compositions to form a bilayer tablet.

Definitions

As used herein, the term "substantially amorphous" refers to a product comprising amorphous constituents in a proportion of at least 90%, preferably at least 95%, as determined by X-ray powder diffraction measurement.

The term "dissolving tablet matrix" refers to a pharmaceutical tablet base formulation having immediate release (fast dissolution) characteristics that readily dissolves in a physiological aqueous medium.

The term "diuretic" refers to thiazide and thiazide-analogue diuretics like hydrochlorothiazide (HCTZ), clopamide, xipamide or chlorotalidone, and any other diuretic suitable in the treatment of hypertension like, e.g., furosemide and piretanide, and combinations thereof with amiloride and triamteren.

The term "disintegrating tablet matrix" refers to a pharmaceutical tablet base formulation having immediate release characteristics that readily swells and disintegrates in a physiological aqueous medium.

Description of the preferred embodiments

The bilayer tablet according to the present invention comprises a first layer containing telmisartan in substantially amorphous form in a dissolving tablet matrix, and a second layer containing a diuretic in a disintregrating tablet matrix.

The active ingredient telmisartan is generally supplied in its free acid form, although pharmaceutically acceptable salts may also be used. Since during subsequent processing telmisartan is normally dissolved and transformed into a substantially amorphous form, its initial crystal morphology and particle size are of little importance for the physical and biopharmaceutical properties of the bilayer tablet formulation obtained. It is however preferred to remove agglomerates from the starting material, e.g. by sieving, in order to facilitate wetting and dissolution during further processing.

Substantially amorphous telmisartan may be produced by any suitable method known to those skilled in the art, for instance, by freeze drying of aqueous solutions, coating of carrier particles in a fluidized bed, and solvent deposition on sugar pellets or other carriers. Preferably, however, the substantially amorphous telmisartan is prepared by the specific spray-drying method described hereinafter.

The other active ingredient, i.e. the diuretic, is usually employed as a fine-crystalline powder, optionally in fine-milled, peg-milled or micronized form. For instance, the particle size distribution of hydrochlorothiazide, as determined by the method of laser light scattering in a dry dispersion system (Sympatec Helos/Rodos, focal length 100 mm) is preferably as follows:

d_{10}: $\leq$ 20 µm, preferably 2 to 10 µm

d_{50}: 5 to 50 µm, preferably 10 to 30 µm

d_{90}: 20 to 100 µm, preferably 40 to 80 µm

The bilayer tablet according to the present invention generally contains 10 to 160 mg, preferably 20 to 80 mg, of telmisartan and 6.25 to 50 mg, preferably 12.5 to 25 mg, of diuretic. Presently preferred forms are bilayer tablets comprising 40/12.5 mg, 80/12.5 mg and 80/25 mg of telmisartan and HCTZ, respectively.

The first tablet layer contains telmisartan in substantially amorphous form dispersed in a dissolving tablet matrix having immediate release (fast dissolution) characteristics. The dissolving tablet matrix may have acidic, neutral or basic properties, although a basic tablet matrix is preferred.

In such preferred embodiments, the dissolving matrix comprises a basic agent, a water-soluble diluent and, optionally, other excipients and adjuvants.

Specific examples of suitable basic agents are alkali metal hydroxides, such as NaOH and KOH; basic amino acids such as arginine and lysine; and meglumine (N-methyl-D-glucamine), NaOH and meglumine being preferred.

Specific examples of suitable water-soluble diluents are carbohydrates such as monosaccharides like glucose; oligosaccharides like sucrose, anhydrous lactose and lactose monohydrate; and sugar alcohols like sorbitol, mannitol, dulcitol, ribitol and xylitol. Sorbitol is a preferred diluent.

The other excipients and/or adjuvants are, for instance, selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers, specific examples of which are given below in connection with the second tablet layer composition. The excipients and/or adjuvants for the first tablet layer composition are preferably chosen such that a non-acidic, fast dissolving tablet matrix is obtained.

The first tablet layer composition generally comprises 5 to 50 wt.%, preferably 5 to 35 wt.%, of active ingredient; 0.25 to 20 wt.%, preferably 0.40 to 15 wt.%, of basic agent; and 30 to 95 wt.%, preferably 60 to 80 wt.% of water-soluble diluent.

