



No. 09-053156- -00007-0000

Fecha: 2011-02-15 15:40:43 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 66

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

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

②

Numero del expediente: **09 053.156**

Solicitante: **F.HOFFMANN-LA ROCHE A.G.**

**SOLICITUD
PUBLICADA**

Apoderado: **ALICIA LLOREDA RICAURTE**

Título de la nueva creación o denominación del signo:

FORMULACION EN POLVO DEL VALGANCICLOVIR

Gaceta: **622**

③

OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: **PROCAPS S.A.**

Dirección: **CALLE 80 No. 78b-201**

Nacionalidad o Domicilio: **COLOMBIA**

Lugar de Constitución: **BARRANQUILLA**

Teléfono: **371 99 00** Fax: **373 0815**

E-mail:

IDENTIFICACION

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Cual

Número **890.106.527-5**

**REPRESENTANTE
O APODERADO**

Nombre: **ELINA ISAURA MORENO
BOHORQUEZ**

Dirección: **CARRERA 104 N°119-95 OF 104**

Teléfono: **2131213** Fax: **6121979**

E-mail: **negocios@optimum-co.com**

IDENTIFICACION

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Número **51.975.664** TP **83823**

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 _____

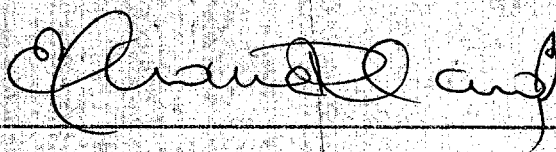
⑥ ANEXOS

- ☒ 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 BOHÓRQUEZ

FIRMA: _____



C.C. 51.975.664

TP. 83823



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° 09 053.156
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIÓN EN POLVO DEL VALGANCICLOVIR"
Solicitante : LABORATORIOS ALMIRALL, S.A.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 622 del 19 de Noviembre de 2010

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 **PROCAPS 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 "FORMULACIÓN EN POLVO DEL VALGANCICLOVIR", cuyo titular es **F. HOFFMANN-LA ROCHE AG**, 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 **VALGANCICLOVIR**. 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 22 de mayo de 2009, reivindicando prioridad bajo la solicitud US20060874634P del 2006-12-13; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 622 del 19 de noviembre de 2010, cuya publicación internacional corresponde a la WO2008/071573 del 2008-06-19.

2.2. La solicitud colombiana 09 053.156 objeto de la presente oposición, se refiere a una forma de dosificación farmacéutica sólida para la administración oral, después de haberse constituido en agua, que consta de: una cantidad terapéuticamente eficaz de valganciclovir clorhidrato; y un ácido orgánico no higroscópico que está presente en una cantidad suficiente para estabilizar al valganciclovir clorhidrato en una cantidad predeterminada de agua; en donde el valganciclovir clorhidrato está presente en una cantidad del 10% al 90% en peso de la composición total; en



donde el ácido orgánico no higroscópico es un aminoácido; en donde el ácido orgánico no higroscópico se elige entre el grupo formado por el ácido fumárico, el ácido succínico y el ácido adípico; en donde el ácido orgánico no higroscópico es el ácido fumárico; en donde el ácido orgánico no higroscópico está presente en una cantidad que baja el pH de la solución constituida del valganciclovir clorhidrato hasta un pH de 3.8 o menos; que contiene además una cantidad eficaz de un agente diluyente no higroscópico; en donde el agente diluyente no higroscópico se elige entre el grupo formado por la manita y la lactosa; en donde el agente diluyente no higroscópico es la manita; en donde el agente diluyente no higroscópico está presente en una cantidad de hasta el 90% en peso de la composición total.

2.3. En primera instancia, se debe advertir que las reivindicaciones 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: WO2005087198 publicada el 22 de septiembre de 2005.
- D2: WO1997027197 publicada el 31 de julio de 1997.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela un procedimiento para la preparación de formas farmacéuticas sólidas de hidrocloviro de valganciclovir amorfa por vía seca. Particularmente en las reivindicaciones 1, 12 y 13 en adelante, define una forma de dosificación sólida que comprende hidrocloviro de valganciclovir amorfa, de relleno, aglutinante disgregante y donde el lubricante preparado comprende por lo menos estearil fumarato sódico. Ahora bien, para el año 1997, como se define en el documento D2, ya se define en la literatura combinaciones farmacéuticamente aceptables en la preparación de una composición farmacéutica que incluye ganciclovir y que define que incluyen sales de adición a partir de ácidos inorgánicos como ácido succínico, ácido málico, ácido maleico y ácido fumárico entre otros como se define en las páginas 14, línea 33 a página 15 línea 8. Así las cosas, como lo evidencia dicho documento D1 y D2, en combinación, la presente solicitud se deriva de manera evidente de lo revelado en el estado de la técnica, ya que de manera obvia una persona versada en la materia puede llegar a combinar valganciclovir con un ácido orgánico como ácido fumárico o ácido succínico a partir del documento D2 de 1997 en combinación con la materia revelada en D1 en el 2005.

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

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 053.156 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. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 13 de diciembre de 2006, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a un compuesto farmacéutico que combine valganciclovir con un ácido orgánico como ácido fumárico o ácido succínico, 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 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 con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada *“FORMULACIÓN EN POLVO DEL VALGANCICLOVIR”*, cuyo titular es F. HOFFMANN-LA ROCHE AG, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 622 del 19 de Noviembre de 2010.

3. PRUEBAS

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

- D1: WO2005087198 publicada el 22 de septiembre de 2005.
- D2: WO1997027197 publicada el 31 de julio de 1997.

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

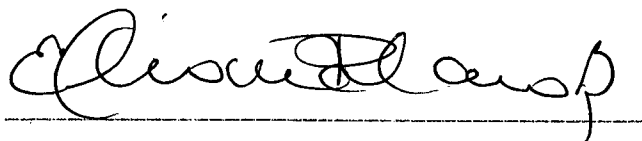
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: WO2005087198 publicada el 22 de septiembre de 2005.
 - D2: WO1997027197 publicada el 31 de julio de 1997.

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 : 800.176.089-2

- / -



RECIBO DE CAJA

No. 11 - 0013913

Bogotá D.C., Febrero 15 de 2011 - 15:28:37

RECIBIDO DE : PROCAPS S.A.

NI 890.106.527

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	382195752	08/02/2011	2.432.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	304.000.00	304.000.00
		12 MARCAS Y LEMAS COMERCIALES		\$304.000.00
			=====	

SON: **TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-053156- -00007-0000

Fecha: 2011-02-15 15:40:43 Dep. 2020 DIR.NUEVASCR
 Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
 Act. 400 OPOSIOBSERVTER Folios: 66

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Linea: 018000-910165 Call Center: (571) 6513240

Febrero 15 de 2011 - 15:28:38



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, 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 **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, 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. 09 053.156, titulada "FORMULACIÓN EN POLVO DEL VALGANCICLOVIR", cuyo titular es **F. HOFFMANN-LA ROCHE AG.**, publicada en la gaceta No. 622 del 19 de noviembre de 2010.

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 administrativamente 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 7 días del mes de Febrero de 2011.


PROCAPS S.A.

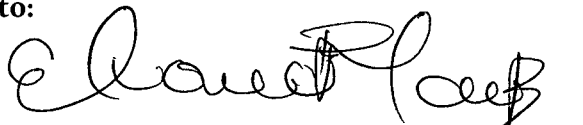
C.C. N° 16'251.923
NIT: 890.106.527-5
Representante Legal

APROBADO

7 FEB. 2011

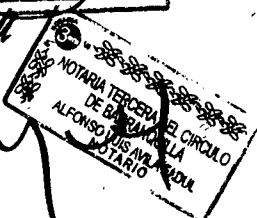
PROCAPS S.A.

Acepto:



ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

NOTARIA 3^{era} NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO
Ante el Notario Tercero de Barranquilla se presento:
Walter Farano Latorre
identificado con: CE 16251923 Palmira
Y declaro que el contenido del anterior Documento es cierto
y suya la firma que lo representa. 10 FEB. 2011
Barranquilla:





***** Pag. 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
03*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

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. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

***** C O N T I N U A *****

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A.
.

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS 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
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

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:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.



***** Pag. 2

CAMARA DE COMERCIO

DE BARRANQUILLA

03*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

Telefono:

3719272

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricacion, importación y comercialización de alimentos procesados y suplementos dietarios. b) La fabricacion de capsulas y otros 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, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercialización interna y externa de los productos terminados. e) 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. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) 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 cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas, 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 PROCAPS S.A., asi como los de publicidad y

***** C O N T I N U A *****

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

promocion de productos quimicos, alimenticios, cosmeticos y farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, 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 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 la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,234,071,000	*****1,234,071	*****1,000
Pagado		
\$*****1,234,071,000	*****1,234,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Represen-

***** C O N T I N U A *****



***** Pag. 3
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
03*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

tacion 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. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. 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. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente

***** C O N T I N U A *****

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades 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), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

***** C O N T I N U A *****



***** Pag. 4
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
03*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

***** C O N T I N U A *****

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

Cargo/Nombre	Identificación
Revisor Fiscal Ppal. Vargas Pertuz Ana Isabel	CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 151 del 31 de Marzo de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 30 de Julio de 2009 bajo el No. 151,129 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal. Duarte Diaz David	CC.*****73,115,965

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, -----
obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y -----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organó Social, otorga los siguientes poderes: Otorgar poder -----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO -----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que ----
representen a la sociedad PROCAPS S.A, ante todo tipo de -----
autoridades administrativas y jurisdiccionales, en asuntos de -----
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y ----
presentar demandas, requerimientos, recursos, pedir y aportar -----
pruebas, recibir, notificarse, ejercer la accion de tutela, -----
tramitar incidente de desacato, comparecer en los procesos que ----
cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de -----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, -----
transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN, de tal forma que en ningun momento quede sin -----
representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ----
confiere poder especial amplio y suficiente a las personas que se

***** C O N T I N U A *****



***** Pag. 5
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
03*****

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

determinan seguidamente, que conforman el grupo A y B, para, para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), ----- liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO ----- CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN ----- VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA ----- DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO ----- CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----- amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA ----- CC.No.8.715.941, para que en nombre y representación de PROCAPS ---- S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad, en el giro normal de sus negocios y operaciones sociales, por tanto quedan facultados para firmarlas, como también los demás documentos relacionados con ellas, ----- notificarse, aportar y solicitar las pruebas que sean necesarias. c.-Otorgar poder especial amplio y suficiente al señor MARLON ----- TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representación de ----- PROCAPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los trámites o registros de Comercio ---- Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN ----- ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y ----- representación de PROCAPS S.A.; endosen los títulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS ----- (1.000.000.000.00) M.L. CUARTO: El representante legal de la ----- sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General ----- Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008 bajo el No. 3,748 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que comparece en su condición de Presidente y Representante Legal de la Sociedad PROCAPS S.A., confiere por medio de este instrumento -----

***** C O N T I N U A *****

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

publico Poder especial Amplio y Suficiente a la doctora MILENA -----
ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y -----
representacion de PROCAPS S.A., suscriba declaraciones cambiarias,
aduaneras y tributarias a que este obligada la sociedad en el giro
normal de sus negocios y operaciones sociales, por tanto queda -----
facultada para firmar, como tambien los demas documentos -----
relacionados con ellas, notificarse, aportar y solicitar las -----
pruebas que sean necesarias.-----

C E R T I F I C A

Que por Documento Privado del 09 de Abril de 2010, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 20 de Abril de
2010 bajo el Nro 4,201 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ----
quien obra en el caracter de Presidente y/o Representante legal de
la sociedad PROCAPS S.A., que por medio de este instrumento -----
publico, otorga Poder Especial Amplio y Suficiente a la Doctora ----
MONICA DE HART DE OCHOA, identificada con C.C. No. 32.676.025, para
que en nombre y representacion de la sociedad, Endose las Facturas
Nacionales e Internacionales hasta por la suma de UN MIL MILLONES DE
PESOS (\$1.000.000.000.00)M.L. La doctora Monica de Hart de Ochoa,
queda facultada para realizar todo acto o tramite necesario para el
cabal cumplimiento del presente mandato.-----

