[redacted] ORIO

Industria y Comercio
SUPERINTENDENCIA

02 083632 00

SUPERINDUSTRIA Y COMERCIO
Radicacion : 02083632 00000000
Fecha (MM/DD): 2002-09-18 15:49:52 Folios: 65
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE:

☒ Patente de Invención ☐ Patente de Modelo de Utilidad

☐ Capítulo I ☒ Capítulo II

(2) SOLICITANTE (71)

Nombre **PHARMACIA & UPJOHN COMPANY**

Dirección 301 Henrietta Street Kalamazoo Michigan 49001, Estados Unidos de América

Nacionalidad o Domicilio Mighigan, Estados Unidos de América

Lugar de Constitución Estado de Delaware, Estados Unidos de América

Teléfono 3264270 Fax 6069701

E-mail jlicco@lloredacamacho com

IDENTIFICACION

C C ☐ NIT ☐

C E ☐ Otro ☐

Cual _____

Número _____

(3) REPRESENTANTE O APODERADO

Nombre **JOSE ANTONIO LLOREDA**

Dirección Calle 72 No 5-83 Piso 5o

Teléfono 3264270 Fax 6069701

E-mail jlicco@lloredacamacho com

C C ☒ NIT ☐

C E ☐ Otro ☐

Cual _____

Número 17 159 681 TP 10 784

(4) INVENTOR(ES) (72)

Nombre Ver Anexo

Dirección Ver Anexo

Nacionalidad o Domicilio Estados Unidos de América

(5) PCT (86)

Solicitud Internacional No **PCT/US01/05810** Fecha Marzo 15, 2001

Publicación Internacional No **WO 01/70170 A1** Fecha Septiembre 27, 2001

(6) Título (54) "RECIPIENTE PARA SOLUCION INTRAVENOSA DE LINEZOLIDA"

(7) Clasificación Internacional (51) A61J 1/00 A61L 2/26

(8) Prioridad SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Marzo 22, 2000	60/191,383

(9) Comprobante de Pago No. 02-1.231 **Fecha:** Enero 10, 2002

(10) ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [x] Documento de Representación Legal
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [ ] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [x] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [x] Arte Final 12X12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional
- [x] Otros Informe Búsqueda Preliminar y Publicación con sus traducciones

(11) FIGURA CARACTERISTICA.

(12) Solicito la concesión de la patente,

NOMBRE JOSE ANTONIO LOBEDA

FIRMA _____

C C 17 159 681 Sta T P 10 784

ANEXO

INVENTORES:

SIMS, Sandra, M
WADE, Daniel, C
VALVANI, Shri, C
BOWMAN, Phil, B

DIRECCIONES:

9922 Wexford Drive, Portage, MI 49024 (US)
6218 Hampton Street, Portage, MI 49024 (US)
5695 Blue Spruce Lane, Kalamazoo, MI 49009 (US)
6456 Torrington Road, Kalamazoo, MI 49009 (US)

3

Industria y Comercio

SUPERINTENDENCIA

NIT . 900176089-2

ECIBO OFICIAL DE CAJA : 2 - 1,231
ECHA . ENERO 10 DE 2002

SUPERINDUSTRIA Y COMERCIO
Radicacion : 02003632 00000000 Folios: 65
Fecha (MM): 2002-09-10 15:49:52
Tramite : 011 PCT-PATENT 379 PARE MACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

C O N S I G N A C I O N

EPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LOREDA Y CIA S.A.	RECIBO DE CAJA			1222	10/01/2002	2,160,200.00
LOREDA Y CIA S.A.	RECIBO DE CAJA			81604	28/12/2001	356,640.00
LOREDA Y CIA S.A.	RECIBO DE CAJA			81605	28/12/2001	356,640.00
LOREDA Y CIA S.A.	RECIBO DE CAJA			81606	28/12/2001	356,640.00
LOREDA Y CIA S.A.	RECIBO DE CAJA			81607	28/12/2001	356,640.00
LOREDA Y CIA S.A.	RECIBO DE CAJA			81608	28/12/2001	356,640.00
LOREDA Y CIA S.A.	RECIBO DE CAJA			81609	28/12/2001	356,640.00
LOREDA Y CIA S.A.	RECIBO DE CAJA			81610	28/12/2001	356,640.00
LOREDA Y CIA S.A.	RECIBO DE CAJA			81611	28/12/2001	356,640.00
LOREDA Y CIA S.A.	RECIBO DE CAJA			81612	28/12/2001	356,640.00
LOREDA Y CIA S.A.	RECIBO DE CAJA			81613	28/12/2001	356,640.00

C O N C E P T O

ANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1	TRAMITES DE SOL. DE PATENTE DE IN	378,000.00
			TOTAL : $	378,000.00

ON: TRESCIENTOS SETENTA Y OCHO MIL PESOS

ESPONSABLE :

ECIBO DE CAJA APLICADO AL EXPEDIENTE No.

Carrera 13 No 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail info@sic gov co
www sic gov co
Bogotá, D C , Colombia

ANEXO

El documento que acredita la calidad de REPRESENTANTES LEGALES en Bogotá de los doctores **JOSE ANTONIO LLOREDA y/o GUSTAVO TAMAYO y/o ANGELA MARIA RESTREPO y/o ALICIA LLOREDA RICAURTE** para TODOS LOS ASUNTOS RELACIONADOS CON LA PROPIEDAD INDUSTRIAL de la sociedad peticionaria, que faculta a cada uno de dichos abogados para actuar individualmente, se está presentando con esta solicitud En consecuencia, ruego a usted reconocer la personería de cada uno de dichos Representantes Legales para actuar dentro del presente expediente, a fin de que cualquiera de ellos pueda intervenir en cualquier tiempo respecto de la solicitud en él contenida

JOSE ANTONIO LLOREDA
T P No. 10.784
Código 231

TRADUCCION OFICIAL NO. 022-2001

DE UN DOCUMENTO ESCRITO EN INGLES

Legalizaciones de un poder otorgado por PHARMACIA & UPJOHN COMPANY, con Certificacion Notarial, escritos ambos simultáneamente en inglés y en español

El poder esta firmado por James D Darnley, Jr, como Jefe Asesor & Director de Operaciones de Patentes de E U

Todo el documento viene adherido con un Sello Dorado

CERTIFICADO NOTARIAL

ANGELA A PULFFIO MAYORGA

Estado de Michigan)
) SS
Condado de Kalamazoo)

27 GO 2002

Yo Debra J Marquette, el Notario Público que suscribe, por el presente declaro que James D Darnley, Jr, quien me consta ser la persona cuyo nombre aparece arriba suscrito, fue quien firmó el documento anexo al presente

EN TESTIMONIO he puesto mi firma y sello oficial este 15 de Enero de 2001

(Firma)_____

Firma del Notario

Sello DEBRA J MARQUETTE

Notario Público, Condado de Kalamazoo, MI

Mi Comisión Expira 9/25/2004

(Sello en Relieve) DEBRA J MARQUETTE, NOTARIO PÚBLICO, CONDADO DE KALAMAZOO, MI

Estado de Michigan)
) SS
Condado de Kalamazoo)

Yo. TIMOTHY A SNOW, Escribano del Condado de Kalamazoo, y de la Corte del Circuito para este Condado, siendo el mismo una Corte Registrada con Sello, por el presente certifico que **DEBRA J. MARQUETTE**, ante quien aparece haberse hecho juramento en el instrumento anexo, a la fecha allí establecida, era Notario Público en y para dicho Condado, debidamente comisionada y calificada, y debidamente autorizada por las leyes de este Estado para recibir juramentos, y para tomar y certificar declaraciones y deposiciones Además certifico que la autenticación anterior se encuentra en debida forma legal. y que conozco bien la firma de dicho Notario Público, y realmente creo que el nombre suscrito a este es la firma genuina de dicho Notario Público

COMO NOTARIO TENGO EL CIRCULO DE BOGOTA HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL
27 AGO 2002
JUAN MANUEL BOTERO MEDINA
NOTARIO

ANGELA PULIDO

Tr...
Resol. No ...

En Testimonio de Ello, he puesto mi firma y he fijado el sello de dicha Corte del Circuito, en la ciudad de Kalamazoo, este 19 de Enero de 2001

(Firma) _____, Escribano del Condado

TIMOTHY A SNOW

(Sello en Relieve) Ilegible

APOSTILLA

(Convención de La Haya de 5 de Octubre de 1961)

1 País ESTADOS UNIDOS DE AMÉRICA

Este documento público

2 ha sido firmado por Timothy A Snow

3 actuando en su capacidad de Escribano del Condado de Kalamazoo

4 Posee el sello/estampilla de Corte del Circuito del Condado de Kalamazoo

CERTIFICADO

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CORRESPONDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
27 AGO 2002
JUAN MANUEL ROTERO MEDINA
NOTARIO

5 en Lansing, Michigan 6 El 9 de Febrero de 2001

7 por el Secretario de Estado del Estado de Michigan

8 1598C-01

9 Sello/Estampilla
(Sello En Relieve) EL GRAN SELLO DEL ESTADO DE MICHIGAN A D MDCCCXXXV

10 Firma
(Firma)
Candice S Miller

ANGELA A PULIDO MAYORGA
Traductor Oficial
Resol No 0177 del 97 MinJusticia

Es traducción fiel y completa, de la cual queda copia en el archivo del Traductor para su confrontación, a la cual me remito.

Bogotá, D C 27 de Febrero de 2001

ANGELA A PULECIO MAYORGA
Traductor é Intérprete oficial
Resol. No. 0177 del 97 Min Justicia

MINISTERIO DE RELACIONES EXTERIORES
OFICINA FIRMA PARA EFECTOS DE EL DOCUMENTO DESCRITO A LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO
2001 MAR -1 P.M. 5:50
JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

COMO NOTARIO ABIERTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL DOCUMENTO QUE ME TRAJO A LA VISTA
27 AGO 2002
JUAN MANUEL BOTERO MEDINA
NOTARIO

El abajo firmante, James D. Darnley, Jr. Jefe y Director de Operaciones de Patentes de Estados Unidos de Pharmacia & UpJohn Company, organizada de conformidad con las leyes de Delaware, U.S.A.

con domicilio en

301 Henrietta Street
Kalamazoo, MI 49001, U.S.A.

nombramos por el presente a JOSE ANTONIO LLOREDA, y/o GUSTAVO TAMAYO, y/o ANGELA MARIA RESTREPO, y/o ALICIA LLOREDA, y/o JOSE LLOREDA CAMACHO, domiciliados en Bogotá, Colombia, con oficinas en dicha ciudad, Calle 72 No 5-83, piso 6°, nuestros representantes legales y verdaderos en Bogotá, con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales, con el fin de dar cumplimiento al parágrafo lo del artículo 543 del decreto 410 de 1971

Los doctores JOSE ANTONIO LLOREDA, y/o GUSTAVO TAMAYO, y/o ANGELA MARIA RESTREPO, y/o ALICIA LLOREDA, y/o JOSE LLOREDA CAMACHO, o los apoderados que cualquiera de ellos designe, quedan especialmente facultados para representarnos ante las autoridades colombianas, administrativas, judiciales o de policía, en todos los trámites relativos a la propiedad industrial, a cuyo efecto les facultamos para dar ante dichas autoridades todos los pasos necesarios al objeto indicado, elevar solicitudes, declaraciones, reclamos y recursos, formular descripciones, enmiendas, oposiciones y apelaciones, instaurar cancelaciones y amparos administrativos, abonar todos los impuestos y cuotas y efectuar todo otro pago determinado por la ley; recibir todos los documentos y valores, dando el descargo respectivo, llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses, y en caso de producirse oposición, pasando los antecedentes a los tribunales, quedan facultados para tomar intervención como demandantes o demandados ante los jueces que sean competentes, pudiendo transar, someter a árbitros, desistir, percibir y apelar, con todas las demás facultades que resulten necesarias, y por el presente declaramos desde ahora válido y bueno cuanto dichos representantes y/o los apoderados que cualquiera de ellos nombre hicieren en nuestro beneficio

Asimismo, facultamos a los doctores JOSE ANTONIO LLOREDA, y/o GUSTAVO TAMAYO, y/o ANGELA MARIA RESTREPO y/o ALICIA LLOREDA, y/o JOSE LLOREDA CAMACHO, para solicitar en la Oficina de Propiedad Industrial la protocolización de este documento y de cualquier poder que cualquiera de ellos otorgue a nombre nuestro

Dado y firmado

The undersigned, James D Darnley, Jr., Chief Counsel & Director of U.S Patent Operations

of Pharmacia & UpJohn Company
301 Henrietta Street
Kalamazoo, MI 49001, USA

hereby appoint, JOSE ANTONIO LLOREDA, and/or GUSTAVO TAMAYO, and/or ANGELA MARIA RESTREPO and/or ALICIA LLOREDA and/or JOSE LLOREDA CAMACHO of Bogota, Colombia, with offices in said town, Calle 72 No 5-83, Sixth Floor, our true and legal representatives in Bogotá, with power to receive notifications and to appoint judicial or extrajudicial agents, so as to comply with paragraph 1 of article, 543 of decree 410 of 1971

Doctors JOSE ANTONIO LLOREDA, and/or GUSTAVO TAMAYO, and/or ANGELA MARIA RESTREPO and/or ALICIA LLOREDA, and/or JOSE LLOREDA CAMACHO or the agents by any one of them appointed, are especially empowered to represent us before the administrative, judicial or police authorities of Colombia, in all proceedings pertaining to industrial property, for which purpose we authorize them to take before the said authorities all the necessary steps to the said end, to file petitions, declarations, claims, recourses, cancellations and administrative injunction proceedings, to draw up specifications, to make amendments, oppositions and appeals, to pay all installments and effect all other payments prescribed by law; to receive proper receipts, to comply with all other requirements and, in short, to take all those measures which they may deem fit for the protection of our interests-, and in cast, of opposition, where the the proceedings be passed over to the courts, we authorize said agents to act on our behalf, as complainants as well as defendants, before the competent judges, with full powers to make arrangements, to submit to arbitrators, to desist, to collect, to appeal and, in short, with [illegible] powers as may be required, and we hereby declare valid and good all that said representatives and/or the agents by any one of them appointed may do for our benefit.