Other (optional) constituents may, for instance, be chosen from one or more of the following excipients and/or adjuvants in the amounts indicated:

10 to 30 wt.%, preferably 15 to 25 wt.%, of binders, carriers and fillers, thereby replacing the water-soluble diluent;

0.1 to 5 wt.%, preferably 0.5 to 3 wt.%, of lubricants;

0.1 to 5 wt.%, preferably 0.3 to 2 wt.%, of flow control agents;
1 to 10 wt.%, preferably 2 to 8 wt.%, of crystallization retarders;
1 to 10 wt.%, preferably 2 to 8 wt.%, of solubilizers;
0.05 to 1.5 wt.%, preferably 0.1 to 0.8 wt.%, of coloring agents;
0.5 to 10 wt.%, preferably 2 to 8 wt.%, of pH control agents;
0.01 to 5 wt.%, preferably 0.05 to 1 wt.%, of surfactants and emulsifiers.

The second tablet layer composition contains a diuretic in a fast disintegrating tablet matrix. In a preferred embodiment, the disintegrating tablet matrix comprises a filler, a binder, a disintegrant and, optionally, other excipients and adjuvants.

The filler is preferably selected from anhydrous lactose, spray-dried lactose and lactose monohydrate.

The binder is selected from the group of dry binders and/or the group of wet granulation binders, depending on the manufacturing process chosen for the second tablet layer. Suitable dry binders are, e.g., cellulose powder and microcrystalline cellulose. Specific examples of wet granulation binders are corn starch, polyvinyl pyrrolidone (Povidon), vinylpyrrolidone-vinylacetate copolymer (Copovidone) and cellulose derivatives like hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl-cellulose and hydroxypropylmethylcellulose.

Suitable disintegrants are, e.g., sodium starch glycolate, Crospovidon, Croscarmellose, sodium carboxymethylcellulose and dried corn starch, sodium starch glycolate being preferred.

The other excipients and adjuvants, if used, are preferably selected from diluents and carriers such as cellulose powder, microcrystalline cellulose, cellulose derivatives like hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxy-propylmethylcellulose, dibasic calcium phosphate, corn starch, pregelatinized starch, polyvinyl pyrrolidone (Povidone) etc.; lubricants such as stearic acid, magnesium stearate, sodium stearylfumarate, glycerol tribehenate, etc.; flow control agents such as colloidal silica, talc, etc.; crystallization retarders such as Povidone, etc.; solubilizers such as Pluronic, Povidone, etc.; coloring agents, including dyes and pigments such as Iron Oxide Red or Yellow, titanium dioxide, talc, etc.; pH control agents such as citric acid, tartaric acid, fumaric acid, sodium citrate, dibasic calcium phosphate, dibasic

sodium phosphate, etc.; surfactants and emulsifiers such as Pluronic, polyethylene etc.; and mixtures of two or more of these excipients and/or adjuvants.

The second tablet layer composition generally comprises 1.5 to 35 wt.%, preferably 2 to 15 wt.%, of active ingredient; 25 to 75 wt.%, preferably 35 to 65 wt.%, of filler; 10 to 40 wt.%, preferably 15 to 35 wt.%, of dry binder; 0.5 to 5 wt.%, preferably 1 to 4 wt.%, of wet granulation binder; and 1 to 10 wt.%, preferably 2 to 8 wt.%, of disintegrant. The other excipients and adjuvants are generally employed in the same amount as in the first tablet layer composition.

For preparing the bilayer tablet according to the present invention, the first and second tablet layer compositions may be compressed in the usual manner in a bilayer tablet press, e.g. a high-speed rotary press in a bilayer tableting mode. However, care should be taken not to employ an excessive compression force for the first tablet layer. Preferably, the ratio of the compression force applied during compression of the first tablet layer to the compression force applied during compression of both the first and second tablet layers is in the range of from 1:10 to 1:2. For instance, the first tablet layer may be compressed at moderate force of 4 to 8 kN, whereas the main compression of first plus second layer is performed at a force of 10 to 20 kN.

During bilayer tablet compression adequate bond formation between the two layers is achieved by virtue of distance attraction forces (intermolecular forces) and mechanical interlocking between the particles.