C E R T I F I C A

Que por Documento Privado del 10 de Junio de 2010, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 13 de Julio de
2010 bajo el Nro 4,228 del libro respectivo,-----
consta que el señor RUBEN MISNKI GONTOVNIK, cc. No. 7.463.982 en su
condicion de Presidente y representante legal de PROCAPS S.A., ----
confiere poder especial, amplio y suficiente al señor RICARDO DORADO
HURTADO cc. No. 79.715.772 para que represente a la sociedad, ante
el INVIMA, Fondo Nnacional de estupefacientes e ICA, con el fin que
gestione, tramite o presente las diferentes solicitudes y -----
peticiones de la empresa, segun la competencia de estas entidades.
Por lo anterior, el Señor RICARDO DORADO HURTADO, queda facultado
para presentar, gestionar, tramitar y firmar las diferentes -----
solicitudes y peticiones de la empresa, segun la competencia de ----
estas entidades, como tambien presentar y firmar todo los -----
documentos relacionados con estas solicitudes, notificarse de -----
cualquier acto administrativo que expidan, aportar y solicitar las
pruebas que sean necesarias, desistir, y en general a realizar todo
tramite o acto necesario de tal forma que la sociedad en ningun ----
momento quede sin representacion legal ante estas entidades, en ----
cumplimiento fiel al mandato otorgado.-----

C E R T I F I C A

Que por Documento Privado del 03 de Agosto de 2010, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 24 de Agosto
de 2010 bajo el Nro 4,258 del libro respectivo,-----



***** Pag. 6
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
03*****

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

consta que RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta vecindad, identificado con la cédula de ciudadanía No.7.463.982, expedida en Barranquilla, en mi condición de Representante legal y/o Presidente de la sociedad PROCAPS S. A., conforme a las ----- facultades otorgadas por los Estatutos Sociales, todo lo cual ----- demuestro con el certificado de existencia y representación legal expedido por la Cámara de Comercio de Barranquilla, que adjunto a este escrito, me permito manifestarles que confiero poder especial, amplio y suficiente al señor MARIO LÓPEZ LEON, varón, mayor de ----- edad, de esta vecindad, identificado con la cédula de ciudadanía No.72.311.558, expedida en Puerto Colombia (Atlántico), para que en nombre y representación de la sociedad, realice los siguientes ----- actos: 1. Endosar las Facturas Nacionales e Internacionales de esas compañías hasta por la suma de UN MIL MILLONES DE PESOS ----- (\$1.000.000.000.00) Moneda Legal. 2. Suscribir Declaraciones ----- Cambiarias, Aduaneras y Tributarias a las que esta obligada la ----- sociedad en el giro ordinario de sus negocios, quedando facultado para notificarse, aportar y solicitar pruebas relacionados con las declaraciones Cambiarias. El señor MARIO LÓPEZ LEÓN, queda ----- facultado para notificarse, aportar y solicitar pruebas, presentar escritos en caso que resulte necesario en general a realizar todo acto, diligencia o tramite que considere indispensable para el ----- cabal cumplimiento del presente mandato.-----

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: 30 de Marzo de 2010.

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

C E R T I F I C A

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

***** C O N T I N U A *****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

mbayon

Anexo 1

Preparation of Intermediate of Formula (IV)
One Pot Reaction, Steps (a) and (b)

To a slurry of ganciclovir and about 3-30 equivalents
of orthoester of Formula (II), preferably 4-8 equivalents
5 of orthoester of Formula (II) and optionally an inert
solvent, preferably a polar solvent such as ethanol,
dimethylformamide or dimethylsulfoxide, is added a small
amount of an organic acid catalyst such as pyridinium p-
toluenesulfonate (PPTS) or p-toluenesulfonic acid
10 monohydrate (PTSA). The reaction is carried out at 20°-
40°C, preferably at ambient temperature from 1-48 hours,
preferably 3-6 hours. Water is added (about 100-1000
equivalents, preferably 200-400 equivalents) and the
slurry is stirred for 0.5 to 3 hours, preferably 0.5 to 1
15 hour. Excess orthoester reagent is then removed by
distillation under vacuum (aspirator). To the resulting
slurry is added about 100-1000 equivalents, preferably
200-400 equivalents of isopropyl acetate. The mixture is
stirred for about 10-100 min, preferably 15-30 min, and
20 then filtered and washed with isopropyl acetate. The
product, a compound of Formula (IV), is dried under vacuum
at 30°-60°C, preferably 45°-50°C for 1-2 days, preferably 1
day.

Preparation of Intermediate of Formula (VI)
25 One Pot Reaction, Steps (a), (b) and (c)

To a slurry of ganciclovir and about 3-30 equivalents
of orthoester of Formula (II), preferably 4-8 equivalents
of orthoester of Formula (II) and optionally an inert
solvent, preferably a polar solvent such as ethanol,
30 dimethylformamide or dimethylsulfoxide, is added a small
amount of an organic acid catalyst such as pyridinium
p-toluenesulfonate (PPTS) or p-toluenesulfonic acid
monohydrate (PTSA). The reaction is carried out at 20°-
40°C, preferably at ambient temperature from 1-48 hours,
35 preferably 3-6 hours. Water is added (about 100-1000
equivalents, preferably 200-400 equivalents) and the

slurry is stirred for 0.5 to 3 hours, preferably 1 to 2 hours. About 200-2000 equivalents, preferably 1000-1500 equivalents of isopropyl acetate is then added to the slurry. The mixture is vacuum distilled at about 100-200 mm (Hg) of pressure until the volume has been largely reduced. To the concentrated mixture is added about 1-2 equivalents, preferably 1.2-1.5 equivalents of Z-valine-NCA and a catalytic amount of DMAP (4-dimethylamino-pyridine). The reaction mixture is stirred at room temperature and the progress of the reaction is followed by HPLC. When the reaction is essentially complete, about 1000-1500 equivalents of isopropyl acetate is added and the reaction mixture is heated to 40° to 60°C, preferably to 50°-55°C for 20 to 100 min, preferably 20 to 40 min. The reaction mixture is then allowed to cool to room temperature and stirred for 5-24 hours, preferably 10 to 15 hours. The product, a compound of Formula (VI), is collected by filtration, washed with isopropyl acetate and dried under vacuum at about 40° to 60°C for 1 to 2 days, preferably 1 day.

Preparation of Salts

One of ordinary skill in the art will also recognize that the compound of Formula (I) may be prepared as an acid addition salt or as the corresponding free base. If prepared as an acid addition salt, the compound can be converted to the free base by treatment with a suitable base such as ammonium hydroxide solution, sodium hydroxide, potassium hydroxide or the like. However, it is important to point out that the free base of Formula (I) is more difficult to characterize than its acid addition salts. When converting the free base to an acid addition salt, the compound is reacted with a suitable organic or inorganic acid (described earlier). These reactions are effected by treatment with an at least stoichiometric amount of an appropriate acid (in case of the preparation of an acid addition salt) or base (in case of liberation

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



82

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 473/18	A1	(11) International Publication Number: WO 97/27197 (43) International Publication Date: 31 July 1997 (31.07.97)
(21) International Application Number: PCT/EP97/00238 (22) International Filing Date: 20 January 1997 (20.01.97) (30) Priority Data: 592,282 26 January 1996 (26.01.96) US (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH). (72) Inventors: ARZENO, Humberto, B.; 7665 Normandy Way, Cupertino, CA 95014-5252 (US). HUMPHREYS, Eric, R.; 3290 Fasman Drive, San Bruno, CA 94066 (US). WONG, Jim-Wah; 2714 Northbrook Place, Boulder, CO 80304 (US). ROBERTS, Christopher, R.; 721 N. County Road 27E, Berthoud, CO 80513 (US). (74) Agent: MEZGER, Wolfgang; Grenzacherstrasse 124, CH-4070 Basle (CH).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PROCESS FOR PREPARING GANCICLOVIR DERIVATIVES		
(57) Abstract Process and novel intermediates for preparing the L-monovaline ester of 2- (2-amino-1,6-dihydro-6-oxo-purin-9-yl) -methoxy-1,3-propanediol (ganciclovir) and its pharmaceutically acceptable salts. The present process and monoester intermediates provide for monoesterification by an L-valine derivative, resulting in a monocarboxylate-monovalinate which is then selectively hydrolyzed under basic or enzymatic conditions to give the monovaline ester of ganciclovir in high yield and purity. These products are of value as antiviral agents with improved absorption.		

FOR THE PURPOSES OF INFORMATION ONLY

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

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

- 1 -

PROCESS FOR PREPARING GANCICLOVIR DERIVATIVES

BACKGROUND OF THE INVENTION

Field of the Invention

5 The present invention relates to a process for preparing a prodrug formulation of ganciclovir and its pharmaceutically acceptable salts. More specifically, the invention relates to a process for preparing the L-
10 monovaline ester derived from 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-propanediol and its pharmaceutically acceptable salts.

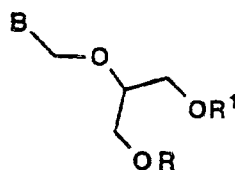
 The invention also relates to novel intermediates useful in the above process and to a process for preparing those intermediates.

15 Background Information

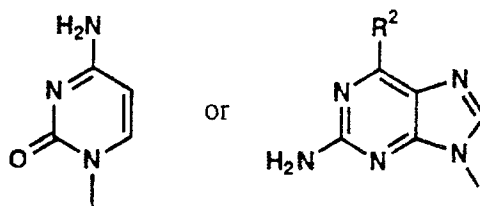
 British Patent 1 523 865 describes antiviral purine derivatives with an acyclic chain in the 9-position. Among those derivatives 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-ethanol with the INN name acyclovir
20 has been found to have good activity against herpes viruses such as herpes simplex.

 U.S. Patent 4,355,032 discloses the compound 9-[(2-hydroxy-1-hydroxymethylethoxy)-methyl]-guanine, 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-
25 propanediol or 9-[(1,3-dihydroxy-2-propoxy)-methyl]-guanine (DHPG) with the INN name ganciclovir. Ganciclovir is highly efficacious against viruses of the herpes family, for example, against herpes simplex and cytomegalovirus.

European Patent Application 0 375 329 A2 discloses prodrug compounds with the following formula



5 wherein R and R¹ are independently selected from hydrogen and an amino acid acyl residue, provided at least one of R and R¹ represents an amino acid acyl residue and B represents a group of the formulae

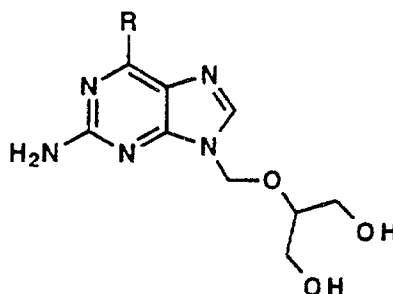


10 in which R² represents a C₁₋₆ straight chain, C₃₋₆ branched chain or C₃₋₆ cyclic alkoxy group, or a hydroxy or amino group or a hydrogen atom and the physiologically acceptable salts thereof. These prodrug compounds are described as having advantageous bioavailability when administered by the oral route, resulting in high levels
15 of the parent compound in the body.

Example 3(b) of European Patent Application 0 375 329 A2 discloses the preparation of the bis-(L-isoleucinate) ester of ganciclovir as a white foam. Example 4(b) discloses the preparation of the bis(glycinate) ester of ganciclovir as a white solid. Example 5(b) discloses the preparation of the bis-(L-valinate) ester of ganciclovir as a solid. Example 6(b) discloses the preparation of the bis-(L-alaninate) ester of ganciclovir as a syrup containing 90% of the bis ester and 10% of the monoester.
20 The bis-esters are prepared by reacting ganciclovir with an optionally protected amino acid or functional equivalent thereof. The reaction may be carried out in a
25

conventional manner, for example in a solvent such as pyridine, dimethylformamide, etc., in the presence of a coupling agent such as 1,3-dicyclohexylcarbodiimide, optionally in the presence of a catalytic base such as
5 4-dimethylaminopyridine. The described bis esters are non-crystalline materials which are difficult to process for the manufacture of oral pharmaceutical dosage forms.

British Patent Application No. 8829571 is the priority patent application for European Patent
10 Application 0 375 329 A2 and US Patent No. 5,043,339, and discloses amino acid esters of the compounds of the formula



(wherein R represents a hydroxy or amino group or a
15 hydrogen atom) and the physiologically acceptable salts thereof. Examples of preferred amino acids include aliphatic acids e.g. containing up to 6 carbon atoms such as glycine, alanine, valine and isoleucine. The amino acid esters include both mono and diesters. The preparation of
20 the diesters is identical to the preparation in European Patent Application 0 375 329 A2; however, this patent application as well as European Patent Application 0 375 329 A2 and US Patent No. 5,043,339 do not disclose the preparation of monoesters, or any data suggesting their
25 usefulness.