2 AGO 2002

We also authorize doctors JOSE ANTONIO LLOREDA, and/or GUSTAVO TAMAYO, and/or ANGELA MARIA RESTREPO and/or ALICIA LLOREDA, and/or JOSE LLOREDA CAMACHO, to apply for protocolization of this document and of any power of attorney by any one of them conferred in our name, before the Office of Industrial Property

By _____
James D. Darnley, Jr., Chief Counsel & Director of U S. Patent Operations

Given and signed this

15th day of January, 2001, 2002

NOTA RY SHOULD EXECUTE OTHER SIDE

28341/6278 1CO

NOTARIAL (INDIVIDUO)

...nidos de América
...o de {ss
...ondado de

A los días del mes de de 19
Compareció personalmente ante mí, Notario Público en y por el condado antes citado,

A quien doy fe de conocer y me consta que es/son la persona descrita y firmante del documento que precede, declarando ante mí que otorga el mismo para los fines y propósitos que en él se expresan

Notary Public (Notario Público)

NOTARIAL CERTIFICATE (INDIVIDUAL)

United States of America
State of {ss
County of

On this day of , 19 , personally appeared before me, a Notary Public, in and for the above mentioned county,

to me known to be the person described in and who executed the foregoing document, and who duly acknowledged to me that executed same for the uses and purposes therein expressed

CERTIFICADO NOTARIAL (INDIVIDUO)

Estados Unidos de América
Estado de {ss
Condado de
A los días del mes de de 19
compareció personalmente ante mí, Notario Público en y por el condado antes citado,

a quien doy fe de conocer y me consta que es/son la persona descrita y firmante del documento que precede, declarando ante mí que otorga el mismo para los fines y propósitos que en él se expresan

Notary Public (Notario Público).

NOTARIAL CERTIFICATE (INDIVIDUAL)

United States of America
State of {ss
County of
On this day of 19 , personally appeared before me, a Notary Public, in and for the above mentioned county,

to me known to be the person described in and who executed the foregoing document, and who duly acknowledged to me that executed same for the uses and purposes therein expressed

CERTIFICADO NOTARIAL (SOCIEDAD)

Estados Unidos de América
Estado de Michigan {ss
Condado de Kalamazoo t
Hoy 15 de Enero de 2001 , compareció James D. Darnley, Jr. , a quien conozco y de quien me consta que firmó el anterior documento, y quien debidamente juramentado declaró y dijo que él es Jefe y Director de Operaciones de Patentes de la compañía nombrada en el documento, que antecede, una sociedad debidamente organizada y existente conforme a las leyes del Estado de , Estados Unidos de América, domiciliada en la ciudad de Kalamazoo , Condado de Kalamazoo Estado de Michigan , Estados Unidos de América y legalmente constituida para un período de duración que aún no ha determinado; que el declarante está a autorizado por dicha Compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y en representación de la expresada Compañía, es el sello oficial de ella y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad

El suscrito Notario ha visto los Estatutos de incorporación firmados en
Estado de Delaware con fecha Mayo 6, 1996 y certifica que de conformidad con la legislación de dicho Estado la anterior declaración juramentada es prueba suficiente de que los hechos sobre que ella versa son ciertos o verdaderos, de lo cual da fe

...v Public (Notario Público)

NOTARIAL CERTIFICATE (CORPORATION)

United States of America
State of Michigan {ss
County of Kalamazoo
On this day of 15 of January 2001 , personally Came James D. Darnley, Jr. to me known, and known to me to be the person who signed the foregoing instrument, who being by me duly sworn did depose and say that he is the Chief Counsel & Director of U.S Patent Operations of Pharmacia & UpJohn Company the company named within, a Corporation organized and existing under the laws of the State of Delaware ,United States of America, domiciled at the City of Kalamazoo , County of Kalamazoo , State of Michigan , United States of America, and legally constituted for a period of tenure not yet expired, that the deponent is authorized by said Company to confer this power of attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purposes of the Company

The undersigned Notary Public has seen the articles of incorporation of said Corporation executed at State of Delaware , under date of May 6, 1996 and hereby certifies that under the laws of said State the foregoing acknowledgment is sufficient proof that the facts therein contained are true, which he attests

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
27 AGO 2002
MANUEL BOTERO MEDINA
NOTARIO

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1. *Country:* **UNITED STATES OF AMERICA**

This public document

2. *has been signed by:* **Timothy A. Snow**

3. *acting in the capacity of:* **Kalamazoo County Clerk**

4. *bears the seal/stamp of:* **Kalamazoo County Circuit Court**

CERTIFIED:

5. *at* **Lansing, Michigan** 6. *the* **9th** *of* **February, 2001**

7. *by* **Secretary of State, State of Michigan**

8. *NO.* **1598C-01**

9. *Seal/Stamp:*

10. *Signature:*

Candice S. Miller

Candice S. Miller

STATE OF MICHIGAN)
) ss
COUNTY OF KALAMAZOO)

I TIMOTHY A SNOW, Clerk of the County of Kalamazoo, and of the Circuit Court for said County, the same being a Court of Record having a Seal, do hereby certify that

DEBRA J. MARQUETTE

before whom oath to the annexed instrument appears to have been made was, at the date hereon stated, a Notary Public in and for said County, duly commissioned and qualified, and duly authorized by the laws of this State to administer oaths, and to take and certify affidavits and depositions I further certify that the foregoing authentication is in due form of law, and that I am well acquainted with the handwriting of the said Notary Public, and verily believe the name subscribed thereto to be the genuine signature of said Notary Public

In Witness Whereof, I have hereunto set my hand and affixed the seal of said Circuit Court, at the City of Kalamazoo, this 19th day of [illegible]
A D 2001

TIMOTHY A. SNOW

County Clerk

JUAN MANUEL BOTERO MEDINA
NOTARIO

B

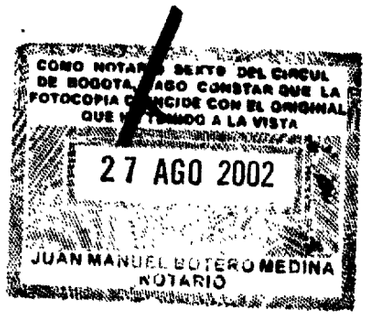
NOTARIAL CERTIFICATE

State of Michigan)
) SS
County of Kalamazoo)
)

I, Debra J. Marquette, the undersigned Notary Public, hereby acknowledge that James D. Darnley, Jr., who is known to me to be the person whose name is subscribed above, executed the document attached thereto.

WITNESS my hand and official seal on this 15th day of January, 2001.

Debra J. Marquette
Notary's Signature
DEBRA J. MARQUETTE
Notary Public, Kalamazoo County, MI
My Commission Expires 9/25/2004



Industria y Comercio

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S A

Item	Expediente No	No de unidades	No de Folio √
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA X	1	√
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS		

Observaciones contiene arte final

Folios 15, 16, 17 : EXTRACTO PUBLICACIONES Y
TARJETAS MACHOP

Pharmacia PDC 00147.PCT1

1/18

15

PCT
REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only
International Application No
International Filing Date
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired)(12 character maximum)* 00147 PCT1

Box No. I TITLE OF INVENTION
CONTAINER FOR LINEZOLID INTRAVENOUS SOLUTION

Box No. II APPLICANT

Name and address *(Family name followed by given name for legal entity full official designation. The address must include postal code and name of country.)*
PHARMACIA & UPJOHN COMPANY
301 Henrietta Street
Kalamazoo, Michigan 49001
United States of America

☐ This person is also inventor

Telephone No.
616-833-1127

Facsimile No
616-833-8897

Teleprinter No

State *(that is, country)* of nationality
US

State *(that is, country)* of residence.
US

This person is applicant for the purpose of ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America Only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address *(Family name followed by given name for legal entity full official designation. The address must include postal code and name of country.)*
SIMS, SANDRA M
9922 Wexford Drive
Portage, Michigan 49024
United States of America

This person is
☐ applicant only
☒ applicant and inventor
☐ inventor only *(if this check-box is marked, do not fill in below)*

State *(that is, country)* of nationality
US

State *(that is, country)* of residence.
US

This person is applicant for the purpose of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America Only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet

Box No. IV AGENT OR COMMON REPRESENTATIVE, OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as ☒ agent ☐ common representative

Name and address *(Family name followed by given name for legal entity, full official designation. The address must include postal code and name of country.)*
STEIN, BRUCE
Intellectual Property Legal Services
Pharmacia & Upjohn Company
301 Henrietta Street
Kalamazoo, Michigan 49001
United States of America

Telephone No
616-833-1127

Facsimile No
616-833-8897

Teleprinter No

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicated a special address to which correspondence should be sent.

Continuation of Box No III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet is not to be included in the request

Name and address *(Family name followed by given name for legal entity, full official designation. The address must include postal code and name of country.)*

WADE, DANIEL C
6218 Hampton Street
Portage, Michigan 49024
United States of America

This person is
☐ applicant only
☒ applicant and inventor
☐ inventor only *(if this check-box is marked, do not fill in below)*

State *(that is, country)* of nationality
US

State *(that is, country)* of residence
US

This person is applicant for the purpose of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America Only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name for legal entity, full official designation. The address must include postal code and name of country.)*

VALVANI, SHRI C
5695 Blue Spruce Lane
Kalamazoo, Michigan 49009
United States of America

This person is
☐ applicant only
☒ applicant and inventor
☐ inventor only *(if this check-box is marked, do not fill in below)*

State *(that is, country)* of nationality
US

State *(that is, country)* of residence.
US

This person is applicant for the purpose of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America Only ☐ the States indicated in the Supplemental Box

Name and address. *(Family name followed by given name for legal entity, full official designation. The address must include postal code and name of country.)*

BOWMAN, PHIL B
6456 Torrington Road
Kalamazoo, Michigan 49009
United States of America

This person is
☐ applicant only
☒ applicant and inventor
☐ inventor only *(if this check-box is marked, do not fill in below)*

State *(that is, country)* of nationality
US

State *(that is, country)* of residence.
US

This person is applicant for the purpose of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America Only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name for legal entity, full official designation. The address must include postal code and name of country.)*

This person is
☐ applicant only
☐ applicant and inventor
☐ inventor only *(if this check-box is marked, do not fill in below)*

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purpose of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America Only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet

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Box No.V DESIGNATI N OF STATES

The following designations are hereby made under Rule 4 9(a) *(mark the applicable check-boxes, at least one must be marked)*

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AE United Arab Emirates
- ☒ AG Antigua and Barbuda
- ☒ AL Albania
- ☒ AM Armenia
- ☒ AT Austria
- ☒ AU Australia
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina
- ☒ BB Barbados
- ☒ BG Bulgaria
- ☒ BR Brazil
- ☒ BY Belarus
- ☒ BZ Belize
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China
- ☒ CR Costa Rica
- ☒ CU Cuba
- ☒ CZ Czech Republic
- ☒ DE Germany
- ☒ DK Denmark
- ☒ DM Dominica
- ☒ DZ Algeria
- ☒ EE Estonia
- ☒ ES Spain
- ☒ FI Finland
- ☒ GB United Kingdom
- ☒ GD Grenada
- ☒ GE Georgia
- ☒ GH Ghana
- ☒ GM Gambia
- ☒ HR Croatia
- ☒ HU Hungary
- ☒ ID Indonesia
- ☒ IL Israel
- ☒ IN India
- ☒ IS Iceland
- ☒ JP Japan
- ☒ KE Kenya
- ☒ KG Kyrgyzstan
- ☒ KP Democratic People's Republic of Korea
- ☒ KR Republic of Korea
- ☒ KZ Kazakhstan
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MA Morocco
- ☒ MD Republic of Moldova
- ☒ MG Madagascar
- ☒ MK The former Yugoslav Republic of Macedonia
- ☒ MN Mongolia
- ☒ MW Malawi
- ☒ MX Mexico
- ☒ MZ Mozambique
- ☒ NO Norway
- ☒ NZ New Zealand
- ☒ PL Poland
- ☒ PT Portugal
- ☒ RO Romania
- ☒ RU Russian Federation
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia
- ☒ SK Slovakia
- ☒ SL Sierra Leone
- ☒ TJ Tajikistan
- ☒ TM Turkmenistan
- ☒ TR Turkey
- ☒ TT Trinidad and Tobago
- ☒ TZ United Republic of Tanzania
- ☒ UA Ukraine
- ☒ UG Uganda
- ☒ US United States of America
- ☒ UZ Uzbekistan
- ☒ VN Viet Nam
- ☒ YU Yugoslavia
- ☒ ZA South Africa
- ☒ ZW Zimbabwe

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ CO. Colombia

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fee) must reach the receiving Office within the 15-month time limit.)*

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TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE BUSQUEDA INTERNACIONAL

(PCT Artículo 18 y Reglas 43 y 44)

Registro de referencia del solicitante o agente	PARA FUTURAS ACCIONES ver Notificación o Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, donde aplique, el ítem 5 a continuación	
00147 PCT1		
Solicitud internacional No PCT/US01/05810	Fecha de registro internacional *(día/mes/año)* 15/03/2001	Fecha de Prioridad (Primera) *(día/mes/año)* 22/03/2000
Solicitante PHARMACIA & UPJOHN COMPANY et al		

Este Reporte de Búsqueda Internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y es transmitido al solicitante Según el Artículo 18 Una copia será transmitida a la Oficina Internacional

Este Reporte de Búsqueda Internacional consta de un total de 2 hojas

☒ También está acompañado de una copia de cada documento técnico anterior citado en este reporte

1 **Bases del reporte**

a Respecto al lenguaje, la búsqueda internacional se llevó a cabo según la solicitud internacional en el lenguaje en el cual se presentó, a menos que se indique de otro modo en este ítem.