The bilayer tablets obtained release the active ingredients rapidly and in a largely pH-independent fashion, with complete release occurring within less than 60 min and release of the major fraction occurring within less than 15 min. The dissolution/-disintegration kinetics of the bilayer tablet may be controlled in different ways. For instance, both layers may dissolve/disintegrate simultaneously. Preferably, however, the second tablet layer containing the diuretic disintegrates first whereas the first tablet layer containing telmisartan dissolves in parallel or subsequently.

In accordance with the present invention, a substantially increased dissolution rate of the active ingredients and, in particular, of telmisartan is achieved. Normally, at least 70% and typically at least 90% of the drug load are dissolved after 30 min.

The bilayer tablets of the present invention tend to be slightly hygroscopic and are therefore preferably packaged using a moisture-proof packaging material such as aluminium foil blister packs, or polypropylene tubes and HDPE bottles which preferably contain a desiccant.

For optimum dissolution/disintegration and drug release properties, a specific method of producing the bilayer tablet according to the present invention has been developed which method comprises

(i) providing a first tablet layer composition by
   a) preparing an aqueous solution of telmisartan, at least one basic agent and, optionally, a solubilizer and/or a crystallization retarder;
   b) spray-drying said aqueous solution to obtain a spray-dried granulate;
   c) mixing said spray-dried granulate with a water-soluble diluent to obtain a premix;
   d) mixing said premix with a lubricant to obtain a final blend for the first layer;
   e) optionally, adding other excipients and/or adjuvants in any of steps a) to d);
(ii) providing a second tablet layer composition by
   f) mixing and /or granulating a diuretic with the constituents of a disintegrating tablet matrix and, optionally, further excipients and/or adjuvants;
   g) admixing a lubricant to obtain a final blend for the second tablet layer;
(iii) introducing the first or the second tablet layer composition into a tablet press;
(iv) compressing said tablet layer composition to form a tablet layer;
(v) introducing the other tablet layer composition into the tablet press; and
(vi) compressing both tablet layer compositions to form a bilayer tablet.

In a preferred embodiment of this method, an aqueous alkaline solution of telmisartan is prepared by dissolving the active ingredient in purified water with the help of one or more basic agents like sodium hydroxide and meglumine. Optionally, a solubilizer and/or a recrystallization retarder may be added. The dry matter content of the starting aqueous solution is generally 10 to 40 wt.%, preferably 20 to 30 wt.%.

The aqueous solution is then spray-dried at room temperature or preferably at increased temperatures of, for instance, between 50 and 100°C in a co-current or countercurrent spray-drier at a spray pressure of, for instance, 1 to 4 bar. Generally

speaking, the spray-drying conditions are preferably chosen in such a manner that a spray-dried granulate having a residual humidity of ≤ 5 wt.%, preferably ≤ 3.5 wt.%, is obtained in the separation cyclone. To that end, the outlet air temperature of the spray-drier is preferably kept at a value of between about 80 and 90°C while the other process parameters such as spray pressure, spraying rate, inlet air temperature, etc. are adjusted accordingly.

The spray-dried granulate obtained is preferably a fine powder having the following particle size distribution:

d_{10} : ≤ 20 μm, preferably ≤ 10 μm

d_{50} : ≤ 80 μm, preferably 20 to 55 μm

d_{90} : ≤ 350 μm, preferably 50 to 150 μm

After spray-drying, the active ingredient (telmisartan) as well as the excipients contained in the spray-dried granulate are in a substantially amorphous state with no crystallinity being detectable. From a physical point of view, the spray-dried granulate is a solidified solution or glass having a glass transition temperature Tg of preferably > 50°C, more preferably > 80°C.

Based on 100 parts by weight of active ingredient (telmisartan), the spray-dried granulate preferably contains 5 to 200 parts by weight of basic agent and, optionally, solubilizer and/or crystallization retarder.

The water-soluble diluent is generally employed in an amount of 30 to 95 wt.%, preferably 60 to 80 wt.%, based on the weight of the first tablet layer composition.

The lubricant is generally added to the premix in an amount of 0.1 to 5 wt.%, preferably 0.3 to 2 wt.%, based on the weight of the first tablet layer composition.