Leon Colla et al., J. Med. Chem. (1983) 26, 602-604, disclose several water-soluble ester derivatives of acyclovir and their salts as prodrugs of acyclovir. The authors indicate that acyclovir cannot be given as eye

87

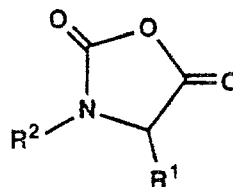
drops or intramuscular injections because of its limited solubility in water and have therefore synthesized derivatives of acyclovir which are more water soluble than the parent compound. The authors disclose the hydrochloride salt of the glycyl ester, the hydrochloride salt of the alanyl ester, the hydrochloride salt of the beta-alanyl ester, the sodium salt of the succinyl ester, and the azidoacetate ester. The alanyl esters were prepared by conventional esterification methods, including reacting acyclovir with the corresponding N-carboxy-protected amino acid in pyridine, in the presence of 1,3-dicyclohexylcarbodiimide and a catalytic amount of p-toluenesulfonic acid and subsequent catalytic hydrogenation to give the alpha- and beta-alanyl esters as their hydrochloride salts.

L. M. Beauchamp et al., Antiviral Chemistry & Chemotherapy (1992), 3 (3), 157-164, disclose eighteen amino acid esters of the antiherpetic drug acyclovir and their effectiveness as prodrugs of acyclovir, evaluated in rats by measuring the urinary recovery of acyclovir. Ten prodrugs produced greater amounts of the parent drug in the urine than acyclovir itself: the glycyl, D,L-alanyl, L-alanyl, L-2-amino-butyrate, D,L-valyl, L-valyl, DL-isoleucyl, L-isoleucyl, L-methionyl, and L-prolyl ester. According to the authors, the L-valyl ester of acyclovir was the best prodrug of the esters investigated. These esters were prepared by methods similar to those employed by Colla et al.

European Patent Application 0 308 065 A2 discloses the valine and isoleucine esters of acyclovir, preferably in the L-form, as showing a large increase in absorption from the gut after oral administration, when compared with other esters and acyclovir. The amino acid esters are prepared by conventional esterification methods, including reacting acyclovir with an N-carboxy-protected amino acid or an acid halide or acid anhydride of the amino acid, in

a solvent such as pyridine or dimethylformamide, optionally in the presence of a catalytic base.

PCT Patent Application WO 94/29311 discloses a process for the preparation of amino acid esters of a nucleoside analogue, including acyclovir and ganciclovir. This process comprises reacting a nucleoside analogue having an esterifiable hydroxy group in its linear or cyclic ether moiety, with a 2-oxa-4-aza-cycloalkane-1,3-dione of the formula



wherein R^1 may represent hydrogen, a C_{1-4} alkyl or alkenyl group or other amino acid side chains, and R^2 may represent hydrogen or a group $COOR^3$ where R^3 is a benzyl, t-butyl, fluorenylmethyl or an optionally halo substituted linear or branched C_{1-8} alkyl group. Preferred R^1 groups include hydrogen, methyl, isopropyl and isobutyl, yielding respectively the glycine, alanine, valine and isoleucine esters of acyclovir or ganciclovir. Examples 1-3 of PCT Patent Application WO 94/29311 disclose only the condensation of acyclovir with the valine-substituted 2-oxa-4-aza-cycloalkane-1,3-dione (Z-valine-N-carboxyanhydride, Z-valine-NCA) by conventional procedures. While the amino acid esters of the PCT application include both the acyclovir and ganciclovir esters, the application does not disclose how to prepare the ganciclovir esters, much less the mono-esters of ganciclovir.

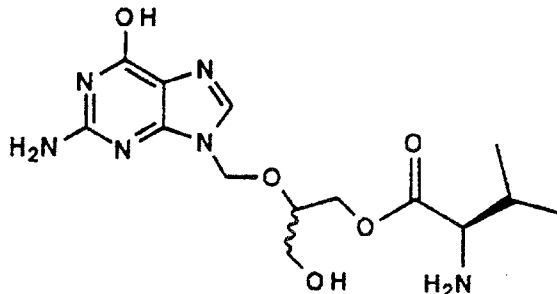
The L-monovaline ester derived from 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-propanediol and its pharmaceutically acceptable salts are potent antiviral agents and are described in European Patent Application 0 694 547 A. These compounds have been found to have

improved oral absorption and low toxicity. This patent application also discloses certain processes for preparing these esters, different from those described herein.

The present invention relates to an improved process whereby a cyclic orthoester, a monocarboxylate and a
5 monocarboxylate-monovalinate of ganciclovir are prepared as intermediates. The monocarboxylate intermediate is formed with high selectivity and in high yields, and provides for mono-esterification by an L-valine
10 derivative. The monocarboxylate-monovalinate can then be selectively hydrolyzed to the monovaline ester which is obtained in good yield and purity.

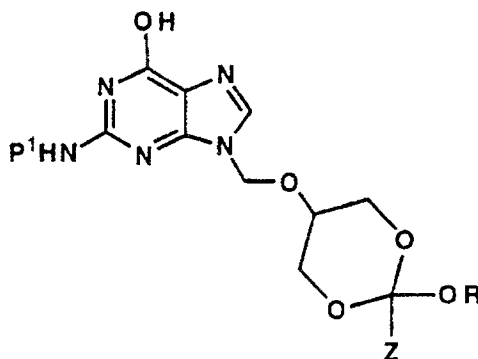
SUMMARY OF THE INVENTION

In a first aspect, this invention provides a process
15 for preparing the compound of Formula (I)

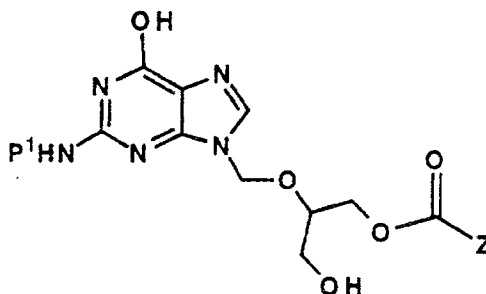


and pharmaceutically acceptable salts thereof, which
compound is named hereinafter 2-(2-amino-1,6-dihydro-6-
20 oxo-purin-9-yl)-methoxy-3-hydroxy-1-propyl-L-valinate or
mono-L-valine ganciclovir.

This process involves the transesterification of an
orthoester of Formula (II), $Z-C(OR)_3$, wherein R is lower
alkyl, allyl or aralkyl, and Z is hydrogen, lower alkyl,
aryl or aralkyl, with ganciclovir to give the
25 corresponding cyclic orthoester of ganciclovir of Formula
(III)

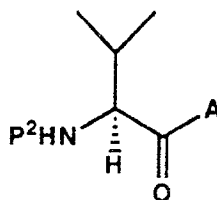


wherein P¹ is hydrogen or an amino protecting group, R is lower alkyl, allyl or aralkyl, and Z is hydrogen, lower alkyl, aryl or aralkyl, followed by the formation of ganciclovir monocarboxylate of Formula (IV))

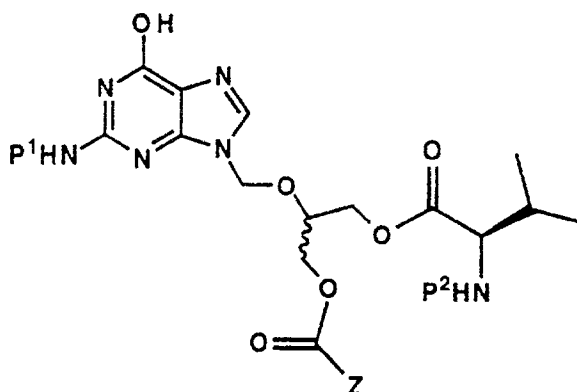


wherein P¹ is hydrogen or an amino protecting group, and Z is hydrogen, lower alkyl, aryl or aralkyl.

This product is then esterified with an L-valine derivative of Formula (V)



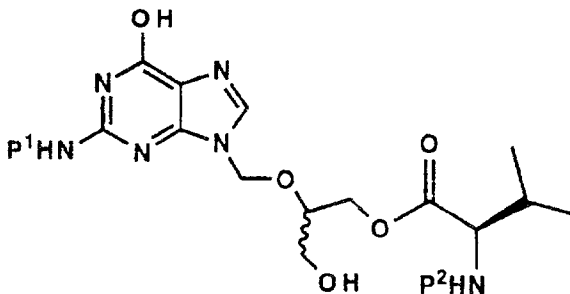
wherein P² is an amino-protecting group and A is a carboxy-activating group, to provide a monocarboxylate-monovalinate of ganciclovir of Formula (VI)



wherein P¹ is hydrogen or an amino protecting group, P² is an amino protecting group, and Z is hydrogen, lower alkyl, aryl or aralkyl, followed by removal of the acyl (e.g., alkanoyl or benzoyl) group by selective hydrolysis and, finally, removal of any protecting groups to yield the prodrug of Formula (I).

Optionally, the process can also include the formation of salts of the prodrug of Formula (I), the conversion of an acid addition salt of the prodrug of Formula (I) into a non-salt form, the optical resolution of a compound of Formula (I), or the preparation of the prodrugs of Formula (I) in crystalline form. Details of the process are described below.

In a second aspect, this invention provides a novel enzymatic hydrolysis in which the monocarboxylate-monovalinate intermediate of Formula (VI) is selectively hydrolyzed via enzymatic catalysis to the monovalinate of Formula (VII)



wherein P¹ is hydrogen or an amino protecting group

and P² is an amino protecting group.

In a third aspect, this invention provides compounds of Formulae (III), (IV) and (VI) which are useful intermediates for preparing mono-L-valine ganciclovir and their pharmaceutically acceptable salts.

In a fourth aspect, this invention provides processes for preparing the intermediates of Formulae (III), (IV) and (VI).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

„BOC“ means t-butoxycarbonyl.

„CBZ“ means carbobenzyloxy (benzyloxycarbonyl).

„Fmoc“ means N-(9-fluorenylmethoxycarbonyl).

„DHPG“ means 9-[(1,3-dihydroxy-2-propoxy)-methyl]-guanine.

„Alkyl“ means a straight or branched saturated hydrocarbon radical having from one to the number of carbon atoms designated. For example, C₁₋₇ alkyl is alkyl having at least one but no more than seven carbon atoms, e.g. methyl, ethyl, i-propyl, n-propyl, n-butyl, n-pentyl, n-heptyl and the like.

„Lower alkyl“ means an alkyl group of one to six carbon atoms.

„Allyl“ means an unsaturated organic radical C₃H₅, such as -CH₂-CH=CH₂, -CH=CH-CH₃, or -C(CH₃)=CH₂.

„Acyl“ means an organic radical derived from an organic acid by the removal of the hydroxyl group; e.g.,

CH₃CO- or acetyl is the acyl radical of CH₃COOH. Other examples for such acyl groups are propionyl, or benzoyl, etc. The term „acyl“ includes the term „alkanoyl“ which is the organic radical RCO- in which R is an alkyl group as defined above.

„Lower alkoxy“, „(lower alkyl)-amino“, „di-(lower alkyl)-amino“, „(lower alkanoyl)-amino“, and similar terms mean alkoxy, alkylamino, dialkylamino, alkanoylamino, etc. in which the or each alkyl radical is a „lower alkyl“ as described above.

„Aprotic polar solvent“ refers to organic solvents which may be either water-immiscible, such as halogenated hydrocarbons, e.g. methylene chloride, chloroform, etc., or water-miscible, such as tetrahydrofuran, dimethoxyethane, bis-(2-methoxyethyl)-ether (diglyme), dimethylformamide, N-methylpyrrolidone, dimethylsulfoxide, etc.

„Aryl“ means an organic radical derived from an aromatic hydrocarbon by the removal of one hydrogen atom. Preferred aryl radicals are aromatic carbocyclic radicals having a single ring (e.g., phenyl) or two condensed rings (e.g., naphthyl). Most preferred is the phenyl radical C₆H₅-.

„Aralkyl“ means an organic radical derived from an alkyl in which a hydrogen atom is replaced by an above-defined aryl group; e.g., benzyl, phenylethyl, phenylpropyl, and the like.

„Benzyl“ is the radical PhCH₂-, derived from toluene.

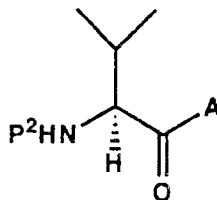
„Benzoyl“ refers to the radical Ph-CO- where Ph- is the phenyl radical C₆H₅-.

„Halogen“ or „halo“ means fluorine, chlorine, bromine, or iodine.

„Derivative“ of a compound means a compound obtainable from the original compound by a simple chemical

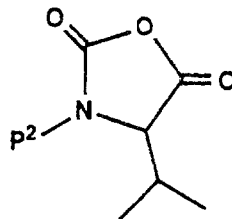
process.