☐ la búsqueda internacional se llevó a cabo según la traducción de la solicitud internacional proporcionada a esta Autoridad (Regla 23 1(b)).

b Respecto a una secuencia de ácido nucleótido y/o amino revelado en la solicitud internacional, la búsqueda internacional se llevó a cabo según la lista de la secuencia.

☐ contenido en la solicitud internacional en forma escrita.

☐ presentada junto con la solicitud internacional en forma legible por computador

☐ proporcionada subsiguientemente a esta Autoridad en forma escrita

☐ proporcionada subsiguientemente a esta Autoridad en forma legible por computador

☐ se ha proporcionado la afirmación de que el listado de secuencias escrito proporcionado subsiguientemente no va más allá de la revelación en la solicitud internacional según se presentó

☐ se ha proporcionado la afirmación de que la información registrada en forma legible por computador es idéntica al listado de la secuencia escrita.

2 ☐ Ciertas reivindicaciones no pudieron localizarse (Ver Casilla I)

3 ☐ Falta unidad de invención (ver Casilla II).

4. Respecto al título,

☐ El texto es aprobado según lo presenta el solicitante

☒ Esta Autoridad ha establecido que el texto se lea así

RECIPIENTE PARA SOLUCION INTRAVENOSA DE LINEZOLIDA

5 Respecto al resumen,

☒ El texto es aprobado según lo presenta el solicitante

☐ Esta Autoridad ha establecido el texto de acuerdo con la Norma 38.2(b), según aparece en el Recuadro III El solicitante puede, un mes después de la fecha de haber enviado por correo este reporte de búsqueda internacional, presentar comentarios a esta Autoridad

6. La figura de los dibujos que se publicará con el resumen es la Figura No. _____

☐ como lo sugirió el solicitante

☐ porque el solicitante no sugirió una figura.

☐ porque esta figura caracteriza mejor a la invención

☐ Ninguna de las figuras.

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REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/US01/05810

A CLASIFICACION DE MATERIA

IPC 7 A61J 1/00 A61L 2/26

Según la Clasificación de Patentes Internacional (CPI) o según la clasificación nacional y la CPI

B CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido de símbolos de clasificación)

IPC 7 A61J A61L B65D A61M

Documentación buscada fuera de documentación mínima hasta donde dichos documentos se incluyan en los campos buscados

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, donde sea práctico, buscar términos usados)

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

C DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría *	Citación de documento, con indicación, donde sea apropiado, de los textos relevantes	Relevante a la reivindicación No.
E	WO 01 34128 A (UPJOHN CO, BATTS DONALD H (US)) Mayo 17, 2001 (2001-05-17) página 5, línea 30 -página 7, línea 2	1-31
A	EP 0 067 420 A (TERUMO CORP) Diciembre 22, 1982 (1982-12-22)	

☐ En el recuadro C se enumeran más documentos

☒ En el anexo se enumeran miembros de la familia de patentes

* Categorías especiales de documentos citados

'A' documento que define el estado general de la técnica el cual no se considera de relevancia particular

'E' documento anterior pero publicado en o después de la fecha de presentación internacional

'L' documento que puede arrojar dudas sobre reivindicaciones de prioridad o que se cita para establecer la fecha de publicación de otra citación u otra razón especial (según se especifica)

'O' documento que se refiere a una revelación oral, uso, exhibición u otros medios

'P' documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada

'T' documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y que no está en conflicto con la solicitud pero citado para entender el principio o teoría que sustenta la invención

'X' documento de relevancia particular; la invención reivindicada no puede considerarse nueva o no puede considerarse que comprende un paso inventivo cuando el documento se toma solo

'Y' documento de relevancia particular; la invención reivindicada no puede considerarse que comprende un paso inventivo cuando el documento se combina con uno o más documentos, siendo dicha combinación obvia para una persona experta en la técnica

'&' documento miembro de la misma familia de patentes

Fecha de la terminación real de la búsqueda internacional	Fecha de envío por correo del reporte de búsqueda internacional
Julio 26, 2001	08/08/2001

Nombre y dirección de correo de ISA	Funcionario autorizado
European Patent Office, P B 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel No (+31-70) 340-2040 Tx 31 651 epo nl Fax No. (+31-70) 340-3016	Cousins-Van Steen, G

Forma PCT ISA 210 (segunda hoja) (Julio 1992)

REPORTE DE BUSQUEDA INTERNACIONAL

Informe sobre miembros de familia de patentes

Solicitud Internacional No
PCT/US01/05810

Documento de patente citado en el reporte de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
WO 0134128 A	17-05-2001	NINGUNO	
EP 0067420 A	22-12-1982	JP 1016502 B	24-03-1989
		JP 1709651 C	11-11-1992
		JP 57206447 A	17-12-1982
		AU 547504 B	24-10-1985
		AU 8447882 A	16-12-1982
		BE 893480 A	01-10-1982
		DE 3277580 D	10-12-1987
		DE 8217197 U	21-04-1983
		US 4657540 A	14-04-1987

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below
00147 PCT1		
International application No	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 01/05810	15/03/2001	22/03/2000
Applicant		
PHARMACIA & UPJOHN COMPANY et al		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18 A copy is being transmitted to the International Bureau

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1 **Basis of the report**

a With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b))

b With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing

[ ] contained in the international application in written form

[ ] filed together with the international application in computer readable form

[ ] furnished subsequently to this Authority in written form

[ ] furnished subsequently to this Authority in computer readble form

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2 [ ] Certain claims were found unsearchable (See Box I)

3 [ ] Unity of invention is lacking (see Box II)

4 With regard to the title,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows.

CONTAINER FOR LINEZOLID INTRAVENOUS SOLUTION

5 With regard to the abstract,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6 The figure of the drawings to be published with the abstract is Figure No —

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure

[ ] because this figure better characterizes the invention

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/05810

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61J1/00 A61L2/26

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 A61J A61L B65D A61M

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, CHEM ABS Data, MEDLINE, BIOSIS, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication where appropriate of the relevant passages	Relevant to claim No.
E	WO 01 34128 A (UPJOHN CO ,BATTS DONALD H (US)) 17 May 2001 (2001-05-17) page 5, line 30 -page 7, line 2	1-31
A	EP 0 067 420 A (TERUMO CORP) 22 December 1982 (1982-12-22)	

☐ 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	Date of mailing of the international search report
26 July 2001	08/08/2001

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

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

INTERNATIONAL SEARCH REP RT

Information on patent family members

International Application No
PCT/US 01/05810

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0134128 A	17-05-2001	NONE	
EP 0067420 A	22-12-1982	JP 1016502 B	24-03-1989
		JP 1709651 C	11-11-1992
		JP 57206447 A	17-12-1982
		AU 547504 B	24-10-1985
		AU 8447882 A	16-12-1982
		BE 893480 A	01-10-1982
		DE 3277580 D	10-12-1987
		DE 8217197 U	21-04-1983
		US 4657540 A	14-04-1987

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACION DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación
Septiembre 27, 2001 (27.09.2001)

PCT

(10) Número de Publicación Internacional
WO 01/70170 A1

(51) Clasificación Internacional de Patentes[7] A61J 1/00
A61L 2/26

(21) Número de Solicitud Internacional PCT/US01/05810

(22) Fecha de Registro Internacional Marzo 15, 2001 (15.03 2001)

(25) Idioma de registro Inglés

(26) Idioma de Publicación Inglés

(30) Información de Prioridad
60/191,383 Marzo 22, 2000 (22 03 2000) US

(71) Solicitante *(para todos los estados designados excepto USA)*
PHARMACIA & UPJOHN COMPANY [US/US], 301 Henrietta Street, Kalamazoo, MI 49001 (US)

(72) Inventores, e
(75) Inventores/Solicitantes *(únicamente para USA)* SIMS, Sandra, M [US/US], 9922 Wexford Drive, Portage, MI 49024 (US) WADE, Daniel, C [US/US], 6218 Hampton Street, Portage, MI 49024 (US). VALVANI, Shri, C. [US/US], 5695 Blue Spruce Lane, Kalamazoo, MI 49009 (US). BOWMAN, Phil, B. [US/US], 6456 Torrington Road, Kalamazoo, MI 49009 (US).

(74) Agentes STEIN, Bruce; Intellectual Property Legal Services, Pharmacia & Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

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

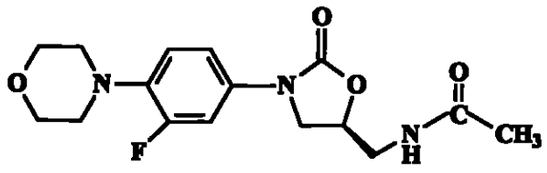
(84) Estados Designados (regionales) Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Patente Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG)

Publicado
— con reporte de búsqueda internacional
— antes de la expiración del límite de tiempo para modificar las reivindicaciones y ser publicada de nuevo en el caso de recibo de modificaciones

Para los códigos de dos letras y otras abreviaturas, refiérase a "Las Notas Guías sobre Códigos y Abreviaturas" que aparecen al comienzo de cada emisión regular de la Gaceta PCT

(54) Título:

"RECIPIENTE PARA SOLUCION INTRAVENOSA DE LINEZOLIDA"



I

(57) Resumen: La presente invención es un recipiente para una solución acuosa intravenosa de un agente gram-positivo de oxazolidinona, por ejemplo, el compuesto de linezolida de fórmula (I) que comprende que el material de la superficie de contacto entre el recipiente y la solución sea una poliolefina

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 September 2001 (27.09.2001)

PCT

(10) International Publication Number
WO 01/70170 A1

(51) International Patent Classification[7] A61J 1/00, A61L 2/26

(21) International Application Number: PCT/US01/05810

(22) International Filing Date: 15 March 2001 (15.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/191,383 22 March 2000 (22.03.2000) US

(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN COMPANY [US/US]. 301 Henrietta Street, Kalamazoo, MI 49001 (US)

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* SIMS, Sandra, M. [US/US], 9922 Wexford Drive, Portage, MI 49024 (US) WADE, Daniel, C [US/US] 6218 Hampton Street, Portage, MI 49024 (US). VALVANI, Shri, C. [US/US], 5695 Blue Spruce Lane, Kalamazoo, MI 49009 (US). BOWMAN, Phil, B. [US/US], 6456 Torrington Road, Kalamazoo, MI 49009 (US).

(74) Agent: STEIN, Bruce, Intellectual Property Legal Services, Pharmacia & Upjohn Company 301 Henrietta Street, Kalamazoo, MI 49001 (US)

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

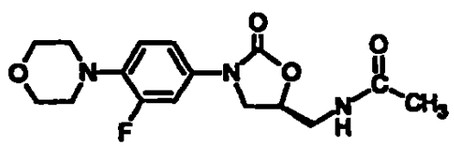
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML,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

WO 01/70170 A1

(54) Title: CONTAINER FOR LINEZOLID INTRAVENOUS SOLUTION



(I)

(57) Abstract: The present invention is a container for an IV aqueous solution of a Gram-positive oxazolidinone agent, such as linezolid as the compound of formula (I) which comprises having the container-solution contact surface material being a polyolefin.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2001 (17.05.2001)

PCT

(10) International Publication Number
WO 01/34128 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US00/28872

(22) International Filing Date
2 November 2000 (02.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/163,990 8 November 1999 (08.11.1999) US

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

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

Published:
— *Without international search report and to be republished upon receipt of that report.*

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

WO 01/34128 A2

(54) Title: ADMIXTURE OF LINEZOLID AND OTHER ANTIBACTERIAL AGENTS

(57) Abstract: The present invention is an aqueous admixture of linezolid and an antibacterial agent selected from the group consisting of gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin, levofloxacin for IV administration.