Mixing is carried out in two stages, i.e. in a first mixing step the spray-dried granulate and the diluent are admixed using , e.g., a high-shear mixer or a free-fall blender, and in a second mixing step the lubricant is blended with the premix, preferably also under conditions of high shear. The method of the invention is however not limited to these mixing procedures and, generally, alternative mixing procedures may be employed in steps c), d), and also in the subsequent steps f) and g), such as, e.g., container mixing with intermediate screening.

free-fall blender. Alternatively and preferably, the second tablet layer composition is prepared using a wet granulation technique wherein an aqueous solution of a wet granulation binder is added to a premix and subsequently the wet granulate obtained is dried, e.g. in a fluidized-bed dryer or drying chamber. The dried mixture is screened and then a lubricant is admixed, e.g. using a tumbling mixer or free-fall blender, whereafter the composition is ready for compression.

For production of the bilayer tablet according to the present invention, the first and second tablet layer compositions are compressed in a bilayer tablet press, e.g. a rotary press in the bilayer tableting mode, in the manner described above. In order to avoid any cross-contamination between the first and second tablet layers (which could lead to decomposition of HTCZ), any granulate residues have to be carefully removed during tableting by intense suction of the die table within the tableting chamber.

In order to further illustrate the present invention, the following non-limiting examples are given.

Example 1

Constituents		mg / 1.684 mg SD granulate	volatile constituent	kg / batch
(01)	Telmisartan	1.000		45.000
(02)	Sodium hydroxide	0.084		3.780
(03)	Povidone K 25	0.300		13.500
(04)	Meglumine	0.300		13.500
(05)	Purified water		5.000	(225.000)
		1.684	5.000	75.780

Manufacturing:

1. Spray solution

225.000 kg of purified water are measured into a suitable stainless steel vessel at a temperature of between 20-40°C. In sequence, 3.780 of kg sodium hydroxide, 45.000 kg of telmisartan (mixture of polymorph A and B), 13.500 kg of Povidone K 25 and 13.500 kg of meglumine are dissolved in the purified water under intensive stirring until a virtually clear, slightly yellowish, alkaline solution is obtained.

2. Spray drying

The solution is sprayed into a suitable spray dryer, e.g. a Niro P 6.3 equipped with Schlick atomizing nozzles of 1.0 mm diameter, with a flow-through heating coil connected upstream of the dryer, and dried to give a white to off-white fine granulate. The spray mode is counter-current at a spray-pressure of about 3 bar, an inlet air temperature of about 125°C and a spray rate of about 11 kg/h, thus resulting in an outlet air temperature of about 85°C. The temperature of the flow through heating coil water bath is set at a temperature of about 80°C.

3. Protective Screening

The dry granulate powder is screened through a screen of 0.5 mm mesh size, e.g. using a Vibra Sieve machine.

The resulting amorphous telmisartan spray-dried granulate may be further processed to telmisartan mono-tablets or the first layer of the said bilayer tablet composition.

Example 2

	Constituents	mg/tablet 1st layer	mg/SD granulate	mg/tablet 2nd layer
(01)	Telmisartan SD granulate	67.360		
	consisting of (02) to (06):			
(02)	Telmisartan		40.000	
(03)	Sodium hydroxide		3.360	
(04)	Polyvidone (Kollidon 25)		12.000	
(05)	Meglumine		12.000	
(06)	Purified water		264.000*	
(07)	Sorbitol P/6	168.640		
(08)	Magnesium stearate, screened	4.000		1.000
(09)	Hydrochlorothiazide			12.500
(10)	Microcrystalline cellulose (Avicel PH 101)			64.000
(11)	Red iron oxide			0.330
(12)	Sodium starch glycolate			4.000
(13)	Lactose monohydrate fine, screened			112.170
(14)	Maize starch, dried at 45 °C			6.000
		240.000	67.360	200.000

* 200 mg in SD granulate, 64 mg in granulation liquid of HCTZ granulate

Manufacturing:

1. Final blend A

168.640 kg of sorbitol are mixed with 67.360 kg of telmisartan spray dried granulate in a suitable high shear mixer, e.g. Diosna P 600, for 4 minutes using both impeller and chopper. Next 4.0 kg of magnesium stearate are added to the resulting pre-mix and admixed in the high shear mixer for further 30 seconds.