„Activated derivative“ of a compound means a reactive form of the original compound which renders the compound active in a desired chemical reaction, in which the original compound is only moderately reactive or non-reactive. Activation is achieved by formation of a derivative or a chemical grouping within the molecule with a higher free energy content than that of the original compound, which renders the activated form more susceptible to react with another reagent. In the context of the present invention activation of the carboxy group is of particular importance and corresponding activating agents or groupings which activate the carboxy group are described in more detail below. An example of an activated derivative of L-valine is the compound of Formula (V)



wherein P² is an amino-protecting group and A is a carboxy-activating group, for example, halo, a lower acyloxy group, a carbodiimide derived group, such as from 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDAC), an isobutyrate group, and the like.

Of particular interest for the present invention is an amino acid anhydride which is an activated form of an amino acid which renders the amino acid (especially L-valine) susceptible to esterification. Amino acid anhydrides are included in the compounds of Formula (V), above. Especially useful for the present invention are the cyclic amino acid anhydrides of L-valine, described in PCT Patent Application WO 94/29311, such as 2-oxa-4-aza-5-isopropyl-cycloalkane-1,3-dione of Formula (Va):



in which P^2 is an amino protecting group. Other examples of the cyclic amino acid anhydrides are protected amino acid N-carboxy anhydrides (NCA's) described in more detail below.

„Orthoesters“ are compounds of Formula (II), $Z-C(OR)_3$, wherein R is lower alkyl, allyl or aralkyl, and Z is hydrogen, lower alkyl, aryl or aralkyl. These compounds are well-known. Some of the more common orthoesters, such as trimethyl and/or triethyl orthoformate, orthoacetate, orthopropionate, orthobutyrate, orthovalerate and orthobenzoate are commercially available, e.g., from Aldrich Chemical Company, Milwaukee, WI.

„Orthoformate“ is a compound of Formula (II), $Z-C(OR)_3$ wherein Z is hydrogen and R is alkyl of 1-6 carbon atoms, allyl or aralkyl. These compounds are well-known. A convenient synthesis of these compounds is described in E.R. Alexander et al., J. Amer. Chem. Soc. 74, 554(1952).

„Alkanoic acid“ refers to an organic acid of Formula $R-COOH$ where R is lower alkyl of 1-6 carbon atoms.

„Alkanoate“ means an ester of an alkanoic acid as defined above, i.e., $R-COOR$.

„Alkanoyl“ refers to the radical $R-CO-$ where R is lower alkyl.

„Transesterification“ means the conversion of an organic acid ester into another ester of the same acid. The ester interchange takes place when the ester is treated with an alcohol, usually in the presence of an

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

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
22 September 2005 (22.09.2005)

PCT

(10) International Publication Number
WO 2005/087198 A1

- (51) International Patent Classification⁷: **A61K 9/14**, 9/20, 31/522, C07D 473/18
- (21) International Application Number: PCT/IB2005/000615
- (22) International Filing Date: 10 March 2005 (10.03.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 410/Del/2004 10 March 2004 (10.03.2004) IN
- (71) Applicant (for all designated States except US): **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Delhi 110019, Delhi (IN).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **SINGH, Romi, Barat** [IN/IN]; A-14, Badshah Bagh, Varanasi 221002, Uttar Pradesh (IN). **NAGAPRASAD, Vishnubhotla** [IN/IN]; 102 Surya Niwas Apartments, Balaji Nagar, Kukatpally, Hyderabad 500072, Andhra Pradesh (IN). **SINGH, Nidhi** [IN/IN]; B-261, Sarita Vihar, New Delhi 110044, Delhi (IN).
- (74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SI, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- 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.

(54) Title: PROCESSES FOR THE PREPARATION OF SOLID DOSAGE FORMS OF AMORPHOUS VALGANCICLOVIR HYDROCHLORIDE

(57) Abstract: The present invention relates to a process for the preparation of solid dosage forms of amorphous valganciclovir hydrochloride by dry method.



WO 2005/087198 A1

PROCESSES FOR THE PREPARATION OF SOLID DOSAGE FORMS OF AMORPHOUS VALGANCICLOVIR HYDROCHLORIDE

Field of the Invention

5 The present invention relates to a process for the preparation of solid dosage forms of amorphous valganciclovir hydrochloride by dry method.

Background of the Invention

Valganciclovir hydrochloride, a prodrug of ganciclovir, is used in the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) and for the prevention of CMV disease in kidney, heart and for kidney-pancreas transplant patients who are at high risk. Valganciclovir hydrochloride is hydrochloride salt of the L-valyl ester of ganciclovir. Chemically, it is L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride. It is available as tablets under the brand name Valcyte® containing crystalline valganciclovir hydrochloride.

10
15

U.S. Patent No. 6,083,953 discloses valganciclovir hydrochloride and processes for its preparation. Therein it is set forth that valganciclovir hydrochloride was developed with a view to improve the bioavailability of ganciclovir, which has a poor bioavailability when administered orally. The higher oral doses of ganciclovir are required to achieve a therapeutic concentration in the blood. Valganciclovir hydrochloride when administered orally is reported to have better bioavailability than ganciclovir given orally.

20

It is known that the amorphous form of a drug may have certain advantages over the crystalline form, for example, amorphous form can be more soluble or can have a higher rate of solubility in water than the crystalline form and consequently the drug may show improved bioavailability, for example, due to the faster dissolution of the drug in the gastrointestinal fluid. It is with this view that we have prepared dosage forms comprising valganciclovir hydrochloride in which valganciclovir hydrochloride is present in the amorphous form. Without being bound by any theory, these dosage forms may further improve the oral bioavailability of valganciclovir and ultimately that of ganciclovir.

25

21
38

However, it has been found that amorphous valganciclovir hydrochloride as such is very fine and fluffy material, with relatively low bulk and tap density. This property can make it difficult to formulate into a dosage form with uniformity of weight, hardness, and other desirable tablet properties. Wet granulation needs to be avoided, as addition of a solvent along with subsequent removal in way of drying the granules at elevated temperatures may convert the amorphous form to crystalline form.

The direct compression technique may not be desirable for a drug with a bulk density less than 0.2 g/cc, due to poor flow of the material leading to non-uniform die-fill and subsequent weight variation. However, direct compression could be a method of choice when the amorphous valganciclovir hydrochloride is so processed that it has a bulk density of at least 0.2 g/cc or more. This can be achieved during chemical manufacturing by variation in the processing parameters or by a physical process of compaction and milling.

There is a need for simple method of production, which does not require wet granulation with organic solvents or water and do not require an additional step of drying.

Summary of the Invention

We hereby report processes for the preparation of solid dosage forms comprising amorphous valganciclovir hydrochloride by a dry process which may be, for example, dry granulation or direct compression. The processes give dosage forms with uniformity of weight, sufficient hardness and friability.

In one general aspect, the present disclosure relates to dry processes for the preparation of solid dosage forms comprising amorphous valganciclovir hydrochloride and one or more pharmaceutically acceptable excipient(s).

In another general aspect, herein are provided processes for the preparation of solid dosage forms of amorphous valganciclovir hydrochloride wherein the processes comprise mixing amorphous valganciclovir hydrochloride with one or more pharmaceutically acceptable excipient(s) and forming into solid dosage forms.

In another general aspect, herein are provided processes for the preparation of solid dosage forms of amorphous valganciclovir hydrochloride wherein the processes comprise

mixing amorphous valganciclovir hydrochloride with one or more pharmaceutically acceptable excipient(s) and compressing into a tablet.

In another general aspect, herein are provided processes for the preparation of solid dosage forms of amorphous valganciclovir hydrochloride wherein the processes comprise compacting valganciclovir hydrochloride alone or mixed with one or more pharmaceutically acceptable excipient(s) by, for example, roller compaction or slugging; sizing the compacts into granules by milling; optionally mixing the granules with one or more of pharmaceutically acceptable excipients and forming a solid dosage form.

In another general aspect, herein are provided processes for the preparation of solid dosage forms of amorphous valganciclovir hydrochloride wherein the processes comprise compacting valganciclovir hydrochloride alone or mixed with one or more pharmaceutically acceptable excipient(s) by, for example, roller compaction or slugging; sizing the compacts into granules by milling; optionally mixing the granules with one or more of pharmaceutically acceptable excipients and compressing into a tablet.

In another general aspect, herein are provided methods of administering amorphous valganciclovir hydrochloride to a patient in need thereof as solid dosage forms prepared by a dry process.

Brief Description of the Drawings

Fig. 1 is a set of x-ray diffractogram of tablets of Example 1 recorded upon production and after storage for two months at 40° C and 75% relative humidity.

Detailed Description of the Invention

The present invention provides solid dosage forms comprising valganciclovir hydrochloride in amorphous form prepared by a dry process. The process is simple and economical as it does not require any solvents, as in the case of wet granulation processes, the most commonly followed process, which requires additional steps of drying the granules. The amorphous form resists conversion to a crystalline form by following the dry processes as described herein.

The term "solid dosage form" as used herein includes granules, tablets or coated tablets and capsules filled with granules or tablets prepared as per the embodiments described herein. Particularly suitable solid dosage forms are tablets.

The amorphous valganciclovir hydrochloride in the solid dosage form is present in a therapeutically effective amount. Typically, the drug may comprise from about 1mg to about 1000 mg, for example, from about 50 mg to about 800 mg. The amorphous valganciclovir can be prepared by methods described in Indian Patent Application
5 No.1052/DEL/2003 filed 28 August 2003.

Additionally, other drugs in a therapeutically effective amount can also be combined with the present dosage forms.

The pharmaceutically acceptable excipients are those known to the skilled in the art and may be selected from fillers, binders, disintegrants, glidant and lubricants. These
10 excipients may be present intragranularly or extragranularly or both.

The fillers may be selected from microcrystalline cellulose, mannitol, sucrose, lactose, dextrose, calcium carbonate, sorbitol and the like. The filler may be present in an amount of about 15% to about 60%, for example, from about 20% to 40% by weight of the dosage form.

15 The binders may be selected from polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, starch and starch based binders, gelatin, gums and the like. The binder may be present in an amount of about 0.1% to about 10%, for example, from about 1% to about 5% by weight of the dosage form.

20 The disintegrant may be selected from croscopovidone, croscarmellose sodium, starch, hydroxypropylcellulose, hydroxypropylmethylcellulose, gums, sodium starch glycolate and the like. The disintegrant may be present in an amount of about 1% to about 40%, for example, from about 2% to about 20% by weight of the dosage form.

25 The lubricants and glidants may be selected from talc, colloidal silicon dioxide, magnesium stearate, stearic acid and sodium stearyl fumarate. These may be present in an amount of about 0.1% to about 2% by weight of the dosage form.

The compaction of the drug or the mixture comprising the drug and excipient(s) into compacts may be carried out by slugging or by roller compaction, particularly suitable is roller compaction.

30 The roller compactor functions by uniformly applying pressure on a mixed powder blend by passing the blend between two counter-rotating rollers. The pressure imparted on

269
41

the blend by the rollers compresses the powder into a compact, such as a sheet or ribbon, which is typically milled to produce granules.

In one general aspect of the process, the valganciclovir hydrochloride can be mixed with one or more of pharmaceutical excipients such as filler, binder, disintegrant and
5 lubricant described above in a suitable blender. The mixing time can vary from about 10 to 60 minutes. The resultant blend can either be directly compressed into solid dosage form or compacted by roller compaction.

The resultant blend for compaction is subsequently transferred to a roller compactor in a known manner. The roller speed, roller gap width and force of compaction
10 are then adjusted and the blend is fed through the roller compactor. The typical force and other conditions can be easily selected and adjusted by those skilled in the art. For example, the compaction pressure may be between 25 to 75 bar, for example, between 35 to 55 bar. For maintaining the steady output of the compact material from the roller compactor, the rollers may be rotated at a speed of between 1 to 20 rpm, for example,
15 between 2 to 10 rpm, or between 3 to 5 rpm. When in contact with the counter rotating rollers of the roller compactor, the compression force imparted on the blend by rollers converts the powdered form into a ribbon or compaction sheet. This compact sheet is fed to a mill, such as an oscillating mill, fitted with a screen. The screen can be selected with variable hole diameters depending upon the size of the granules required. After passing
20 through the mill and the screen, the compact is converted into granules of the desired particle size distribution.

The granules obtained as above may be filled into capsules or packed in a sachet. The granules can also be mixed with one or more of pharmaceutically acceptable excipients and compressed into tablets.

25 As an alternative to roller compaction, slugging may be used for preparing solid dosage forms such as a tablet. The process is simple, low cost and effective. Slugging may be carried out by means of a tablet press. The drug either alone or mixed with other excipients is precompressed on a heavy duty press. The slug so formed is milled into granules and recompressed into tablet. The granules may also optionally be mixed with
30 other extragranular excipients prior to compression into a tablet.