ADMIXTURE OF LINEZOLID AND OTHER ANTIBACTERIAL AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

None

BACKGROUND OF THE INVENTION

1 Field of the Invention

The present invention is a mixture of sterile solutions of linezolid and particular antibacterial agents

2 Description of the Related Art

US Patent 5,688,792 (EXAMPLE 5) discloses the antibacterial agent, linezolid

The 53rd edition of the Physicians Desk Reference (PDR), Medical Economics Company, Montvale, NJ, 1999 discloses the other antibacterial agents of the invention See for gentamicin (p 964) , tobramycin (599, 1562) aztreonam (p 820), cefazolin (p 3023), ceftazidime (p 1100), piperacillin (p 1531), ciprofloxacin (p 647), ofloxacin (p 2180), and levofloxacin (2192)

It is known to those skilled in the art that mixing solutions of pharmaceutical agents can result in physical and/or chemical instability rendering the mixture unfit for pharmaceutical use

US provisional patent application Serial No 60/191,383 discloses a polyolefin lined container for linezolid IV pharmaceutical formulations

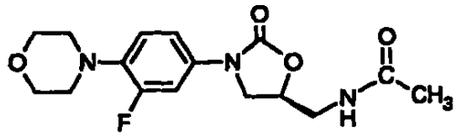
SUMMARY OF INVENTION

Disclosed is an aqueous pharmaceutical composition for IV administration of linezolid and one or more antibacterial agents selected from the group consisting of an aminoglycosides, cephalosporins, aztreonam, quinolones and penicillins and pharmaceutically acceptable salts thereof where such exist

Also disclosed is a method of treating a human with a bacterial infection which comprises IVadministeration to the infected human an aqueous pharmaceutical composition of linezolid and one or more antibacterial agents selected from the group consisting of an aminoglycosides, cephalosporins, aztreonam, quinolones and penicillins and pharmaceutically acceptable salts thereof where such exist

DETAILED DESCRIPTION OF THE INVENTION

Linezolid, (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,



is a known antibacterial agent, see US Patent 5,688,792 (EXAMPLE 5) Linezolid can be used as an oral tablet, capsule or oral suspension or given by IV as a sterile solution

Gentamicin is a known antibacterial agent, see page 964 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution

Tobramycin is a known antibacterial agent, see page 599 and 1562 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution

Aztreonam is a known antibacterial agent, see page 820 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution

Cefazolin is a known antibacterial agent, see page 3023 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution

Ceftazidime is a known antibacterial agent, see page 1100 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution

Piperacillin is a known antibacterial agent, see page 1531 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution

Ciprofoxacin is a known antibacterial agent, see page 647 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution.

Ofloxacin is a known antibacterial agent, see page 2180 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution

Levofloxacin is a known antibacterial agent, see page 2192 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution

Linezolid is a member of a new class of antibacterial agent known as an oxazolidinone and is useful in treating infections caused by gram positive bacteria including gram positive infections that are resistant to other gram positive antibacterial agents

Often in medical treatment a physician does not know for sure whether or not a bacterial infection is caused by gram positive bacteria or gram negative bacteria or both. Therefore, often a physician desires to use an agent(s) which are effective against both gram positive and gram negative bacteria. Hence, often a physician will

combine two agents, one useful against gram positive bacteria and the other useful against gram negative bacteria The following agents are known to be useful against gram negative bacteria, gentamicin, tobramycin, aztreonam The following antibacterial agents are known as 'broad spectrum antibacterials" because they are active against both gram positive and gram negative bacteria, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin

If one combines sterile solutions of two different agents it is quite possible that there will not be chemical or physical compatibility between the two different sterile solutions and/or agents In fact, for this very reason, the corporation conducting the clinical trials on linezolid specifically warned physicians against combining the sterile solution of linezolid and other antibacterial agents.

It now has been found that there is both chemical and physical stability between linezolid sterile solution and sterile solutions of the following antibacterial agents, aminoglycosides, cephalosporins, aztreonam, quinolones and penicillins and pharmaceutically acceptable salts thereof where such exist It is preferred that the antibacterial agent be selected from the group consisting of gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin

When combining an aqueous composition of linezolid with an aqueous composition of the other antibacterial agents the concentration of both linezolid and the other antibacterial agents will be affected by a dilution factor as is well known to those skilled in the art. The actual final concentration of linezolid and/or the other antibacterial agents is not very important The concentration can vary considerably What is critical is that the patient receive an antibacterial effective amount of linezolid and an antibacterial effective amount of the other antibacterial agent _The effective amounts for each of these agents, for adults, is as follows linezolid (about 200 mg to about 600 mg/dose), gentamicin (about 1 mg/kg to about 7 5 mg/kg/dose), tobramycin (about 1 mg/kg to about 7 5 mg/kg/dose), aztreonam (about 500 mg to about 2 g/dose), ciprofloxacin (about 200 mg to about 400 mg/dose), ofloxacin (about 200 mg to about 400 mg/dose), levofloxacin (about 250 mg to about 500 mg/dose), piperacillin sodium (about 2 g to about 4 g/dose), piperacillin/tazobactam (about 2 g to about 4 g/dose based on piperacillin), ceftazidime (about 250 mg to about 2 g/dose) and cefazolin (about 500 mg to about 1 g/dose). One skilled in the art would be able

to calculate an effective amount for children (of various ages and weights) as well as the elderly

It is preferred that the aqueous pharmaceutical composition of the present invention be an aqueous solution It is further preferred that the aqueous solution be a sterile solution

There are different ways that one skilled in the art could make an aqueous pharmaceutical composition of linezolid and an antibacterial agent selected from the group consisting of gentamicin, tobramycin, aztreonam, cefazolin ceftazidime piperacillin, ciprofloxacin, ofloxacin and levofloxacin

First, one can combine an aqueous pharmaceutical composition of linezolid and an aqueous pharmaceutical composition of one of the following agents, gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin If this is done it must be realized that the concentration of each antibacterial agent is being diluted by the other as explained above Alternatively, so as not to dilute the linezolid aqueous pharmaceutical composition, it is preferred to add solid antibacterial agent selected from the group consisting of gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin to the linezolid aqueous pharmaceutical composition Also so as not to dilute an aqueous pharmaceutical composition of one of the following antibacterial agents, gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin, solid linezolid powder can be added to the aqueous pharmaceutical composition of one of the other antibacterial agents. In addition, should more than one of the non-linezolid antibacterial agents be desired for use with linezolid, it can be added in the same way Besides adding solid antibacterial agent to a solution, to keep the dilution factor low, the solid antibacterial agent or linezolid can be suspended or dissolved in an appropriate solvent such as water, ethanol, polyethylene glycol, propylene glycol, DMSO, DMAC, DMI, glycerine and M-pyrol and mixtures thereof The concentrate can then be added to the aqueous pharmaceutical composition

The advantage of admixing is to lower the total volume administered and/or to use the same infusion line The lowering of the total volume to be given to the patient is accomplished in a number of ways by using the admixing of the present invention For example, an number of antibacterial agents come as concentrates to be diluted

with acceptable diluents With these concentrates the diluent used is the linezolid sterile solution there by saving the volume of diluent normally used to dilute the other antibacterial agent Alternatively, other antibacterial agents are marketed as sterile powders which are then compounded into concentrates for dilution With these sterile powders the first step is performed in making the concentrate But rather then using a diluent that has no active ingredient, the concentrate is added to linezolid sterile solution (as described above) This reduces the overall volume of aqueous composition administered to the patient In situations where the antibacterial agent is marketed as a ready to use large volume parenteral sterile solution, there is no way to reduce the volume unless it is combined with linezolid in a concentrated form If it is combined with sterile aqueous linezolid solution the advantage is that the same infusion line can be used for administering both the linezolid and the other antibacterial agent

US Patent 5,688,792 discloses that oxazolidinones can be administered IV The preferred formulation for linezolid IV solution is

Linezolid	2 0 mg/mL
Sodium Citrate Dihydrate (USP)	1 64 mg/mL
Citric Acid Anhydrous (USP)	0 85 mg/mL
Dextrose Monohydrate (USP)	50 24 mg/mL
Hydrochloric Acid (10%) q s to pH 4 8 (pH 4 6 to 5 0)	
Sodium hydroxide (10%) q s to pH 4 8 (pH 4 6 to 5.0)	
Water for Injection (USP)	q s ad 1 0 mL

The linezolid IV solution is formulated by heating water for injection to 60°. Next the sodium citrate, citric acid and dextrose are added and stirred until dissolved An aqueous slurry of linezolid is added to the previous mixture and stirred until dissolved The mixture is cooled to 25° with stirring The pH is measured and adjusted if necessary Last the mixture is brought to volume, if necessary, with water for injection The mixture is filtered, filled into infusion containers, over wrapped and terminally moist heat sterilized

The aqueous solution for IV administration can be placed in the container which is selected from the group consisting of a bag, a bottle, a vial, a large volume parenteral, a small volume parenteral, a prefilled syringe and a cassette It is realized that a vial is a bottle. However, those skilled in the art use the term "bottle" to refers

to larger bottles and "vials" to refer to smaller bottles It is preferred that the container be a bag, a bottle, a vial or a prefilled syringe It is more preferred that the container be a bag or bottle It is most preferred that the container be a bag The shape and/or size of the container is unimportant It is preferred that the container be a bag sufficient to hold 25 to 2,000 mL of IV solution It is preferred that the linezolid mixture be put in bags in amounts of 100, 200 or 300 mL of solution however smaller or larger volumes are acceptable

It is well known to those skilled in the art that pharmaceutical agents administered IV must be sterile While there are a number of methods to sterilize an IV solution, it is preferred to terminally moist heat or steam sterilize IV solutions of oxazolidinones including those of linezolid When the term terminally "moist heat sterilize" is used, it refers to and includes steam sterilization

When terminally moist heat sterilizing an IV solution, the solution is placed in the container in which (1) it will be stored and then transferred to the container from which it will ultimately be administered, or (2) stored and then ultimately administered from the same container to deliver the IV solution to the patient Therefore, it is imperative that the pharmaceutically active ingredient (oxazolidinone, linezolid) not react with the container in which it is to be terminally moist heat sterilized and stored/stored-administered

It has been found that when the container-solution contact surface is made of at least 50% polyolefin there is significantly much less loss of linezolid during and following terminal moist heat sterilization What is essential is that the container-solution contact surface material be primarily a polyolefin; the remainder of the container can be made from polyolefin or other materials It is preferred that the container-solution contact surface is made of from about 50 to about 100% polyolefin It is more preferred that the container-solution contact surface is made of from about 70 to about 90% polyolefin It is more preferred that the container-solution contact surface is made of from about 80% polyolefin It is even more preferred that the container-solution contact surface is made of polyolefin

Polyolefins include, for example, polyethylene, polypropylene, polybutenes, polyisoprenes and polypentenes and copolymers and mixtures thereof It is preferred that the polyolefin be selected from the group consisting of polyethylene and

polypropylene It is more preferred that the polyolefin be polypropylene or mixture of polypropylene and polyethylene

The exact dosage and frequency of administration of the aqueous pharmaceutical composition depends on the particular combination of linezolid and antibacterial agent used the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the antibacterial agents in the patient's blood and/or the patient's response to the particular condition being treated

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims

DEFINITIONS

All temperatures are in degrees Centigrade

Linezolid refers to (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and pharmaceutically acceptable salts thereof

Physiological saline refers to an aqueous 0 9% sodium chloride solution

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v)

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v)

qsad refers to addition of a sufficient quantity of that material to bring the final composition to the specified volume

DMSO refers to dimethylsulfoxide [CH_3-SO-CH_3]

DMAC refers to dimethylacetamide [CH_3-CO-N(CH_3)$_2$]

DMI refers to dimethyl isosorbide.

M-PYROL refers to N-methyl-2-pyrrolidone.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques

PREPARATION 1 Linezolid sterile solution

Linezolid	2 0 mg/mL
Sodium Citrate Dihydrate (USP)	1 64 mg/mL
Citric Acid Anhydrous (USP)	0 85 mg/mL
Dextrose Monohydrate (USP)	50 24 mg/mL
Hydrochloric Acid (10%) q s to pH 4 8 (pH 4 6 to 5 0)	
Sodium hydroxide (10%) q s to pH 4 8 (pH 4 6 to 5 0)	
Water for Injection (USP)	q s ad 1 0 mL

EXAMPLE 1 Linezolid and Gentamicin Sulfate

Linezolid sterile solution (PREPARATION 1) is admixed with commercial gentamicin concentrate. One admixture is stored at 4° and another at 23° The admixtures were sampled at one, three, five days and seven days The samples were tested for both chemical and physical stability The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 5 days at 23°. It is concluded that the admixture of linezolid and commercial gentamicin concentrate is acceptable for human use.