2. Final blend B

9.000 kg of purified water of about 70°C are transfered to a suitable mixing vessel, 6.000 kg of maize starch, dried at 45°C, are suspended in the water. This suspension is stirred into 55.000 kg of purified water of about 90°C using e.g. an Ekato stirrer.

Next, 112.170 kg of lactose monohydrate, 12.500 kg of hydrochlorothiazide, 64.000 kg of microcrystalline cellulose (Avicel PH 101), 0.330 kg of red iron oxide and 4.000 kg of sodium starch glycolate are mixed in a suitable high shear granulator, e.g. Diosna P 600, until homogeneous, and moistened with 70.000 kg of the above-prepared aqueous granulating liquid.

Process parameters for wet granulation:

Process step	Duration (min)	Impeller (setting)	Chopper (setting)
Pre-mixing	3	1	1
Moistening	2	1	1
Wet mixing	4	2	2
Emptying	About 0.5	1	0

After moistening, the resulting wet granulate is dried in a suitable fluid bed dryer, e.g. Glatt WSG 120 at an inlet air temperature of 100°C, an inlet air flow of 2000-3000 m^3/h until a product temperature of about 55°C is reached.

The dry granulate is screened to reduce the particle size using a suitable screening machine, e.g. a Comil screen machine equipped with a rasp screen of 2 mm mesh size. Finally 1.000 kg of prescreened magnesium stearate are admixed to the screened granulate material and mixed in a suitable tumbling mixer, e.g. a Lermer rotating spike mixer, for 100 revolutions at a speed of 8-10 rpm.

3. Bilayer tablet compression

Using a suitable rotary tablet press, 240 kg of the final blend (A) and 200 kg of the final blend (B) are compressed into bilayer tablets. The target weight for the first layer is 240 mg, the target weight for the second layer is 200 mg.

Process parameters for tableting:

Tablet press	Fette 3090	
Tabletting speed	100.000 (80.000 – 120.000) tabl./h	
Stirrer blade speed:	1st layer about 30 rpm	2nd layer about 75 rpm
Compression force	5 (4 – 6) KN	12 (10 – 14) KN

As a rule, the tablet hardness is adjusted by variation of the main compression force of the second layer.

The resulting bilayer tablets have the following characteristics:

Shape / diameter	oval, both faces convex / 14 x 6.8 mm
Colour	first layer: white to off-white second layer: red
Weight	440 mg (total) 240 mg (layer 1: with telmisartan) 200 mg (layer 2: with hydrochlorothiazide)
Thickness	about 5.2 mm
Hardness	about 120 N
Disintegration time	NMT 15 min (total)

Example 3

	Constituents	mg/tablet 1st layer	mg/SD granulate	mg/tablet 2nd layer
(01)	Telmisartan SD granulate	67.360		
	consisting of (02) to (06):			
(02)	Telmisartan		40.000	
(03)	Sodium hydroxide		3.360	
(04)	Polyvidone (Kollidon 25)		12.000	
(05)	Meglumine		12.000	
(06)	Purified water		(200.000)	
(07)	Sorbitol P/6	168.640		
(08)	Magnesium stearate, screened	4.000		1.000
(09)	Hydrochlorothiazide			25.000
(10)	Microcrystalline cellulose (Avicel PH 101)			64.000
(11)	Yellow iron oxide			0.330
(12)	Sodium starch glycolate			4.000
(13)	Lactose monohydrate fine, screened			105.67
		240.000	67.360	200.000

Manufacturing:

Manufacturing is carried out as in Example 2. Instead of the wet granulation process described in Example 2, the second layer composition is manufactured by dry mixing of (09) to (13) in a suitable free fall blender, e.g. a 1 m^3 container mixer, for 200 revolutions at a speed of 10 rpm. Then, (08) is admixed to the main mixture for further 50 revolutions in the container mixer. In order to achieve a homogenous distribution of the color pigment, an additional premix with yellow iron oxide and a portion of the microcrystalline cellulose, e.g. 2.000 kg, which is screened through an 0.8 mm mesh screen manually before transfer to the main mixture, may be performed. The resulting bilayer tablets display virtually the same physical characteristics as described in example 2, except for the color.