Both the processes, i.e., roller compaction and slugging generate fines during the milling step. A portion of these fines can be mixed with granules and compressed into a tablet or can be easily recycled by collecting them and again compacted.

The tablet must be of sufficient hardness to withstand the packaging, transport or coating process without chipping or breaking. The hardness of the tablets can be measured by known methods. The hardness should not be so high that it adversely affects disintegration and dissolution rates of the tablets. Preferably, the hardness of these amorphous valganciclovir hydrochloride tablets is about 10 kP to about 30 kP, for example, about 15 kP to about 25 kP.

Another measure of durability of the tablet is the test for friability. A friability values of about 1% is acceptable, but friability below about 0.8% is particularly suitable. The tablets prepared as per the process can have friability of less than 0.8%, for example, less than 0.5%.

In one embodiment, processes provided herein comprise mixing amorphous valganciclovir hydrochloride with one or of pharmaceutically acceptable excipients and compressing the blend into a tablet.

In one embodiment, processes provided herein comprise compacting amorphous valganciclovir hydrochloride alone or mixed with a lubricant using roller compactor; milling and sizing the compacts into granules with a desired particle size distribution; mixing with extragranular pharmaceutically acceptable excipient(s) and compressing into a tablet using appropriate tooling.

In another embodiment, processes herein comprise mixing amorphous valganciclovir hydrochloride, filler, binder, disintegrant and lubricant and compacting the mixture using roller compactor; milling and sizing the compacts into granules with a desired particle size distribution; mixing with lubricant and compressed into a tablet using appropriate tooling.

In still another embodiment, processes provided herein comprise mixing amorphous valganciclovir hydrochloride, filler, binder, disintegrant and lubricant and compacting the mixture using roller compactor; milling and sizing the compacts into

granules with a desired particle size distribution; mixing with one or more of filler, binder, disintegrant and lubricant and compressed into a tablet using appropriate tooling.

In yet another embodiment, processes provided herein comprise compacting amorphous valganciclovir hydrochloride alone or mixed with one or more of filler, binder, disintegrant and lubricant, milling and sizing the compacts into granules with a desired particle size distribution and filling into a capsule dosage form.

In still another embodiment, processes provided herein comprise compacting amorphous valganciclovir hydrochloride alone or mixed with one or of pharmaceutically acceptable excipients by slugging; milling and sizing the slugs into granules with a desired particle size distribution; optionally mixing the granules with one or more of filler, binder, disintegrant and lubricant and compressed into a tablet.

When the solid dosage form is a tablet then it may additionally be coated with coating compositions like Opadry® AMB (with or without a non aqueous subcoat) sold by Colorcon to impart moisture protection on stability. Such a coating may comprise about 3 - 10%w/w of the tablet. The tablet may also be coated with coating compositions like Opadry® or Lustreclear® sold by Colorcon using non-aqueous or aqueous systems, preferably non-aqueous system to impart aesthetic appeal as well as a barrier to the external environment. Such a coating may comprise about 3-10%w/w of the tablet.

The invention described herein can further be illustrated by the following examples but these do not limit the scope of the invention.

EXAMPLE 1

Ingredients	Quantity (mg)
Valganciclovir hydrochloride (amorphous) eq. to 450 mg of valganciclovir	496.3
Microcrystalline cellulose	159.95
Cross-linked polyvinylpyrrolidone	21.0
Polyvinylpyrrolidone	14.0
Magnesium stearate	8.75
Total	700

Procedure:

Valganciclovir hydrochloride (amorphous) was mixed in a blender with microcrystalline cellulose, cross-linked polyvinylpyrrolidone, polyvinylpyrrolidone and magnesium stearate and compressed into tablet using appropriate tooling.

5

EXAMPLE 2

Ingredients	Quantity (mg)
Intragranular	
Valganciclovir hydrochloride (amorphous) eq. to 450 mg of Valganciclovir	496.3
Microcrystalline cellulose	159.95
Cross-linked polyvinylpyrrolidone	21.0
Polyvinylpyrrolidone	14.0
Magnesium stearate	3.50
Extragranular	
Magnesium stearate	5.25
Total	700

Procedure:

Valganciclovir hydrochloride (amorphous) was mixed with microcrystalline cellulose, cross-linked polyvinylpyrrolidone, polyvinylpyrrolidone and magnesium stearate and compacted with a roller compactor. The compacts were sized into granules by milling, mixed with magnesium stearate and compressed into tablet using appropriate tooling.

10

The tablets of Example 1 were subjected to accelerated stability testing. The tablets were kept at 40°C and 75% relative humidity for two months. The XRD data at the end of the two months period showed no change in amorphous nature in comparison to the initial scan of the amorphous valganciclovir hydrochloride, as shown in Fig. 1.

15

27
45**EXAMPLE 3**

Ingredients	Quantity (mg)
Intragranular	
Valganciclovir hydrochloride (amorphous) eq. to 450 mg of Valganciclovir	496.3
Magnesium stearate	3.50
Extragranular	
Microcrystalline cellulose	159.95
Cross-linked polyvinylpyrrolidone	21.0
Polyvinylpyrrolidone	14.0
Magnesium stearate	5.25
Total	700

Procedure:

- Valganciclovir hydrochloride (amorphous) and magnesium stearate were mixed in a
- 5 blender and compacted using a roller compactor. The compacts were sized into granules by milling, mixed with microcrystalline cellulose, cross-linked polyvinylpyrrolidone, polyvinylpyrrolidone and magnesium stearate and compressed into tablet using appropriate tooling.

EXAMPLE 4

Ingredients	Quantity (mg)
Intragranular	
Valganciclovir hydrochloride (amorphous) eq. to 450 mg of Valganciclovir	496.3
Microcrystalline cellulose	79.975
Cross-linked polyvinylpyrrolidone	21.0
Polyvinylpyrrolidone	14.0
Magnesium stearate	3.50
Extragranular	
Microcrystalline cellulose	79.975
Magnesium stearate	5.25
Total	700

Procedure:

Valganciclovir hydrochloride (amorphous) was mixed with microcrystalline cellulose, cross-linked polyvinylpyrrolidone, polyvinylpyrrolidone and magnesium stearate and compacted with a roller compactor. The compacts were sized into granules by milling, mixed with microcrystalline cellulose and magnesium stearate and compressed into tablet using appropriate tooling.

EXAMPLE 5

Ingredients	Quantity (mg)
Intragranular	
Valganciclovir hydrochloride (amorphous) eq. to 450 mg of Valganciclovir	496.3
Microcrystalline cellulose	79.975
Cross-linked polyvinylpyrrolidone	10.5
Polyvinylpyrrolidone	14.0
Magnesium stearate	3.50
Extragranular	
Microcrystalline cellulose	79.975
Cross-linked polyvinylpyrrolidone	10.5
Magnesium stearate	5.25
Total	700

10 **Procedure:**

Valganciclovir hydrochloride (amorphous) was mixed with microcrystalline cellulose, cross-linked polyvinylpyrrolidone, polyvinylpyrrolidone and magnesium stearate and compacted with a roller compactor. The compacts were sized into granules by milling, mixed with microcrystalline cellulose, cross-linked polyvinylpyrrolidone and magnesium stearate and compressed into tablet using appropriate tooling.

WE CLAIM:

1. A dry process for the preparation of valganciclovir hydrochloride solid dosage forms wherein the process comprises mixing amorphous valganciclovir hydrochloride with one or more pharmaceutically acceptable excipient(s) and forming into a solid dosage form.
2. The process according to claim 1 wherein the pharmaceutically acceptable excipient is one or more of filler, binder, disintegrant, glidant and lubricant.
3. The process according to claim 1 wherein the process comprises compacting valganciclovir hydrochloride alone or mixed with one or more of pharmaceutically acceptable excipient(s) by roller compactor or slugging; sizing the compacts or slugs into granules by milling; optionally mixing the granules with one or more of pharmaceutically acceptable excipients and forming a solid dosage form.
4. The process according to claim 3 wherein the compaction is done by roller compactor.
5. The process according to claims 3 wherein the solid dosage form is a tablet.
6. The process according to claim 3 wherein the solid dosage form is a capsule.
7. The process according to claim 1 wherein the mixture is directly compressed into a tablet.
8. The process according to claim 2 wherein the filler is one or more of microcrystalline cellulose, mannitol, sucrose, lactose, dextrose, calcium carbonate and sorbitol.
9. The process according to claim 2 wherein the binder is one or more of polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, starch and starch based binders, gelatin and gums.
10. The process according to claim 2 wherein the disintegrant is one or more of crospovidone, croscarmellose sodium, starch, hydroxypropylcellulose, hydroxypropylmethylcellulose, gums and sodium starch glycolate.
11. The process according to claim 2 wherein the glidant is one or more of talc and colloidal silicon dioxide.
12. The process according to claim 2 wherein the lubricant is one or more of magnesium stearate, stearic acid and sodium stearyl fumarate.

13. A solid dosage form comprising amorphous valganciclovir hydrochloride, filler, disintegrant, binder and lubricant prepared by the process of claim 1.
14. A solid dosage form comprising amorphous valganciclovir hydrochloride, microcrystalline cellulose, cross-linked polyvinylpyrrolidone, polyvinylpyrrolidone and magnesium stearate prepared by the process of claim 2.
15. The solid dosage form according to claim 13 wherein the solid dosage form is a tablet.
16. The solid dosage form according to claim 13 wherein the solid dosage form is a capsule.
17. A solid dosage form according to claim 13 wherein it additionally comprises another drug in a therapeutically effective amount.
18. A method of administering amorphous valganciclovir hydrochloride to a patient in need thereof as a solid dosage form prepared by a dry process wherein the process comprises mixing amorphous valganciclovir hydrochloride with one or more of pharmaceutically acceptable excipient(s) and forming into a solid dosage form.

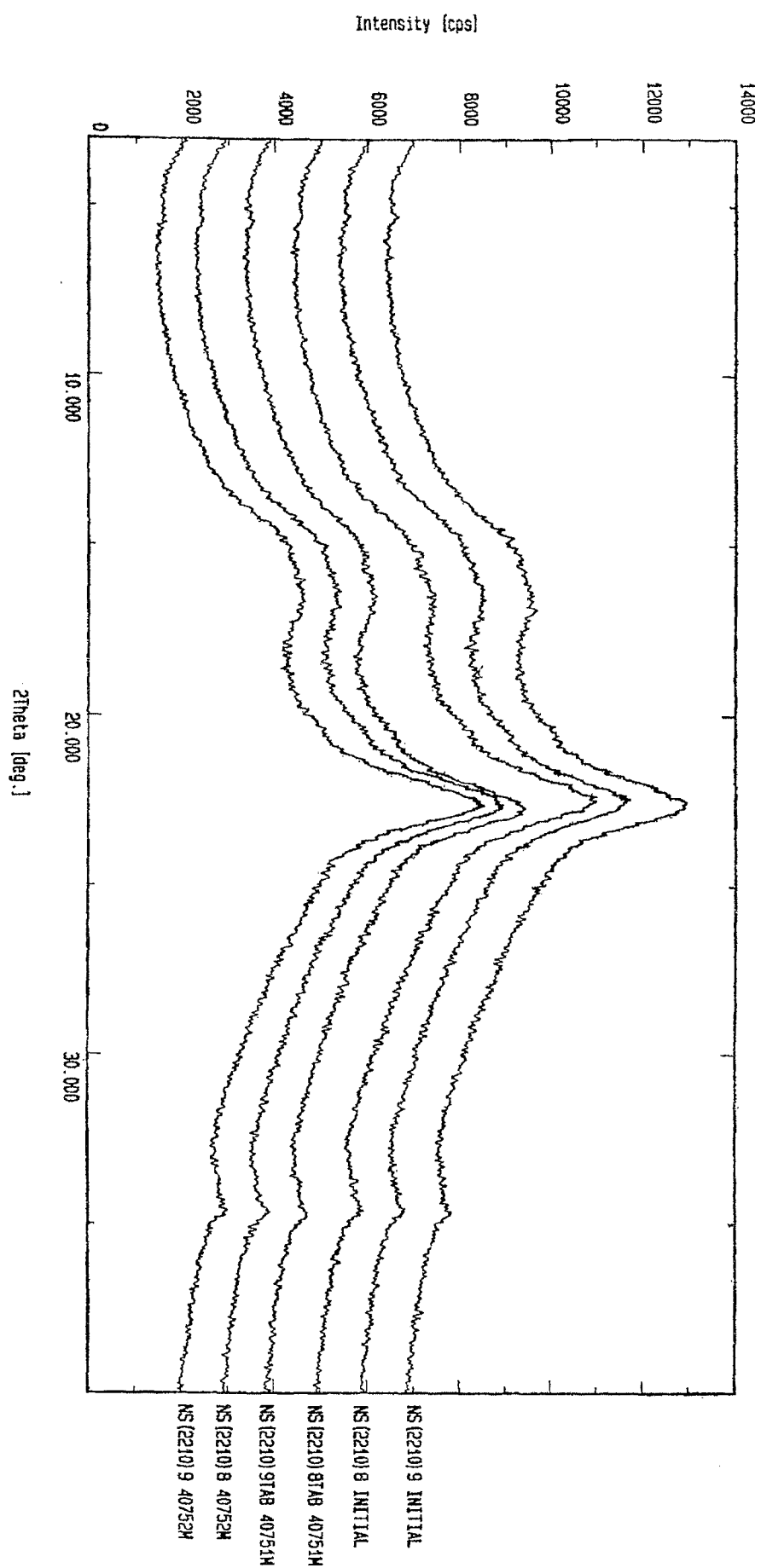


FIGURE 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/000615

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/14 A61K9/20 A61K31/522 C07D473/18