EXAMPLE 2 Linezolid and Tobramycin Sulfate

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial tobramycin concentrate The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 1 day at 23° It is concluded that the admixture of linezolid and commercial tobramycin concentrate is acceptable for human use

EXAMPLE 3 Linezolid and Aztreonam

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with

commercial reconstituted aztreonam The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 7 days at 23° It is concluded that the admixture of linezolid and commercial reconstituted aztreonam is acceptable for human use

EXAMPLE 4 Linezolid and Cefazolin Sodium

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial reconstituted cefazolin The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 3 day at 23° It is concluded that the admixture of linezolid and commercial cefazolin concentrate is acceptable for human use

EXAMPLE 5 Linezolid and Ceftazidime

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial reconstituted ceftazidime The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 1 day at 23° It is concluded that the admixture of linezolid and commercial ceftazidime concentrate is acceptable for human use

EXAMPLE 6 Linezolid and Piperacillin Sodium

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial reconstituted piperacillin The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 3 days at 23° It is concluded that the admixture of linezolid and commercial piperacillin concentrate is acceptable for human use

EXAMPLE 7 Linezolid and Ciprofloxacin

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial ciprofloxacin concentrate The results of the samples show there is good chemical and physical stability over 7 days at 23° It is concluded that the admixture of linezolid and commercial ciprofloxacin concentrate is acceptable for human use

EXAMPLE 8 Linezolid and Ofloxacin

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial ofloxacin concentrate The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 7 days at 23° It is concluded that the admixture of linezolid and commercial ofloxacin concentrate is acceptable for human use

EXAMPLE 9 Linezolid and Levofloxacin

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial levofloxacin concentrate The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 7 days at 23° It is concluded that the admixture of linezolid and commercial levofloxacin concentrate is acceptable for human use

CLAIMS

1 An aqueous pharmaceutical composition for IV administration of linezolid and one or more antibacterial agents selected from the group consisting of an aminoglycosides, cephalosporins, aztreonam, quinolones and penicillins and pharmaceutically acceptable salts thereof where such exist

2 An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is selected from the group consisting of gentamicin tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin, levofloxacin

3 An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is gentamicin

4 An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is tobramycin

5 An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is aztreonam

6 An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is cefazolin.

7 An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is ceftazidime

8 An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is piperacillin

9 An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is ciprofloxacin

10 An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is ofloxacin.

11 An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is levofloxacin

12 An aqueous pharmaceutical composition according to claim 1 where the aqueous composition is a solution

13 An aqueous pharmaceutical composition according to claim 12 where the solution is sterile

14 An aqueous pharmaceutical composition according to claim 1 where the linezolid-antibacterial agent mixture is made by combining an aqueous solution of linezolid and an aqueous solution of the antibacterial agent

15 An aqueous pharmaceutical composition according to claim 1 where the linezolid-antibacterial agent mixture is made by combining an aqueous solution of linezolid and solid antibacterial agent

16 An aqueous pharmaceutical composition according to claim 1 where the linezolid-antibacterial agent mixture is made by combining an aqueous solution of the antibacterial agent and solid linezolid

17 An aqueous pharmaceutical composition according to claim 1 where the linezolid-antibacterial agent mixture is made by combining an aqueous solution of linezolid and a concentrate of the antibacterial agent

18 An aqueous pharmaceutical composition according to claim 1 where the linezolid-antibacterial agent mixture is made by combining an aqueous solution of the antibacterial agent and a concentrate of linezolid

19 An aqueous pharmaceutical composition according to claim 1 where the IV pharmaceutical composition is in a container where the container-solution contact surface material made of at least 50% polyolefin.

20 An aqueous pharmaceutical composition according to claim 19 where the container is selected from the group consisting of a bag, a bottle, a vial, a large volume parenteral, a small volume parenteral, a prefilled syringe and a cassette

21 An aqueous pharmaceutical composition according to claim 20 where the container is a bag, a bottle, a vial and a prefilled syringe

22 An aqueous pharmaceutical composition according to claim 19 where the container-solution contact surface is made of polyolefin or made primarily of polyolefin

23 An aqueous pharmaceutical composition according to claim 22 where the container-solution contact surface is made of from about 50 to about 100% polyolefin

24 An aqueous pharmaceutical composition according to claim 23 where the container-solution contact surface is made of from about 70 to about 90% polyolefin

25 An aqueous pharmaceutical composition according to claim 22 where the container-solution contact surface is made of polyolefin

26 An aqueous pharmaceutical composition according to claim 22 where the polyolefin is selected from the group consisting of polyethylene, polypropylene, polybutenes, polyisoprenes and polypentenes and copolymers and mixtures thereof

27 A method of treating a human with a bacterial infection which comprises IV administration to the infected human an aqueous pharmaceutical composition of linezolid and one or more antibacterial agents selected from the group consisting of an aminoglycosides, cephalosporins, aztreonam, quinolones and penicillins and pharmaceutically acceptable salts thereof where such exist

28 A method of treating a human with a bacterial infection according to claim 27 where the antibacterial agent is selected from the group consisting of gentamicin,

tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin, levofloxacin

29 A method of treating a human with a bacterial infection according to claim 17 where the aqueous composition is a solution

30 A method of treating a human with a bacterial infection according to claim 29 where the solution is sterile

31 A method of treating a human with a bacterial infection according to claim 27 where IV pharmaceutical composition is in a container where the container-solution contact surface material made of at least 50% polyolefin

32 A method of treating a human with a bacterial infection according to claim 31 where the container-solution contact surface is made of polyolefin or made primarily of polyolefin

33 A method of treating a human with a bacterial infection according to claim 32 where the container-solution contact surface is made of polyolefin

34 A method of treating a human with a bacterial infection according to claim 33 where the polyolefin is selected from the group consisting of polyethylene, polypropylene, polybutenes, polyisoprenes and polypentenes and copolymers and mixtures thereof

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number 0 067 420
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number 82105080.4

(22) Date of filing 09.06.82

(51) Int Cl.³ B 65 B 55/02
B 65 D 85/50, A 61 L 2/06
A 61 J 1/00, A 61 M 5/00

(30) Priority 12.06.81 JP 90392/81

(43) Date of publication of application:
22.12.82 Bulletin 82/51

(84) Designated Contracting States:
DE FR SE

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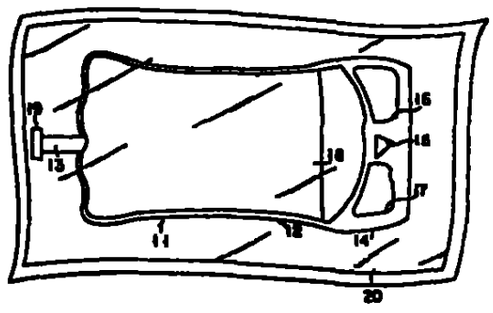
(54) High pressure steam sterilized plastic container holding infusion solution and method for manufacturing the same.

(57) A high pressure steam sterilized plastic container (11) holding an infusion solution (18) therein is prepared first by providing a flexible container (11) made of plastic material and holding an infusion solution (18). The container (11) is then sterilized in a saturated steam atmosphere which is pressurized by a gas inert to the infusion solution (18) and does not contain oxygen. The infusion solution (18) in the container (11) is not deteriorated after the sterilization.

FIG. 1



EP 067 42 A1

High pressure steam sterilized plastic container holding infusion solution and method for manufacturing the same

The present invention relates to a high pressure steam sterilized plastic container holding an infusion solution and to a method for manufacturing the same.

In an attempt to prevent infection by administration of an injection infusion at a hospital, a closed system which does not use an air needle has been recently proposed. In order to provide such a closed system, a flexible plastic container must be used as a container holding an infusion solution in place of a conventional glass bottle or ampoule. This is because fluid therapy in a closed system utilizes flexibility of the container.

Such a plastic container holding an infusion solution must be sterilized before fluid therapy as in the prior art. Sterilization is most commonly performed by high pressure steam sterilization which utilizes saturated steam at a high temperature. However, a plastic material, such as polyvinyl chloride, which has a low permeability to gases will have a high permeability to gases during sterilization in a high pressure steam. Then, oxygen in the atmosphere permeates the container wall to deteriorate the infusion solution therein. Such deterioration of the infusion solution presents a big problem if the infusion solution contains

components, such as a fat emulsion or a concentrated amino acid solution containing tryptophane, which are easily subject to deterioration upon contact with oxygen. Furthermore, a flexible container may be damaged under the normal high pressure steam sterilization conditions.

It is an object of the present invention to provide a high pressure steam sterilized plastic container which holds an infusion solution which has not been deteriorated by sterilization and to a method for manufacturing the same.

In order to achieve this object, there is provided according to the present invention a high pressure steam sterilized plastic container holding an infusion solution, comprising a flexible container of a plastic material and the infusion solution held therein, the container being sterilized in a saturated steam atmosphere which is pressurized by a gas inert to the infusion solution and which contains substantially no oxygen, so that the infusion solution is not substantially deteriorated after sterilization.

The wall of the container is preferably made of polyvinyl chloride or a cross-linked ethylene-vinyl acetate copolymer (to be referred to as an EVA copolymer for brevity hereinafter). Although the EVA copolymer is preferable from the viewpoint of purity since it does not contain a plasticizer, it has a low heat resistance. In order to improve the heat resistance of the EVA copolymer, it is necessary to irradiate the EVA copolymer with an electron beam or the like to obtain a gel content of 50% or more. In order to obtain satisfactory flexibility, the container wall preferably contains vinyl acetate in the amount of 10 to 35% by weight.

The present invention is particularly advantageous where the infusion solution contains at least one component which is easily deteriorated upon contact with oxygen. Examples of such components are parenteral nutrition components such as a fat emulsion and

a concentrated amino acid solution containing tryptophane.

The plastic container holding an infusion solution of the present invention is manufactured by preparing a flexible container of a plastic material holding the infusion solution, and sterilizing the container in a saturated steam atmosphere which is pressurized by a gas inert to the infusion solution and which does not substantially contain oxygen.

The sterilization temperature is usually selected to be 100 to 130°C and preferably 115 to 126°C.

The saturated steam pressure at the sterilization temperature is generally increased by the inert gas by about 10 to 200%. The sterilization atmosphere pressure (gauge pressure) is preferably 1.2 to 2.0 kg/cm^2. The inert gas is preferably nitrogen.

When the container is cooled after sterilization, it is preferable to pressurize the interior of the container by the inert gas in order to maintain the pressure during sterilization. The plastic container holding the infusion solution manufactured in this manner is conveniently packed with a gas-impermeable packing material.

According to the present invention, a flexible plastic container which is sterilized and which holds an infusion solution which is not deteriorated is readily provided.

This invention can be more fully understood from the following detailed description when taken in conjunction with the accompanying drawings, in which:

Fig. 1 is a plan view of a plastic container holding an infusion solution packed with a gas-impermeable packing material, according to the present invention;

Fig. 2 is a schematic view of a high pressure steam sterilizing apparatus used according to the present invention; and

Fig. 3 is a graph showing transmittance T (%) of

the infusion solution which is sterilized according to the present invention as a function of wavelength (nm).

The preferred embodiments of the present invention will now be described with reference to the accompanying drawings.

As shown in Fig. 1, a plastic container holding an infusion solution of the present invention has a flexible container 11. The container 11 is made of a plastic material having a high heat resistance such that it can withstand the steam sterilization. Such material includes polyvinyl chloride, a cross-linked EVA copolymer, or a high-density polyethylene. The container 11 may be prepared by stacking two sheets of such a plastic material and adhering peripheries 12 of these sheets under heating. If the sheets are made of an EVA copolymer, it is preferable to prepare a container body in the manner to be described above and to cross-link it with an electron beam or the like such that the gel content of the copolymer is 50% or more. The gel content is defined as the weight of the cross-linked EVA copolymer after sufficient extraction with a good solvent such as hot xylene divided by the weight before the extraction.

The container 11 has at its one end an infusion solution port 13. The container 11 has at its other end a relatively wide region 14. Within the region 14, a suspension hole 15 for suspending the container 11 and through holes 16 and 17 for other purposes are formed.

An infusion solution 18 is fed into the container 11. The infusion solution 18 may contain components which are easily deteriorated upon contact with oxygen. Examples of such components include the total parenteral nutrition components such as a fat emulsion or a concentrated (generally 10 to 12%) amino acid solution containing tryptophane. After filling the container 11 with the infusion solution 18, the port 13 is closed with a sealing member 19 by thermal sealing, high-frequency

adhesion or the like.