Example 4

Composition of Telmisartan/Hydrochlorothiazide Bilayer Tablets (mg per tablet):

Ingredient	40/12.5 mg	80/12.5 mg
Telmisartan layer		
Telmisartan	40.000	80.000
Sodium hydroxide	3.360	6.720
Povidone	12.000	24.000
Meglumine	12.000	24.000
Purified water*	(200.000)	(400.000)
Sorbitol	168.640	337.280
Magnesium stearate	4.000	8.000
Total telmisartan layer	240.000	480.000
Hydrochlorothiazide layer		
Hydrochlorothiazide	12.500	12.500
Lactose monohydrate	112.170	112.170
Microcrystalline Cellulose	64.000	64.000
Corn starch	6.000	6.000
Red iron oxide	0.330	0.330
Sodium starch glycolate	4.000	4.000
Purified water*	(64.000)	(64.000)
Magnesium stearate	1.000	1.000
Total HCTZ layer	200.000	200.000
Total tablet weight	440.000	680.000

*Does not appear in final product

CLAIMS

1. A bilayer pharmaceutical tablet comprising a first layer containing telmisartan in substantially amorphous form in a dissolving tablet matrix, and a second layer containing a diuretic in a disintegrating tablet matrix.

2. A bilayer pharmaceutical tablet as claimed in claim 1 wherein the diuretic is selected from at least one of hydrochlorothiazide, furosemide, chlorotalidone, piretanide and amiloride.

3. A bilayer pharmaceutical tablet as claimed in claim 2 wherein the diuretic is hydrochlorothiazide.

4. A bilayer pharmaceutical tablet as claimed in any one of claims 1-3 wherein the dissolving tablet matrix has immediate release characteristics.

5. A bilayer pharmaceutical tablet as claimed in any one of claims 1-4 wherein the dissolving tablet matrix comprises a basic agent, a water-soluble diluent and, optionally, other excipients and adjuvants.

6. A bilayer pharmaceutical tablet as claimed in claim 5 where the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

7. A bilayer pharmaceutical tablet as claimed in claims 5 or 6 wherein the water-soluble diluent is selected from carbohydrates such as monosaccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, dulcitol, ribitol and xylitol.

8. A bilayer pharmaceutical tablet as claimed in any one of claims 5-7 wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

9. A bilayer pharmaceutical tablet as claimed in any one of claims 1-8 wherein the first tablet layer has been produced by spray-drying an aqueous solution comprising [illegible] granulate with a water-soluble diluent to obtain a premix, mixing said premix with a lubricant to obtain a final blend and compressing the final blend to form the first tablet layer.

10. A bilayer pharmaceutical tablet as claimed in any one of claims 1-10 wherein the disintegrating tablet matrix comprises a filler, a binder, a disintegrant and, optionally, other excipients and adjuvants.

11. A bilayer pharmaceutical tablet as claimed in claim 10 wherein the other excipients and adjuvants are selected from carriers, diluents, lubricants, flow control agents, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

12. A bilayer pharmaceutical tablet as claimed in any one of claims 1-11 containing 10 to 160 mg, preferably 20 to 80 mg, of telmisartan and 6.25 to 50 mg, preferably 12.5 to 25 mg, of diuretic.

13. A bilayer pharmaceutical tablet as claimed in any one of claims 1-12 packaged in a moisture proof packaging material such as aluminium foil blister packs, or polypropylene tubes and HDPE bottles.

14. A method of producing a bilayer pharmaceutical tablet comprising the steps of:
   (i) providing a first tablet layer composition by
   a) preparing an aqueous solution of telmisartan, at least one basic agent and, optionally, a solubilizer and/or a crystallization retarder;
   b) spray-drying said aqueous solution to obtain a spray-dried granulate;
   c) mixing said spray-dried granulate with a water-soluble diluent to obtain a premix;
   d) mixing said premix with a lubricant to obtain a final blend for the first tablet layer;

e) optionally, adding other excipients and/or adjuvants in any of steps a) to d);

(ii) providing a second tablet layer composition by

f) mixing and/or granulating a diuretic with the constituents of a disintegrating tablet matrix and, optionally, further excipients and/or adjuvants;

g) admixing a lubricant to obtain a final blend for the second tablet layer;

(iii) introducing the first or the second tablet layer composition into a tablet press;

(iv) compressing said tablet layer composition to form a tablet layer;

(v) introducing the other tablet layer composition into the tablet press; and

(vi) compressing both tablet layer compositions to form a bilayer tablet.