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 C07D

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, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/010998 A (PHARMACIA CORPORATION; AMIDON, GREGORY, E; GANORKAR, LOKSIDH, D; HEIML) 5 February 2004 (2004-02-05) page 14, line 27, paragraph 62-64	1-18
A	US 6 395 029 B1 (LEVY ROBERT J) 28 May 2002 (2002-05-28) paragraphs '0144!, '0209!	1-18
A	US 6 248 363 B1 (PATEL MAHESH V ET AL) 19 June 2001 (2001-06-19) column 9, line 28 column 50, lines 4-11	1-18
P,A	US 2004/062805 A1 (VANDECRUYS ROGER PETRUS GEREBERN ET AL) 1 April 2004 (2004-04-01) paragraphs '0073!, '0166! - '0177!, '0180!	1-18

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

1 July 2005

Date of mailing of the international search report

11/07/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Uhl, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2005/000615

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004010998	A	05-02-2004	AU 2003256834 A1	16-02-2004
			AU 2003256921 A1	16-02-2004
			AU 2003261241 A1	16-02-2004
			AU 2003261265 A1	16-02-2004
			BR 0312870 A	14-06-2005
			BR 0312891 A	14-06-2005
			BR 0312948 A	14-06-2005
			BR 0312960 A	14-06-2005
			CA 2492424 A1	05-02-2004
			CA 2492854 A1	05-02-2004
			CA 2493179 A1	05-02-2004
			CA 2493629 A1	05-02-2004
			EP 1531814 A1	25-05-2005
			EP 1539165 A1	15-06-2005
			EP 1536791 A1	08-06-2005
			EP 1536792 A1	08-06-2005
			WO 2004010997 A1	05-02-2004
			WO 2004011002 A1	05-02-2004
			WO 2004010998 A1	05-02-2004
			WO 2004010999 A1	05-02-2004
			US 2005079217 A1	14-04-2005
US 6395029	B1	28-05-2002	AU 2853700 A	01-08-2000
			WO 0041647 A1	20-07-2000
US 6248363	B1	19-06-2001	AU 1798101 A	04-06-2001
			CA 2391923 A1	31-05-2001
			EP 1233756 A1	28-08-2002
			JP 2003517470 T	27-05-2003
			WO 0137808 A1	31-05-2001
			US 2003077297 A1	24-04-2003
			US 2003180352 A1	25-09-2003
			US 2003215496 A1	20-11-2003
			US 2003064097 A1	03-04-2003
US 2004062805	A1	01-04-2004	AU 776645 B2	16-09-2004
			AU 3963800 A	23-10-2000
			BG 105857 A	30-04-2002
			BR 0009437 A	15-01-2002
			CA 2371940 A1	12-10-2000
			CN 1345233 A	17-04-2002
			CZ 20013375 A3	15-05-2002
			EA 5291 B1	30-12-2004
			EE 200100505 A	16-12-2002
			WO 0059477 A1	12-10-2000
			EP 1169024 A1	09-01-2002
			HR 20010700 A1	30-04-2003
			HU 0200611 A2	29-07-2002
			JP 2002541090 T	03-12-2002
			MX PA01009877 A	06-05-2002
			NO 20014724 A	28-09-2001
			NZ 514890 A	30-05-2003
			PL 355096 A1	22-03-2004
			SK 13542001 A3	06-08-2002
			US 6667060 B1	23-12-2003

Anexo 2

34
53

acid or base.

„Protecting group“ means a chemical group that (a) preserves a reactive group from participating in an undesirable chemical reaction; and (b) can be easily removed after protection of the reactive group is no longer required. For example, the benzyl group is a protecting group for a primary hydroxyl function.

„Amino-protecting group“ means a protecting group that preserves a reactive amino group that otherwise would be modified by certain chemical reactions. The definition includes the acetyl group or lower alkanoyl groups with 2 to 4 carbon atoms, in particular the acetyl or propionyl group, the trityl or substituted trityl groups, such as the monomethoxytrityl group, dimethoxytrityl groups such as the 4,4'-dimethoxytrityl, the trichloroacetyl group, the trifluoroacetyl group, and the N-(9-fluorenylmethoxycarbonyl) or „Fmoc“ group, the allyloxycarbonyl group or other protecting groups derived from halocarbonates such as (C₆-C₁₂)aryl lower alkyl carbonates (such as the N-benzyloxycarbonyl group derived from benzylchloro-carbonate), or derived from biphenylalkyl halo-carbonates, or tertiary alkyl halocarbonates, such as tertiary butylhalocarbonates, in particular t-butyl chloro-carbonate, or di(lower)alkyl dicarbonates, in particular di(t-butyl) dicarbonate, the phthalyl group and triphenylmethyl halides such as triphenylmethyl chloride, and trifluoroacetic anhydride.

„Trityl“ means the triphenylmethyl radical (Ph)₃C-.

„Leaving group“ means a labile group that is replaced in a chemical reaction by another group. Examples of leaving groups are halogen, the optionally substituted benzyloxy group, the isopropyloxy group, the mesyloxy group, the tosyloxy group or the acyloxy group.

All the activating and protecting agents employed in the preparation of the compound of Formula (I) must meet

35
54

the following qualifications: (1) their introduction should proceed quantitatively and without racemization of the L-valine component; (2) the protecting group present during the desired reaction should be stable to the
5 reaction conditions to be employed; and (3) the group must be readily removable under conditions in which the ester bond is stable and under which racemization of the L-valine component of the ester does not occur.

The process of the invention may also include the
10 optical resolution of a prodrug of Formula (I). Terminology relating to the stereochemistry and optical resolution of these compounds is described in EP A 0694 547.

„Optional“ or „optionally“ means that a described
15 event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, „optionally substituted phenyl“ means that the phenyl may or may not be substituted and that the
20 description includes both unsubstituted phenyl and phenyl wherein there is substitution;

„optionally followed by converting the free base to the acid addition salt“ means that said conversion may or may not be carried out in order for the process described
25 to fall within the invention, and the invention includes those processes wherein the free base is converted to the acid addition salt and those processes in which it is not.

„Pharmaceutically acceptable“ means that which is useful in preparing a pharmaceutical composition that is
30 generally safe and non-toxic and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

„Pharmaceutically acceptable salts“ means salts which possess the desired pharmacological activity and which are
35 neither biologically nor otherwise undesirable. Such

38/5

salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentane-propionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxy-benzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylene-bis(3-hydroxy-2-naphthoic)acid, 3-phenylpropionic acid, trimethylacetic acid, t-butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxy-naphthoic acids, salicylic acid, stearic acid, muconic acid, and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzene-sulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid and camphorsulfonic acid.

„Enzymatic hydrolysis“ means the hydrolysis of an ester, e.g., an alkanoate such as acetate or propionate, or an aralkanoate such as benzoate, by enzymatic action. The choice of a suitable enzyme is dependent on the structure of the substituent of Z in compound VI, e.g., for Z = lower alkyl, aryl or aralkyl, suitable enzymes are found in the classes of enzymes with EC numbers 3.1.1.1., 3.1.1.3. and 3.1.1.6. For Z = benzyl, a suitable enzyme would be penicillin acylase, EC number 3.5.1.1. A further restriction criterion would be selectivity for non-hydrolysis of the valine ester moiety. Suitable enzyme

preparation are, for example, pig liver esterase,
available from Sigma Chemical Co., St. Louis, MO; Amano
AK, a pseudomonas species lipase, available in crude form
from Amano International; or in purified form as Chiro-
5 CLEC® PC, an enzyme polymer available from Altus Biologics
Inc.

Synthetic Reaction Parameters

Unless specified to the contrary, the reactions
described herein take place at atmospheric pressure within
10 a temperature range from 5°C to 170°C (preferably from
10°C to 50°C; most preferably at „room“ or „ambient“
temperature, e.g., about 20°-30°C). However, there are
clearly some reactions where the temperature range used in
the chemical reaction will be above or below these
15 temperature ranges. Further, unless otherwise specified,
the reaction times and conditions are intended to be
approximate, e.g., taking place at about atmospheric
pressure within a temperature range of about 5°C to about
100°C (preferably from about 10°C to about 50°C; most
20 preferably about 20°-30°C) over a period of about 1 to
about 100 hours (preferably about 5 to 60 hours).
Parameters given in the Examples are intended to be
specific, not approximate. For chemical reactions that
take place at elevated pressures, e.g., hydrogenation/
25 hydrogenolysis reactions, the pressure is given in psi
and/or atm units and indicates pressure above normal or
atmospheric pressure.

Isolation and purification of the compounds and
intermediates described herein can be effected, if
30 desired, by any suitable separation or purification
procedure, such as, for example, filtration, extraction,
crystallization, column chromatography, thin-layer
chromatography or thick-layer chromatography, or a
combination of these procedures. Specific illustrations
35 of suitable separation and isolation procedures can be had
by reference to the examples hereinbelow. However, other

equivalent separation or isolation procedures can, of course, also be used.

Presently Preferred Embodiments

5 While the broadest definition of this invention is set forth in the Summary of the Invention as a process for preparing the compound of Formula (I) and its pharmaceutically acceptable salts, the (R,S) mixture and certain salts are preferred.

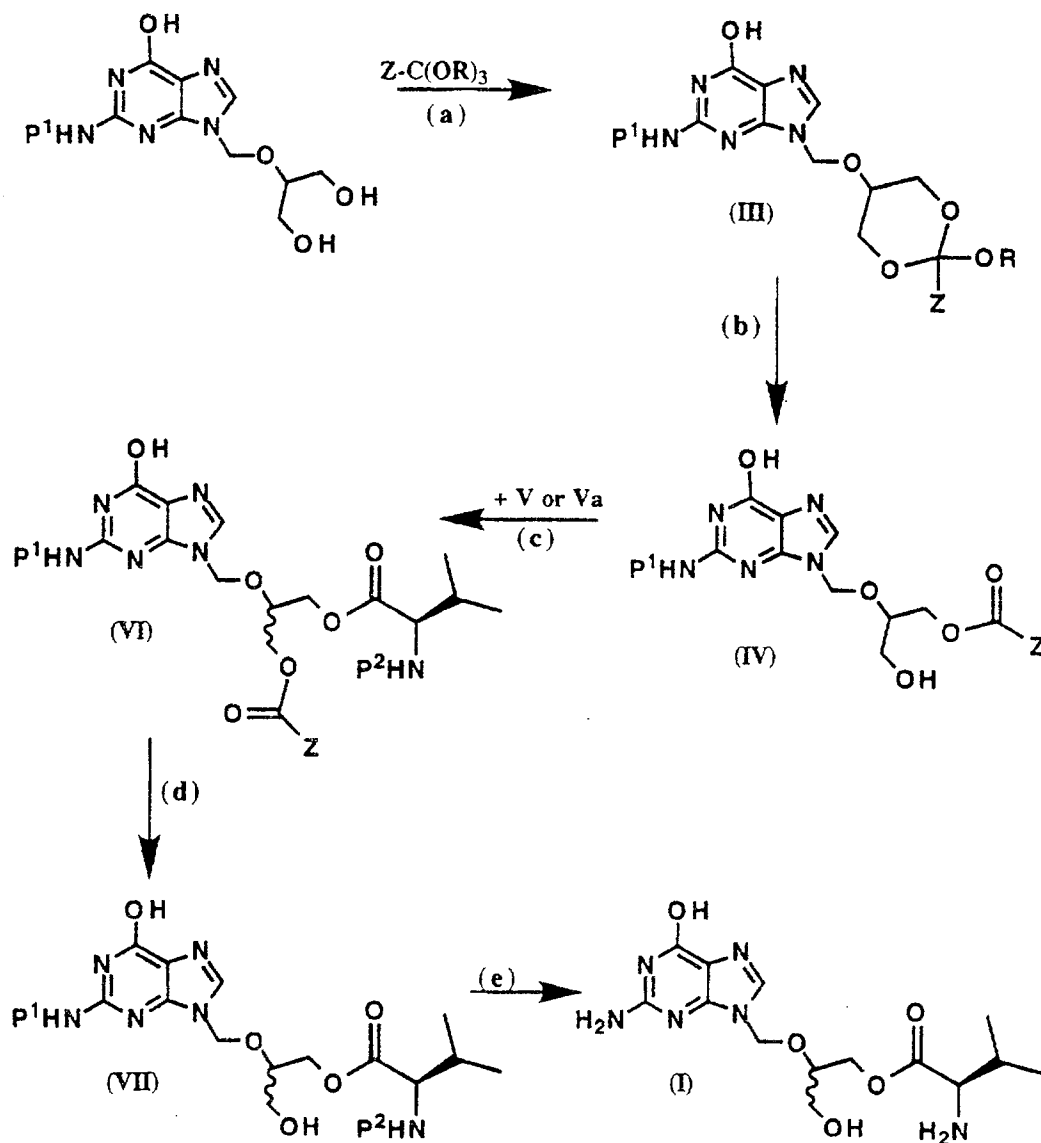
10 The following acids are preferred to form pharmaceutically acceptable salts with the compound of Formula (I): hydrochloric, sulfuric, phosphoric acid, acetic, methanesulfonic, ethanesulfonic, 1,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, p-chlorobenzenesulfonic, 2-naphthalenesulfonic, 15 p-toluenesulfonic and camphorsulfonic acid. Most preferred are strong inorganic acids, such as hydrochloric, sulfuric or phosphoric acid.