After high pressure steam sterilization, the plastic container holding the infusion solution according to the present invention is preferably packed with a packaging material 20. Preferably the material 20 is a laminate film having a biaxially stretched polypropylene film as an outer film, an ethylene-vinyl alcohol copolymer film as an intermediate film, and a monoaxially stretched polypropylene film as an inner layer. Then, the container is not brought into contact with the ambient air after sterilization, and deterioration of the infusion solution held therein is prevented over a long period of storage time. In order to reduce the amount of air remaining in the package to the minimum, it is preferable to vacuum-pack the container 11 with the packaging material 20. More preferably, a deoxidizer (not shown) is also sealed within the package. The deoxidizer serves to absorb oxygen which may be present in the package and prevents deterioration of the infusion solution 18 due to oxidation during storage.

The container 11 holding the infusion solution 18 is sterilized by a high pressure sterilizing apparatus shown in Fig. 2. This apparatus has an autoclave 21 for sterilization. One end of the autoclave 21 is connected to a steam source such as a boiler 22 through a line 25 via a valve 28. An inert gas source 23 is connected to the autoclave 21 through a line 27, a valve 30, an inert gas reservoir 24, a line 26, and a valve 29. Further, an exhaust valve 32 is connected to the autoclave 21. The inert gas reservoir 24 need not be incorporated. If the inert gas reservoir 24 is omitted, the line 26 and the valve 29 can also be omitted. A cooling water source 33 is also connected to the autoclave 21 through a line 34 and a valve 35.

For sterilization, a plurality of plastic containers holding the infusion solution are placed in the autoclave

21. Steam is introduced into the interior of the autoclave 21 for a predetermined period (e.g., 2 to 10 minutes) to substantially remove air or oxygen therein from the exhaust valve 32. Then, the valve 32 is closed, and steam at a predetermined temperature from the boiler 22 is introduced into the autoclave 21 until it fully fills the autoclave 21, and the valve 28 is closed. An inert gas such as argon, helium or nitrogen (most preferable) from the inert gas reservoir 24 which is used for stocking of the inert gas from the inert gas source 23 is introduced into the autoclave 21 to pressurize the interior of the autoclave 21. After closing the valve 29, sterilization is performed. The sterilization temperature is generally kept within the range of 100 to 130°C and preferably within the range of 115 to 126°C. In order to obtain the satisfactory results, the sterilization atmosphere pressure is increased to a pressure (e.g., about 0.3 to 0.8 kg/cm^2) about 10 to 200% greater than the saturated steam pressure at the sterilization temperature. Conventionally, the pressure during sterilization is regulated and is about 1.2 to 2.0 kg/cm^2 in gauge pressure. The sterilization time is suitably selected to be 10 to 40 minutes. The inert gas is supplemented through the valve 29 during sterilization to keep the predetermined pressure.

After sterilization, a predetermined amount of cooling water from the cooling water source 33 is introduced into the autoclave 21 through the line 34. During cooling, the internal pressure inside the autoclave 21 relatively rapidly decreases. For this reason, the container may be damaged due to the pressure of the infusion solution which is still hot. In order to prevent this, it is preferable to open the valve 29 as the cooling water is introduced into the autoclave 21 to introduce the inert gas into the autoclave 21 and to maintain the internal pressure of

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the autoclave 21 substantially the same as that during sterilization. After the infusion solution within the container is cooled well, the gas within the autoclave 21 is discharged through the exhaust valve 32 to place the interior of the autoclave 21 at normal atmospheric pressure.

The present invention will now be described in further details by way of examples.

Example 1

A 12% amino acid solution (containing tryptophane) was prepared according to the conventional method and filled in a container made of a soft polyvinyl chloride resin. Some samples of containers filled with the infusion solution in this manner were prepared. After placing these containers in a retort-type sterilizer, sterilization was performed at a temperature of 117°C and a gauge pressure of 1.8 kg/cm^2 for 37 minutes. In order to maintain the interior of the sterilizer at the pressure mentioned, saturated steam was pressurized by nitrogen gas. After sterilization was completed, the inert gas was introduced into the autoclave during cooling to maintain the interior of the sterilizer at the pressure same as that during sterilization. In this manner, each container was sterilized without any damage. Table 1 shows sterile states of the 12% amino acid solution with those obtained by the conventional sterilization method.

Table 1

Test Item	Before Sterilization	After Sterilization	
Appearance 1)	Colorless and Transparent	Prior Art	Pale Yellow and Transparent
		Present Invention	Colorless and Transparent
pH 2)	5.89	Prior Art	5.90
		Present Invention	5.89
Dissolved Oxygen (ppm) 3)	1.8	Prior Art	4.8
		Present Invention	0.6

Note: 1) Samples were filled in Nessler tubes in amounts of 30 mm each and were compared with distilled water with naked eyes.

2) The pH was measured with a pH meter (HM-6A) manufactured by Toa Denki K.K.

3) Dissolved oxygen was measured with a DO meter (DO-3) manufactured by Denki Kagaku Keiki K.K.

Fig. 3 is a graph showing light transmittance curves of the 12% amino acid solution within a wavelength range of 600 to 370 nm. The transmittance was measured with a spectrophotometer (200-20 type manufactured by Hitachi, Ltd.) Curve 1 represents the transmittance after sterilization according to the conventional method. Curve 2 represents the transmittance after sterilization according to the present invention. Curve 3 represents the transmittance before sterilization.

Example 2

Refined soy oil, egg yolk lecithin and glycerin were emulsified in distilled water for injection to prepare a fat emulsion which contained refined soy oil in the amount of 10%. The fat emulsion was filled in flexible containers of a cross-linked EVA copolymer. These containers were sterilized in the same manner as in Example 1 except that the sterilization time was 30 minutes. No damage to the containers was observed. Table 2 shows the characteristics of the fat emulsion after sterilization together with those of the fat emulsion after sterilization according to the conventional method.

Table 2

Test Item	Before Sterilization	After Sterilization	
Appearance 1)	White, Non-transparent	Prior Art	Slightly Colored
		Present Invention	White, Non-transparent
pH 2)	7.78	Prior Art	7.52
		Present Invention	7.75
Dissolved Oxygen (ppm) 3)	0.3	Prior Art	6.5
		Present Invention	0.3
Acid Value 4)	0.245	Prior Art	0.253
		Present Invention	0.247

Note: 1) Emulsions in the containers were observed with naked eyes.

2), 3) Same as in Example 1.

4) The acid value was measured according to the ninth amended fat test method of Japanese Pharmacopeia.

Although the present invention has been described with reference to particular embodiments, the present invention is by no means limited to this. For example, the infusion solution is not limited to the total parenteral nutrition components but may be elemental diet components for oral administration. Although these elemental diet components need not be sterilized, they may be stored without deterioration over a long period of time if they are sterilized according to the method of the present invention.

According to the present invention, a flexible plastic container (e.g., heat-resistant polyvinyl chloride or cross-linked EVA copolymer) holding an infusion solution is sterilized in a saturated steam atmosphere (at a gauge pressure of 1.2 to 2.0 kg/cm^2) which is pressurized with the inert gas and which does not substantially contain oxygen and at a high temperature such as 100 to 130°C. Since the inert gas is introduced, deterioration of the infusion solution due to oxidation may be substantially prevented. Since sterilization is performed at a predetermined pressure, damage to the container due to expansion of the infusion solution may also be prevented. Accordingly, the container of the present invention is most conveniently used as a plastic container for holding an infusion solution containing components which are easy to deteriorate upon contact with oxygen such as a fat emulsion and a concentrated amino acid solution containing tryptophane. When the container wall is particularly preferably made of the cross-linked EVA copolymer, the heat-resistance of the cross-linked EVA copolymer is excellent and does not produce any elute.

In summary, the present invention provides a flexible plastic container which is sterilized and which holds an infusion solution which is not deteriorated.

Claims:

1. A high pressure steam sterilized plastic container holding an infusion solution, comprising a flexible container of a plastic material and the infusion solution held therein, the container being sterilized in a saturated steam atmosphere which is pressurized by a gas inert to the infusion solution and which contains substantially no oxygen, so that the infusion solution is not substantially deteriorated after sterilization.

2. A container according to claim 1, wherein a wall of the container is made of a member selected from the group consisting of polyvinyl chloride and an ethylene-vinyl acetate copolymer.

3. A container according to claim 1, wherein the infusion solution contains at least one component which is easily deteriorated upon contact with oxygen.

4. A container according to claim 3, wherein the infusion solution is at least one total parenteral nutrition component.

5. A container according to claim 4, wherein the infusion solution is a concentrated amino acid solution containing tryptophane.

6. A container according to claim 4, wherein the infusion solution is a fat emulsion.

7. A container according to any one of claims 1 to 6, wherein the container is packaged in a packaging material which is impermeable to gases.

8. A method for manufacturing a high pressure steam sterilized plastic container holding an infusion solution, comprising the steps of: preparing a flexible container of a plastic material holding the infusion solution, and sterilizing the container in a saturated steam atmosphere which is pressurized by a gas inert to the infusion solution and which does not substantially contain oxygen.

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9. A method according to claim 8, wherein a sterilization temperature is 100 to 130°C.

10. A method according to claim 8, wherein a saturated steam at the sterilization temperature is pressurized by the inert gas by about 10 to 200%.

11. A method according to claim 8, wherein a sterilization temperature is 115 to 126°C and an atmosphere pressure is 1.2 to 2.0 kg/cm^2 in a gauge pressure.

12. A method according to claim 8, wherein the inert gas is nitrogen.

13. A method according to claim 8, wherein a wall of the container is made of a member selected from the group consisting of polyvinyl chloride and an ethylene-vinyl acetate copolymer.

14. A method according to any one of claims 8 to 13, wherein the infusion solution contains at least one component which is easy to deteriorate upon contact with oxygen.

15. A method according to claim 14, wherein the infusion solution is at least one total parenteral nutrition component.

16. A method according to claim 15, wherein the infusion solution is a concentrated amino acid solution containing tryptophane.

17. A method according to claim 15, wherein the infusion solution is a fat emulsion.

18. A method according to claim 14, further comprising the step of cooling the container after sterilization.

19. A method according to claim 18, wherein sterilization is performed in an autoclave.

20. A method according to claim 19, wherein an inert gas is introduced into the autoclave for maintaining the interior of the autoclave at the pressure during sterilization.

21. A method according to claim 20, wherein

cooling is performed by introducing water into the autoclave.