15. A method as claimed in claim 14 wherein spray-drying in step b) is carried out under conditions so as to obtain a spray-dried granulate having a residual humidity of ≤ 5 wt.%, preferably ≤ 3.5 wt.%.

16. A method as claimed in claims 14 or 15 wherein spray-drying in step b) is carried out at an outlet air temperature of the spray-drier of between about 80 and 90°C.

17. A method as claimed in any one of claims 14-16 wherein mixing in any of steps c), d), f) and g) is carried out in a high shear mixer or a free-fall blender.

18. A method as claimed in any one of claims 14-17 wherein mixing in step f) is carried out under conditions of dry-mixing or, preferably, under wet granulation conditions.

19. A method as claimed in any one of claims 14-18 wherein the ratio of the compression force applied during compression of the first tablet layer to the compression force applied during compression of both the first and second tablet layers is in the range of from 1:10 to 1:2.

INTERNATIONAL SEARCH REPORT

PCT/EP 02/00395

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K31/635 A61K31/54 A61K31/495 A61K31/415

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

B. FIELDS SEARCHED

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

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 27397 A (BOEHRINGER INGELHEIM INT ;GLAXO GROUP LTD (GB)) 18 May 2000 (2000-05-18)	1,4-9,14
Y	page 1, line 16 - line 24 page 5, line 8 - line 11 page 9, line 27 -page 10, line 7; example 2	12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 September 2002	23/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/00395

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LACOURCIERE Y ET AL: "COMPARISON OF THE ANTIHYPERTENSIVE EFFECTS OF A FIXED DOSE COMBINATION OF TELMISARTAN AND HYDROCHLOROTHIAZIDE VERSUS TELMISARTAN MONOTHERAPY IN MILD TO MODERATE HYPERTENSIVE PATIENTS" CANADIAN JOURNAL OF CARDIOLOGY, PULSUS GROUP, INC, XX, vol. 16, no. SUPPL F, September 2000 (2000-09), page 107F XP001053460 ISSN: 0828-282X	12
A	abstract	1-11, 13-19
A	WO 99 47123 A (SQUIBB BRISTOL MYERS CO) 23 September 1999 (1999-09-23) page 1, line 26 - line 30 page 2, line 34 - line 10 page 6, line 29 -page 7, line 24 page 8, line 1 - line 10; example 1	1-19

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/EP 02/00395

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box I.2

Present claims 1-3, 12, and 14 relate to a compound defined by reference to a desirable characteristic or property, namely a diuretic. The term diuretic as used in the present claims 1-3, 12, and 14 defines the active agent by its pharmacological effect. However, a compound canot be sufficiently characterised by its pharmacological effect as it is done by an expression like diuretic, because it is impossible to know which substances are encompassed in this expression.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds used in examples 1-4, those mentioned in the description at page 4, lines 27-30 and in claim 2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

130 42
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INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/EP 02/00395

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0027397 A	18-05-2000	WO 0027397 A1	18-05-2000
		AU 1042199 A	29-05-2000
		AU 1157500 A	29-05-2000
		WO 0027396 A1	18-05-2000
		US 6071939 A	06-06-2000
WO 9947123 A	23-09-1999	US 6235311 B1	22-05-2001
		AU 2901599 A	11-10-1999
		BR 9908690 A	05-12-2000
		CA 2324283 A1	23-09-1999
		EP 1071403 A1	31-01-2001
		JP 2002506809 T	05-03-2002
		WO 9947123 A1	23-09-1999
		US 2002034546 A1	21-03-2002

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°: 1835

ASUNTO:

Radicación PCT Nº	07-37959
Trámite	011
Evento	378
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 Nº 10 de 2001.

DORIS ELENA POLO CORDOBA
Jefe de la División de Nuevas Creaciones (E).

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

202021