20 The most preferred compounds are 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-3-hydroxy-1-propyl L-valinate hydrochloride and acetate. These compounds can be prepared as crystalline materials and therefore can be easily manufactured into stable oral formulations.

25 In any of the processes described herein, a reference to Formulae I, II, III, IV, V, Va, VI or VII refers to such Formulae wherein R, Z, P¹, and P², and A are as defined in their broadest definitions set forth in the Summary of the Invention, with the processes applying particularly to the presently preferred embodiments.

Details of the Synthetic Processes

30 The process of the present invention is depicted in the Reaction Sequence shown below:



wherein P^1 is hydrogen or an amino protecting group, P^2 is an amino protecting group, R is lower alkyl, allyl or aralkyl, and Z is hydrogen, lower alkyl, aryl or aralkyl.

Description of Reaction Sequence

The process for the preparation of a compound of Formula (I) comprises:

Step (a): Transesterification of an orthoester of Formula (II), i.e., $Z-C(OR)_3$, wherein R is lower alkyl,

allyl or aralkyl, and Z is hydrogen, lower alkyl, aryl or aralkyl, with 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-propanediol (ganciclovir) yielding the cyclic orthoester of ganciclovir (Formula (III));

5 Step (b): Hydrolysis of the cyclic orthoester of Formula (III) giving ganciclovir monocarboxylate of Formula (IV);

10 Step (c): Esterification of ganciclovir monocarboxylate of Formula (IV) with an L-valine derivative of Formula (V) or (Va) affording the monocarboxylate-monovalinate of ganciclovir of Formula (VI);

15 Step (d): Selective hydrolysis of the compound of Formula (VI) under basic conditions or alternatively under enzymatic conditions yielding the monovalinate ganciclovir of Formula (VII); and

 Step (e): Removal of any protecting groups affording the compound of Formula (I).

20 Steps (a) through (e) may be carried out as individual steps, that is, the reaction product(s) of each step is/are isolated, purified and identified as necessary.

25 Alternatively, reaction Steps (a) and (b) or Steps (a) through (c) may be carried out without the discrete isolation of the intermediates obtained in Step (a) or Steps (a) and (b). These "one-pot" reactions may afford a key intermediate compound more quickly and directly. Repetitive and time-consuming isolation and purification procedures are avoided, thereby reducing the overall cost
30 of the processes.

One-pot Reaction for Preparing a Compound of Formula (IV)
Steps (a) and (b).

5 An orthoester of Formula (II) is transesterified with
2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-
propanediol (ganciclovir) to yield the cyclic orthoester
of ganciclovir (Formula III), which is directly hydrolyzed
to ganciclovir monocarboxylate (Formula IV).

One-pot Reaction for Preparing a Compound of Formula (VI)
Steps (a), (b) and (c)

10 An orthoester of Formula (II) is transesterified with
2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-
propanediol (ganciclovir) to yield the cyclic orthoester
of ganciclovir (Formula III), which is directly hydrolyzed
to ganciclovir monocarboxylate (Formula IV).

15 The ganciclovir monocarboxylate is then esterified
with an L-valine derivative of Formula (V) or (Va) to form
the compound of Formula (VI), the monocarboxylate-
monovalinate of ganciclovir.

20 In Steps (a) and (b) of the above reaction sequence,
the ganciclovir monoalkanoic ester intermediate of Formula
(IV) is formed with high selectivity and in high yield.
This intermediate allows for mono-esterification by an L-
valine derivative (Step c) to provide the monocarboxylate-
monovalinate of Formula (VI). The acyl (e.g., alkanoyl or
25 benzoyl) group in this intermediate is then selectively
hydrolyzed with base or under enzymatic conditions (Step
d) to give the monovaline ester of Formula (VII) in high
yield.

Pharmaceutically Acceptable Salts

30 Compounds of Formula (I) can optionally be converted
into a pharmaceutically acceptable salt thereof. This
process can also include the conversion of an acid
addition salt of the prodrug of Formula (I) into a non-

41
salt form, the optical resolution of a compound of Formula (I) or the preparation of the compound of Formula (I) in crystalline form.

Protection of Amino Groups

5 The process for producing the compound of Formula (I) may or may not involve protection of the amino group in the 2-position of the guanine base (see the detailed description below of Steps (a) through (c) for the case in which the process is carried out without a protected amino group). For the case when the ganciclovir starting material has a protected 2-amino group the protecting group may be removed by conventional procedures, well-known in the art. For example, if the amino-protecting group is a lower alkanoyl group, basic conditions (pH
10 between 8 to 11) are employed to remove the protecting group. For example, 2-N-acetyl-ganciclovir is treated with an alkaline reagent such as ammonium hydroxide, sodium or potassium carbonate or sodium or potassium hydroxide until the removal of the acetyl group is complete. In general,
15 this reaction will be conducted in the presence of a suitable solvent such as a lower alkanol. Preferably the starting material is dissolved in methanol and a stoichiometric excess of ammonium hydroxide is added. The reaction temperature is kept between 0°C to 50°C,
20 preferably at room temperature. After the reaction is complete (which can be determined by TLC), another solvent may be added to facilitate isolation of the de-protected product, such as ethyl ether, which leads to precipitation of the de-acylated product which can be isolated using
25 conventional separation methods, e.g., filtration.
30

Starting Materials

 All starting materials employed to make the compound of Formula (I) are known, such as ganciclovir, the orthoesters of Formula (II), and the protecting and
35 carboxylic-group-activating reagents.

82

Prior to carrying out Step (b) (esterification step), the amino group of the L-valine derivative must be protected to avoid its interference with the esterification by undesirable amide formation. The various amino-protected L-valine derivatives useful in this invention, such as N-benzyloxycarbonyl-L-valine, BOC-L-valine and FMOC-L-valine, N-acetyl-L-valine and N-benzyloxycarbonyl-N-carboxy-L-valine anhydride, are all commercially available (SNPE Inc., Princeton, NJ, Aldrich Chemical Co., Milwaukee, WI, and Sigma Chemical Co., St. Louis, MO.), or are described in the literature, such as N-allyloxycarbonyl-L-valine. Cyclic amino-protected L-valine derivatives are also described in the literature, as noted above. Of particular interest for the present invention is the benzyloxycarbonyl valine-substituted 2-oxa-4-aza-cycloalkane-1,3-dione (Z-valine-N-carboxy-anhydride, or Z-valine-NCA), which is also commercially available (SNPE Inc., Princeton, NJ). Alternatively, the protecting step may be carried out by conventional methods.

A preferred ganciclovir starting material for the preparation of the compound of the invention is the unprotected ganciclovir (2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-propanediol) which is described in US Patent No. 4,355,032. Other preferred ganciclovir starting materials may have protection at the 2-amino group, such as 2-(2-acyl-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-propanediol, including 2-(2-trifluoroacetyl-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-propanediol, and 2-(2-trichloroacetyl-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-propanediol, and 2-(2-acetyl-amino-1,6-dihydro-6-oxo-purin-9-yl)-methoxy-1,3-propanediol.

Preparation of Activated Derivative of L-valine:

Prior to carrying out Step (c) (esterification step), L-valine must also be activated. At least 1 equivalent of

the protected amino acid and 1 equivalent of a suitable coupling agent or dehydrating agent, for example 1,3-dicyclohexylcarbodiimide or salts of such diimides with basic groups should be employed from the start. Other
5 activators such as N,N'-carbonyldiimidazole may also be used. Further useful dehydrating agents are trifluoroacetic anhydride, mixed anhydrides, acid chlorides, 1-benzotriazolyloxy-tris(dimethylamino)phosphonium
10 hexafluorophosphate, benzotriazole-1-yl-oxy-trispyrroli-dinophosphonium hexafluorophosphate, 1-hydroxybenzotriazole, 1-hydroxy-4-azabenzotriazole, 1-hydroxy-7-azabenzotriazole, N-ethyl-N'-(3-(dimethylamino)propyl)-carbodiimide hydrochloride, 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine, O-(benzotriazol-1-yl)-1,1,3,3-
15 tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, O-(1H-benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate, or O-(7-azabenzotriazol-1-yl)-1,1,3,3-
20 bis(tetramethylene)uronium hexafluorophosphate.

A description of these coupling agents by L. A. Carpino can be found in J. Am. Chem. Soc. 1993, 115, p. 4397-4398.

25 Also useful for this purpose are urethane-protected amino acid N-carboxy anhydrides (UNCAs) which have been described by William D. Fuller et al., J. Am. Chem. Soc. 1990, 112, 7414-7416, which is incorporated herein by reference. Other protected amino acid N-carboxy
30 anhydrides are described in PCT Patent Application WO94/29311, discussed above. In summary, any other reagent that produces an anhydride or another activated derivative of the protected amino acid under mild conditions can be used as the coupling agent.

35 The amino-protected amino acid is dissolved in an inert solvent such as a halogenated lower alkane,

64

preferably dichloromethane under an inert atmosphere, for example nitrogen, and the coupling agent is added (preferably 1,3-dicyclohexylcarbodiimide). The reaction mixture is stirred at temperatures between 0°C and 50°C, preferably at about room temperature. The reaction mixture is filtered and the reaction product (the anhydride of the protected amino acid) isolated. The resulting product is dissolved in a dry inert solvent, such as dimethylformamide, and placed under nitrogen.

10 Preparation of Mono-L-valine Ganciclovir

Step (a): Transesterification

An orthoester of Formula (II), i.e., $Z-C(OR)_3$, where Z is hydrogen, lower alkyl, aryl or aralkyl and R is lower alkyl, allyl or aralkyl, is transesterified with ganciclovir, with the 2-amino group optionally protected, to give the cyclic orthoester of ganciclovir (Formula (III)). Suitable amino-protecting groups are lower alkanoyl groups with 2 to 4 carbon atoms, in particular the acetyl group, especially the trifluoroacetyl and trichloroacetyl groups, and the propionyl group. Other suitable amino-protecting groups are the trityl or substituted trityl groups, such as the monomethoxytrityl group, and the 4,4'-dimethoxytrityl group. Preferred orthoesters are the trimethyl, triethyl and tribenzyl orthoesters. Most preferred are the trimethyl and triethyl orthoacetates and orthopropionates.

To a slurry of ganciclovir and about 3-20 equivalents of orthoester, preferably 2-6 equivalents of orthoester and optionally an inert solvent, preferably a polar solvent such as ethanol, dimethylformamide or dimethylsulfoxide, is added a small amount of an organic acid catalyst such as pyridinium p-toluenesulfonate (PPTS), p-toluenesulfonic acid monohydrate (PTSA), trifluoroacetic acid (TFA), or (1S)-(+)-10-camphorsulfonic acid.