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FIG. 1

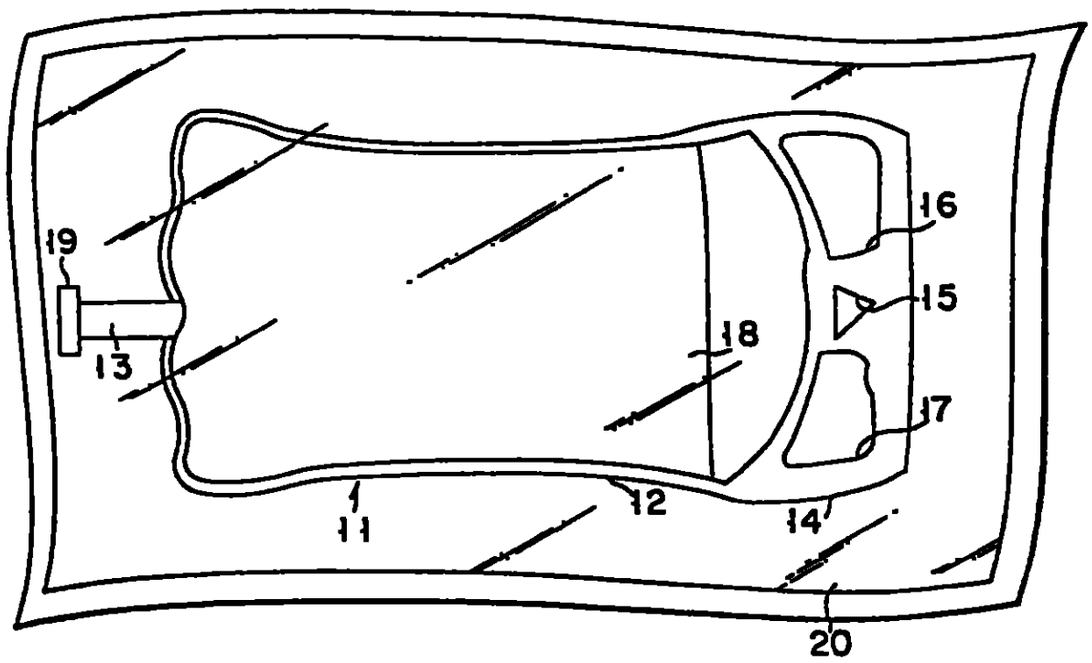


FIG. 2

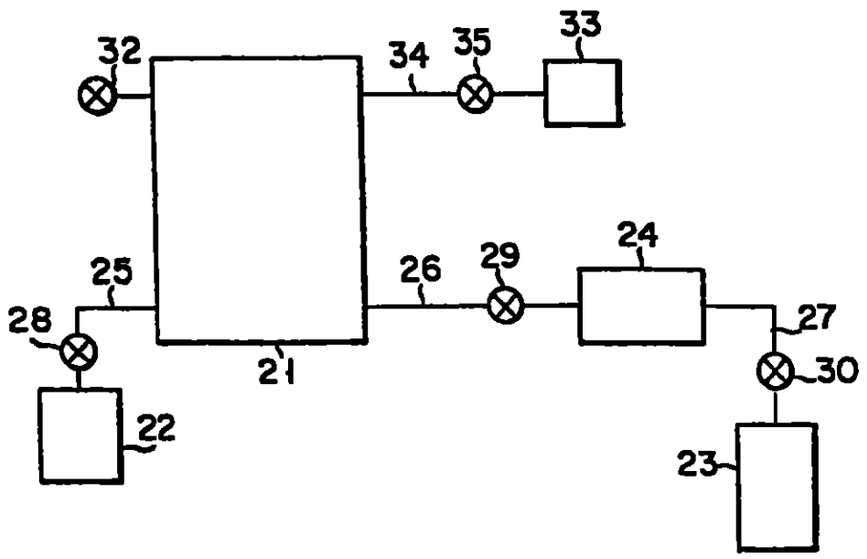
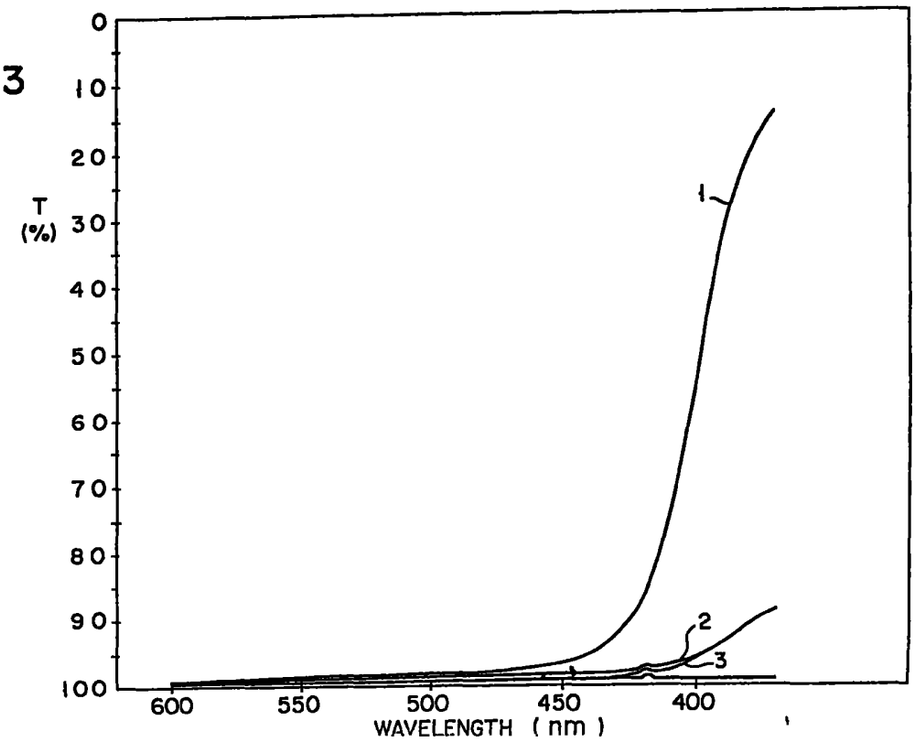


FIG. 3



0067420

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 82105080.4

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
Category	Citation of document with indication where appropriate of relevant passages	Relevant to claim	
X	DE - A1 - 2 363 468 (NEISS O.) * Fig.; pages 4-6 * --	1,4,8-11,15,18-20	B 65 B 55/02 B 65 D 85/50 A 61 L 2/06 A 61 J 1/00 A 61 M 5/00
X	DE - B - 1 933 542 (NEISS M.E.) * Claims 1-3 * --	1,4,8-11,15,18-20	
A	DE - B2 - 2 800 484 (TERUMO CORP.) * Column 11, lines 13-16; column 12, lines 12, 13; column 13, lines 30-44 * --	2,4,7,9,11,13,15,19	TECHNICAL FIELDS SEARCHED (Int.Cl. ³)
A	DE - A1 - 2 933 071 (PHARMACIA AB) * Fig.; page 6, example * ----	4,7,15	A 61 J 1/00 A 61 L 2/00 A 61 M 5/00 B 65 B 55/00 B 65 D 85/00

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same category
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: earlier patent document but published on or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	07-09-1982	LUDWIG

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FIG. 1

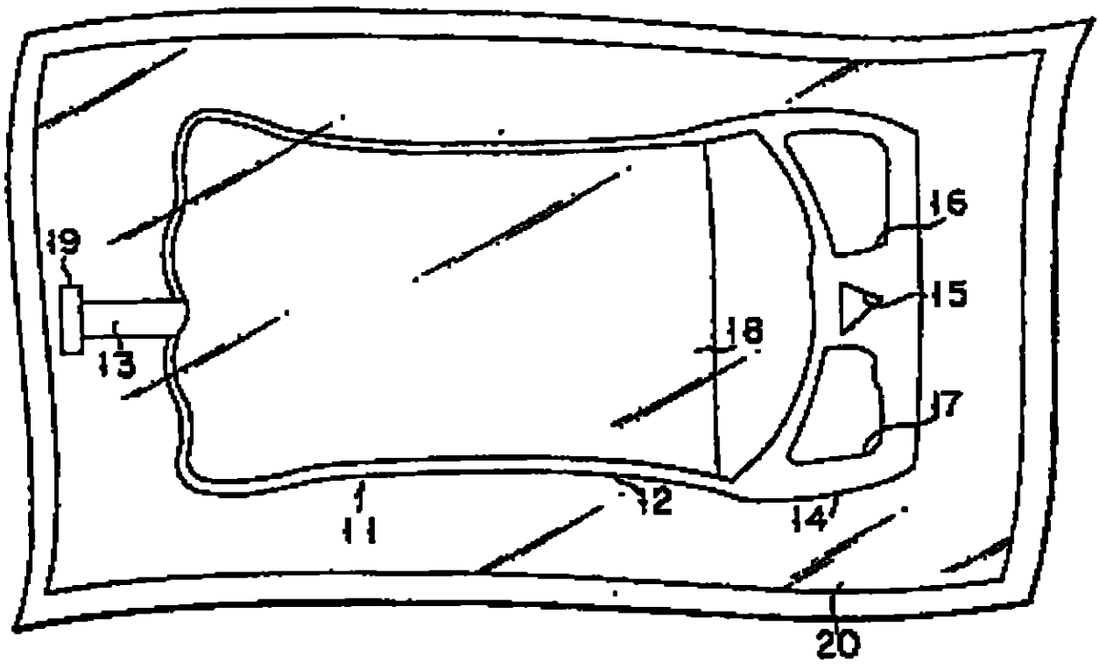


FIG. 2

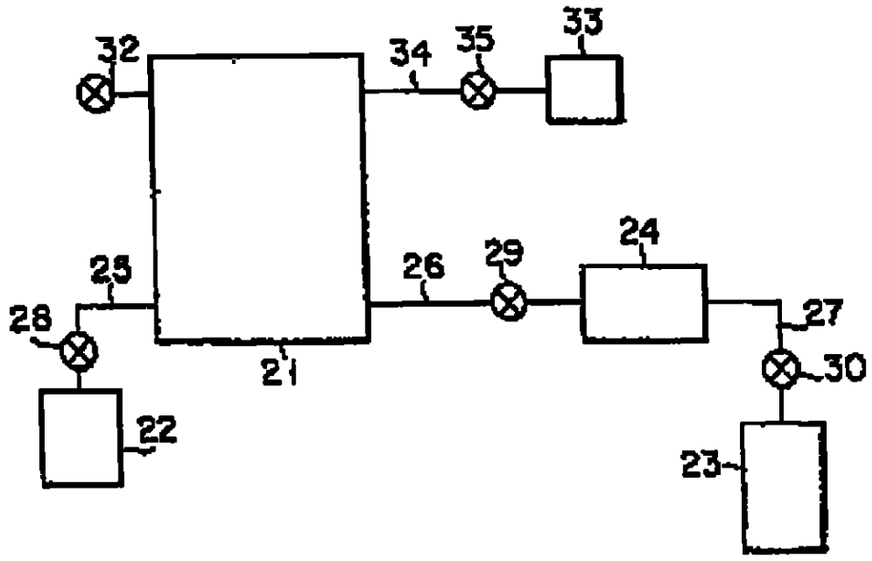
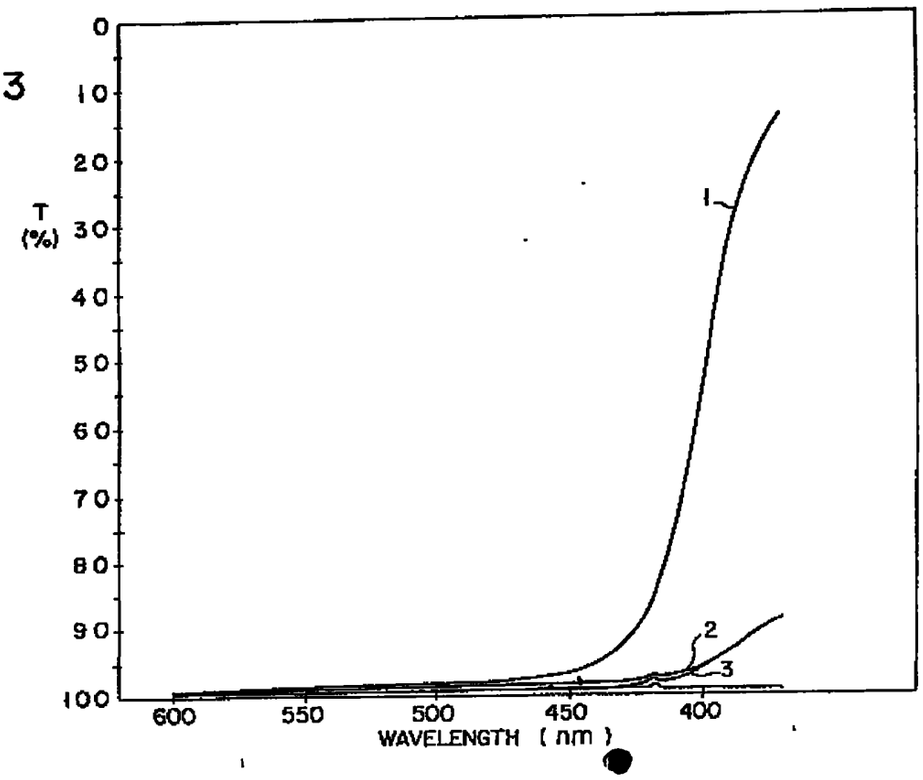


FIG. 3



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0067420

The demand must be filed directly with the competent International Preliminary Examining Authority or if two or more Authorities are competent with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below.

43 46 43

IPEA/_____

PCT

Chapter II

DEMAND

under Article 31 of the Patent Cooperation Treaty

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated)

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of Receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 00147 PCT1
International application No PCT/US01/05810	International filing date *(day/month/year)* 15 March 2001 (15 03 01)	(Earliest) Priority date *(day/month/year)* 22 March 2000 (22 03 00)

Title of invention
CONTAINER FOR LINEZOLID INTRAVENOUS SOLUTION

Box No. II APPLICANT(S)

Name and address *(Family name followed by given name for a legal entity; full official designation. The address must include postal code and name of country.)*	Telephone No 616-833-1127
PHARMACIA & UPJOHN COMPANY 301 Henrietta Street Kalamazoo, Michigan 49001 United States of America	Facsimile No 616-833-8897
	Telephone No

State *(that is, country)* of nationality	State *(that is, country)* of residence
US	US

Name and address *(Family name followed by given name for a legal entity; full official designation. The address must include postal code and name of country.)*

SIMS, SANDRA M
9922 Wexford Drive
Portage, Michigan 49024
United States of America

State *(that is, country)* of nationality	State *(that is, country)* of residence:
US	US

Name and address *(Family name followed by given name for a legal entity; full official designation. The address must include postal code and name of country.)*

WADE, DANIEL C
6218 Hampton Street
Portage, Michigan 49024
United States of America

State *(that is, country)* of nationality	State *(that is, country)* of residence
US	US

☒ Further applicants are indicated on a continuation sheet

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Sheet No 2 | International application No PCT/US01/05810

Continuation of Box No II APPLICANT(S)

If none of the following sub-boxes is used, this sheet is not to be included in the demand

Name and address *(Family name followed by given name for a legal entity full official designation The address must include postal code and name of country.)*

VALVANI, SHRI C
5695 Blue Spruce Lane
Kalamazoo, Michigan 49009
United States of America

State *(that is, country)* of nationality	State *(that is, country)* of residence
US	US

Name and address *(Family name followed by given name, for a legal entity, full official designation The address must include postal code and name of country.)*

BOWMAN, PHIL B
6456 Torrington Road
Kalamazoo, Michigan 49009
Unites States of America

State *(that is, country)* of nationality	State *(that is, country)* of residence
US	US

Name and address *(Family name followed by given name for a legal entity full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality	State *(that is, country)* of residence

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality	State *(that is, country)* of residence