The reaction is carried out at 20°-40°C, preferably at ambient temperature from 1-4 days, preferably 3-12 hours. Optional isolation of the product is achieved by conventional means such as filtration, followed by washing and drying.

Step (b): Hydrolysis

The product of Step (a), the cyclic orthoester of Formula (III) is converted into the monocarboxylate of Formula (IV) by hydrolysis under either acidic or hydrogenolytic conditions.

Acid Hydrolysis

The cyclic orthoester of Formula (III) obtained in Step (a), wherein R is lower alkyl, allyl or aralkyl, and Z is hydrogen, lower alkyl, aryl or aralkyl, is converted into the monocarboxylate of Formula (IV) by acid hydrolysis, preferably with dilute aqueous acetic acid (or formic acid if the orthoester of Formula (III) is an orthoformate), at a temperature of 10°-80°C, preferably at room temperature to 55°C. A polar solvent such as ethanol, isopropylacetate or tert-butyl methyl ether (MTBA), is added to the reaction mixture and the slurry is cooled on an ice bath for 0.5 to 2 hours, preferably 1 hour. The monoalkanoic ester is collected by filtration, washed and dried under vacuum at ambient temperature.

Hydrogenolysis

Alternatively, when R is aralkyl, e.g., benzyl, the conversion to a compound of Formula (IV) can be done under non-hydrolytic conditions by reacting the compound of Formula (III) where R is benzyl with hydrogen under palladium catalysis, resulting in hydrogenolytic removal of the benzyl group. The hydrogenolysis is preferably carried out by dissolving the orthoester intermediate (III) in a solvent under conventional hydrogenation

conditions at 5-100 psi (0.35-7 atm), preferably 10-40 psi (0.7-2.8 atm) hydrogen, in the presence of a catalyst such as a palladium compound, in particular palladium hydroxide on carbon (Pearlman's catalyst), at about 20°-60°C, preferably 20°-35°C, until completion of the reaction. Other suitable catalysts include hydrogenation catalysts in general such as Pd, Pd on carbon and homogeneous hydrogenation catalysts. The solvent system includes aprotic solvents such as dimethylformamide, lower alkanol such as methanol or ethanol. Generally the reaction will be carried out at temperatures between room temperature and the reflux temperature of the solvent system, for example in refluxing ethanol under a hydrogen atmosphere and under exclusion of air. The reaction vessel is preferably swept with nitrogen before charging it with hydrogen.

Step (c): Esterification

In this step, the ganciclovir monocarboxylate intermediate of Formula (IV) obtained in Step (b) is esterified with an activated derivative of amino-protected L-valine of Formula (V) or (Va). Suitable amino-protecting groups for the L-valine derivative are the N-benzyloxycarbonyl (CBZ) group, the tertiary butyloxycarbonyl (t-BOC) group and the N-(9-fluorenylmethoxycarbonyl) or "Fmoc" group.

A solution of at least 1 equivalent (preferably 1.2-1.6 equivalents) of the L-valine derivative, preferably valine anhydride or cyclic valine anhydride, most preferably Z-valine-NCA, in an aprotic polar solvent, preferably dimethylformamide is added to a suspension/slurry of ganciclovir monocarboxylate of Formula (IV) obtained in Step (b) in the presence of 4-dimethylaminopyridine at -10° to 20°C, preferably at 5°-15°C. The reaction mixture is allowed to stir at ambient temperature for 1-5 hours, preferably 2-3 hours. To the reaction mixture is added isopropylacetate. The precipitate is

collected by filtration, washed and dried under vacuum at 30°-60°C, preferably 45°-50°C for 1-3 days, preferably 2 days.

Step (d): Selective Hydrolysis

- 5 The acyl (e.g., alkanoyl or benzoyl) group can be removed from the monocarboxylate-monovalinate of Formula (VI) obtained in Step (c) by basic, acidic or enzymatic hydrolysis.

Basic Hydrolysis

- 10 Alkanoyl groups such as acetyl, propionyl and butyryl are selectively removed, preferably under basic conditions. For example, the monocarboxylate-monovalinate of Formula (VI) is mixed with isopropylacetate/dimethyl-formamide (5:1 to 10:1) and an equal amount of
15 concentrated ammonium hydroxide is added. The reaction mixture is stirred at 10°-50°C, preferably at ambient temperature for 4-100 hours, preferably 12-24 hours. The reaction mixture is then neutralized with 5% aqueous
20 hydrochloric acid, most of the isopropyl acetate is removed under reduced pressure and the product, a white solid, is collected by filtration.

Acidic Hydrolysis

- The formyl group is removed from the monoformate-monovaline ester obtained in Step III preferably by acid
25 hydrolysis. For example, the monoformate-valinate of Formula (VI) is preferably dissolved in methanol/dichloro-methane, preferably methanol/dichloromethane 2:1, and an equal amount of dilute aqueous acid, preferably 2M
30 hydrochloric acid, is added. The reaction mixture is stirred at 10°-50°C, preferably at ambient temperature for 4-30 hours, preferably 8-16 hours. The methanol/aqueous hydrochloric acid layer is separated, and aqueous ammonium hydroxide is added until the pH of the solution is 5-6, preferably 5.5. The solid product is collected by

400
filtration, washed and dried under vacuum at 40°-60°C, preferably at 50°-55°C for 20 to 60 hours, preferably about 40 hours.

Enzymatic Hydrolysis

5 Alternatively, the acyl (e.g., alkanoyl or benzoyl) group can be removed by enzymatic hydrolysis. For example, the monocarboxylate-monovalinate of Formula (VI), obtained in Step (c), is added to propylene glycol/0.2 M phosphate buffer. To the suspension is added either a
10 crude enzyme preparation such as Amano AK, available from Amano International, or preferably a purified enzyme preparation, such as Chiro-CLEC® PC suspension, a pseudomonas species lipase preparation, available from
15 Altus Biologics Inc. This mixture is incubated in a rotary shaker at 100 to 400 rpm, preferably 200-300 rpm for 3 to 30 days, preferably for 12-16 days, at RT to 50°C, preferably about 35°-40°C. The pH is maintained at 6-8 by adding 5% NaOH as necessary. The monovalinate product is isolated by filtration and dried. Further
20 purification can be accomplished by preparative thin layer chromatography or column chromatography. Other cosolvents, such as methanol, polyethyleneglycol (MW 200 or 400) can also be used.

25 Step (e): Final De-protection to Give the Product of Formula (I)

 The valine amino-protecting group in the product of step (d) (Formula (VII)) is removed by a de-protection reaction, preferably in an acidic medium or solvent. For example, for the benzyloxycarbonyl (i.e., carbobenzyloxy =
30 CBZ) group hydrogenolysis is preferred. De-protection under acidic conditions is preferred, as this will ensure that the amino group liberated in the de-protection reaction will be protonated; that is, the free amino group as it is formed in the de-protection reaction will be
35 captured by an at least stoichiometric amount of acid

49

present. Isolating the compound of Formula (I) as an acid addition salt will protect the desired stereoconfiguration of the compound of Formula (I). Therefore, those examples given below that show the de-protection step also show the concomitant salt formation step.

The de-protection reaction is carried out by dissolving the product of Step (d) in an inert solvent, preferably in an acidic solvent, using a hydrogenation catalyst, such as palladium hydroxide on carbon, palladium on carbon or platinum, using elevated hydrogen pressure between 1 and 2000 psi (0.07-140 atm), preferably 5 to 200 psi (0.35-14 atm). Preferably, the inert solvent is a polar solvent, most preferably methanol, containing aqueous 2-12M hydrochloric acid. The hydrogenation is carried out at 5-20 psi (0.35-1.4 atm), preferably 6-8 psi (0.42-0.6 atm) in the presence of palladium hydroxide on carbon (Pearlman's catalyst) at ambient temperature for 2-48 hours, preferably 16-24 hours. After completion of the reaction, the catalyst is removed by filtration and the solution is concentrated under reduced pressure. Crystallization yields the desired product as the hydrochloride salt.

If present, any protecting group at the 2-amino group of the guanine moiety may be removed by conventional procedures, as described above.

If the tertiary butyloxycarbonyl (t-BOC) group is being used as amino-protecting group, its removal is effected with acid, such as HCl and isopropanol as solvent or with trifluoroacetic acid as solvent and acid.

Alternatively, if the esterification step has been carried out with a trityl or substituted trityl-protected ganciclovir derivative, such protecting groups can be removed by treatment with an aqueous alkanoic acid, for example aqueous acetic or trifluoroacetic acid, or hydrochloric acid at temperatures between -20°C and 100°C.

Copia

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-053156- -00007-0000

Fecha: 2011-02-15 15:40:43 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 400 OPOSIOBSERVTER Folios: 66

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 09 053.156
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIÓN EN POLVO DEL VALGANCICLOVIR"
Solicitante : LABORATORIOS ALMIRALL, S.A.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 622 del 19 de Noviembre de 2010

Yo, *ELLANA 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 *PROCAPS 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 "FORMULACIÓN EN POLVO DEL VALGANCICLOVIR", cuyo titular es *F. HOFFMANN-LA ROCHE AG*, 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 **VALGANCICLOVIR**. 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 22 de mayo de 2009, reivindicando prioridad bajo la solicitud US20060874634P del 2006-12-13; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **Nº 622 del 19 de noviembre de 2010**, cuya publicación internacional corresponde a la WO2008/071573 del 2008-06-19.

2.2. La solicitud colombiana **09 053.156** objeto de la presente oposición, se refiere a una forma de dosificación farmacéutica sólida para la administración oral, después de haberse constituido en agua, que consta de: una cantidad terapéuticamente eficaz de valganciclovir clorhidrato; y un ácido orgánico no higroscópico que está presente en una cantidad suficiente para estabilizar al valganciclovir clorhidrato en una cantidad predeterminada de agua; en donde el valganciclovir clorhidrato está presente en una cantidad del 10% al 90% en peso de la composición total; en

donde el ácido orgánico no higroscópico es un aminoácido; en donde el ácido orgánico no higroscópico se elige entre el grupo formado por el ácido fumárico, el ácido succínico y el ácido adípico; en donde el ácido orgánico no higroscópico es el ácido fumárico; en donde el ácido orgánico no higroscópico está presente en una cantidad que baja el pH de la solución constituida del valganciclovir clorhidrato hasta un pH de 3.8 o menos; que contiene además una cantidad eficaz de un agente diluyente no higroscópico; en donde el agente diluyente no higroscópico se elige entre el grupo formado por la manita y la lactosa; en donde el agente diluyente no higroscópico es la manita; en donde el agente diluyente no higroscópico está presente en una cantidad de hasta el 90% en peso de la composición total.

2.3. En primera instancia, se debe advertir que las reivindicaciones 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: WO2005087198 publicada el 22 de septiembre de 2005.
- D2: WO1997027197 publicada el 31 de julio de 1997.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela un procedimiento para la preparación de formas farmacéuticas sólidas de hidroclicloruro de valganciclovir amorfa por vía seca. Particularmente en las reivindicaciones 1, 12 y 13 en adelante, define una forma de dosificación sólida que comprende hidroclicloruro de valganciclovir amorfa, de relleno, aglutinante disgregante y donde el lubricante preparado comprende por lo menos estearil fumarato sódico. Ahora bien, para el año 1997, como se define en el documento D2, ya se define en la literatura combinaciones farmacéuticamente aceptables en la preparación de una composición farmacéutica que incluye ganciclovir y que define que incluyen sales de adición a partir de ácidos inorgánicos como ácido succínico, ácido málico, ácido maleico y ácido fumárico entre otros como se define en las páginas 14, línea 33 a página 15 línea 8. Así las cosas, como lo evidencia dicho documento D1 y D2, en combinación, la presente solicitud se deriva de manera evidente de lo revelado en el estado de la técnica, ya que de manera obvia una persona versada en la materia puede llegar a combinar valganciclovir con un ácido orgánico como ácido fumárico o ácido succínico a partir del documento D2 de 1997 en combinación con la materia revelada en D1 en el 2005.

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

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 053.156 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. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 13 de diciembre de 2006, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a un compuesto farmacéutico que combine valganciclovir con un ácido orgánico como ácido fumárico o ácido succínico, 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 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 con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada *“FORMULACIÓN EN POLVO DEL VALGANCICLOVIR”*, cuyo titular es **F. HOFFMANN-LA ROCHE AG**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 622 del 19 de Noviembre de 2010.

3. PRUEBAS

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

- D1: WO2005087198 publicada el 22 de septiembre de 2005.
- D2: WO1997027197 publicada el 31 de julio de 1997.

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 **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: WO2005087198 publicada el 22 de septiembre de 2005.
 - D2: WO1997027197 publicada el 31 de julio de 1997.

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.