☐ Further applicants are indicated on a continuation sheet

International application No
PCT/US01/05810

45 47 44

Box No. III AGENT OR COMMON REPRESENTATIVE, OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked

☒ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier

Name and address *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PERRY, Robert Edward
Gill Jennings & Every
Broadgate House
7 Eldon Street
London EC2M 7LH
United Kingdom

Telephone No
071-377-1377

Facsimile No
071-377-1310

Teleprinter No
22765

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments.*

1 The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☐ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2 ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed

3 ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)) *(This check box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purpose of international preliminary examination: ENGLISH

☒ which is the language in which the international application was filed

☐ which is the language of a translation furnished for the purposes of international search

☐ which is the language of publication of the international application

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

 | International application No PCT/US01/05810

Box No. IV CHECKLIST

The demand is accompanied by the following elements, referred to in Box No IV, for the purposes of international preliminary examination		For International Preliminary Examining Authority use only: received	not received
1 translation of international application	sheets	☐	☐
2 amendments under Article 34	sheets	☐	☐
3 copy (or, where required translation) of amendments under Article 19	sheets	☐	☐
4 copy (or where required translation) of statement under Article 19	sheets	☐	☐
5 letter	sheets	☐	☐
6 other (*specify*)	sheets	☐	☐

The demand is also accompanied by the item(s) marked below

1 ☐ fee calculation sheet

2 ☐ separate signed power of attorney

3 ☐ copy of general power of attorney' reference number, if any

4 ☐ statement explaining lack of signature

5 ☐ nucleotide and/or amino acid sequence listing in computer readable form

6 ☐ other *(specify)*

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Bruce Stein, Attorney for all Applicants

For International Preliminary Examining Authority use only		
1	Date of actual receipt of DEMAND	
2	Adjusted date of receipt of demand due to CORRECTIONS under Rule 60 1(b)	
3	☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5 below, does not apply	☐ The applicant has been informed accordingly
4	☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80 5	
5	☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82	
For International Bureau use only		
Demand received from IPEA on		

See Notes to the demand form

47 48 45

Box No. VI PRIORITY CLAIM — Further priority claims are indicated in the Supplemental Box ☐

Filing Date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application country	regional application * regional Office	international application receiving Office
item (1) 22 March 2000 (22 03 00)	60/191,383	US		
item(2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) (1)

**Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) ISA/ EP

Request to use results of earlier search — **Date** *(day/month/year)* — **reference to that search** — **Number** — **Country (or regional Office)**

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following	number of sheets
request	04
description (excluding sequence listing part)	08
claims	04
abstract	01
drawings	00
sequence listing part of description	00
Total number of sheets	17

This international application is accompanied by the item(s) marked below

1 ☒ fee calculation sheet
2 ☒ separate signed power of attorney
3 ☒ copy of general power of attorney; reference number if any:
4 ☐ statement explaining lack of signature
5 ☐ priority document(s) identified in Box No VI as item(s)
6 ☐ translation of international application into (language):
7 ☐ separate indications concerning deposited microorganism or other biological material
8 ☐ nucleotide and/or amino acid sequence listing in computer readable form
9 ☒ other (specify) receipt post card, transmittal

Figure of the drawings which should accompany the abstract

Language of filing of the international application English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Bruce Stein

Bruce Stein

For receiving Office use only

1 Date of actual receipt of the purported international application

2 Drawings ☐ received ☐ not received

3 Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application

4 Date of timely receipt of the required corrections under PCT Article 11(2)

5 International Searching Authority (if two or more are competent) ISA/

6. ☐ Transmittal of search copy delayed until search fee is paid

For International bureau use only

Date of receipt of the record copy by the International Bureau

TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(PCT Artículo 36 y Regla 70)

Registro de referencia del solicitante o agente 00147 PCT1	PARA FUTURAS ACCIONES	Ver Notificación o Transmisión del Reporte de Examen Preliminar Internacional (Formato PCT/IPEA/416)
Solicitud Internacional No PCT/US01/05810	Fecha de registro internacional (día/mes/año) 15/03/2001	Fecha de prioridad (día/mes/año) 22/03/2000
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC A61J 1/00		
Solicitante PHARMACIA & UPJOHN COMPANY et al.		

1 Este informe de examen preliminar internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional y se transmite al solicitante de conformidad con el Artículo 36

2 Este REPORTE consta de un total de 2 páginas, incluyendo la carátula

☐ Este reporte también está acompañado de ANEXOS, es decir, páginas de descripción, reivindicaciones y/o dibujos que han sido modificados y son la base de este informe y/o páginas que contienen rectificaciones hechas ante esta Autoridad (ver Regla 70 16 y la Sección 607 de las Instrucciones Administrativas de conformidad con el PCT)

Estos anexos constan de un total de _____ páginas

3 Este informe contiene indicaciones relacionadas con los siguientes ítems.

- I ☒ Bases del Reporte
- II ☐ Prioridad
- III ☒ No establecimiento de opinión respecto a novedad, nivel inventivo y aplicabilidad Industrial
- IV ☐ Falta de unidad de invención
- V ☒ Afirmación razonada de conformidad con el Artículo 35(2) con respecto a novedad, nivel inventivo o aplicabilidad industrial, citaciones y explicaciones que sustentan dicha afirmación
- VI ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos en la solicitud internacional
- VIII ☐ Ciertas observaciones sobre la solicitud internacional

Fecha de presentación de la demanda 01/10/2001	Fecha de terminación de este reporte 19/02/2002
Nombre y dirección de correo de IPEA/ European Patent Office D-80298 Munich Tel (+49-89) 2399-0, Tx 523656 epmu d Fax (+49-89) 2399-4465	Funcionario autorizado FLETCHER A S Tel (+49-89) 2399 2828

I. BASE DEL REPORTE

1 La base de este examen preliminar internacional es la solicitud según se presentó originalmente

III. No establecimiento de opinión respecto a la novedad, nivel inventivo y aplicabilidad industrial

2 La pregunta de si la invención reivindicada parece ser nueva, comprende un nivel inventivo o ser aplicable industrialmente no ha sido ni será el tema del examen internacional preliminar (Artículo 34(4)(a) (i) (ii) PCT, ver también reporte de búsqueda internacional) respecto de

2 1 Solicitudes que tengan una pluralidad innecesaria de reivindicaciones independientes (generalmente no es necesario más de 1 reivindicación independiente en la misma categoría, Artículo 6 PCT),

2 2 Materia tratada no buscada (Artículo 17 (2) (a), Regla 66 1 (e) PCT)

V. Afirmación razonada de conformidad con el Artículo 35(2) respecto a la novedad, nivel inventivo o aplicabilidad industrial, citaciones y explicaciones que soporten dichas afirmaciones.

3 Hasta el punto de que se ha llevado a cabo el examen preliminar internacional (ver el ítem III anterior), se indica lo siguiente (Artículo 35 (2) y (3) (b) y Regla 70 7 y 70 8 (ii) PCT)

A la luz de los documentos citados en el reporte de búsqueda internacional, se considera que la invención tal como es reivindicada en las reivindicaciones independientes, llena los criterios mencionados en el Artículo 33(1) del PCT, es decir, parece ser novedosa, tener un nivel inventivo y ser aplicable industrialmente

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To.
PERRY, Robert Edward
GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
GB-EC2M 7LH London
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

	Date of mailing (day/month/year) 22/02/2002
Applicant's or agent's file reference 00147.PCT1	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US 01/05810	15/03/2001	22/03/2000

Applicant

PHARMACIA & UPJOHN COMPANY et al

1 The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2 A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3 Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4 REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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Form PCT/IPEA/416 (July 1992) P20473

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00147 PCT1		
International application No	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US 01/ 05810	15/03/2001	22/03/2000
International Patent Classification (IPC) or national classification and IPC		
A61J1/00		
Applicant		
PHARMACIA & UPJOHN COMPANY et al		

1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36

2 This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT)

These annexes consists of a total of _____ sheets.

3 This report contains indications relating to the following items:

I ☒ Basis of the report

II ☐ Priority

III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

IV ☐ Lack of unity of invention

V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

VI ☐ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/10/2001	19/02/2002
Name and mailing address of the IPEA/	Authorized officer
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Form PCT/IPEA/409 (cover sheet) (July 1998)

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49-49

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Internation application No PCT/US 01/ 05810

I **Basis of report**

1 The basis of international preliminary examination report is the application as originally filed

III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

2 The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination (Article 34 (4) (a) (i) (ii) PCT, see also international search report) in respect of

2 1 Applications having an unnecessary plurality of independent claims (generally not more than 1 independent claim in the same category is necessary, Article 6 PCT),

2 2 unsearched subject-matter (Article 17 (2) (a), Rule 66 1 (e) PCT)

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

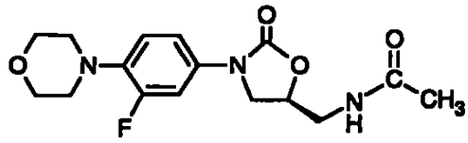
3 To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out (Article 35 (2) and (3) (b) and Rule 70.7 and 70 8 (ii) PCT)

In light of the documents cited in the international search report, it is considered that the invention as claimed in the independent claims meets the criteria mentioned in Article 33 (1) PCT, i e it appears to be novel, to involve an inventive step and to be industrially applicable

RECIPIENTE PARA SOLUCIÓN INTRAVENOSA DE LINEZOLIDA

RESUMEN, OBJETO Y FINALIDAD DE LA INVENCION

La presente invención es un recipiente para una solución acuosa intravenosa de un agente gram-positivo de oxazolidinona, por ejemplo, el compuesto de linezolida de fórmula



que comprende que el material de la superficie de contacto entre el recipiente y la solución sea una poliolefina

RECIPIENTE PARA SOLUCIÓN INTRAVENOSA DE LINEZOLIDA

REFERENCIAS A APLICACIONES RELACIONADAS

Ninguna

ANTECEDENTES DE LA INVENCIÓN

1 Campo de la invención

La invención es el uso de poliolefinas como material de recipientes para soluciones intravenosas que están en contacto con agentes de oxazolidinona, útiles desde el punto de vista farmacéutico, durante y después de la esterilización por calor húmedo

2 Descripción de la técnica relacionada

Las oxazolidinonas son bien conocidas por las personas versadas en la técnica como agentes antibacterianos gram-positivos, véase, por ejemplo, las patentes de los Estados Unidos 5,688,792, 5,529,998, 5,547,950, 5,627,181, 5,700,799, 5,843,967, 5,792,765, 5,684,023, 5,861,413, 5,827,857, 5,869,659, 5,698,574, 5,968,962 y 5,981,528

Existen varios tipos de recipientes conocidos para soluciones acuosas que se administran al paciente por vía intravenosa Los recipientes más comunes para soluciones intravenosas son las botellas de vidrio y de plástico y las bolsas de plástico

La patente de los Estados Unidos 4,803,102 presenta recipientes para soluciones intravenosas en los que el material que está en contacto con la solución acuosa a administrar por vía intravenosa está compuesto principalmente de poliolefina(s)

RESUMEN DE LA INVENCIÓN

Se presenta un recipiente para una solución acuosa intravenosa de un agente gram-positivo de oxazolidinona, en el que el material de la superficie de contacto entre el recipiente y la solución se compone de por lo menos un 50% de poliolefina.

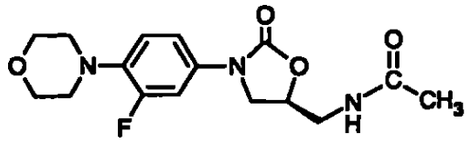
También se presenta un método para evitar la pérdida de un agente gram-positivo de oxazolidinona durante y después de la esterilización final por calor húmedo en una solución acuosa intravenosa cuya esterilización final se llevará a cabo por calor húmedo, método que comprende

(1) colocar la solución acuosa intravenosa en un recipiente a esterilizar, donde la superficie de contacto entre el material del recipiente y la solución se compone de por lo menos un 50% de poliolefina y

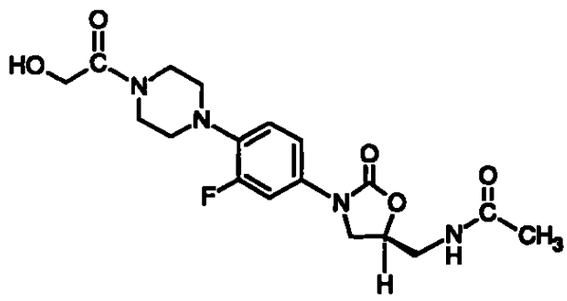
(2) esterilizar el recipiente con la solución por calor húmedo

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Las oxazolidinonas son una nueva clase de agentes antibacterianos gram-positivos que son conocidos por las personas versadas en la técnica, véase por ejemplo la patente de los Estados Unidos 5,688,792 La (S)-N-[[3-[3-fluoro-4-(4-morfolinil)fenil]-2-oxo-5-oxazolidinil]metil]acetamida, que se conoce como linezolida, el compuesto del Ejemplo 5 de la patente de los Estados Unidos 5,688,792, es conocida y tiene la siguiente fórmula química



La (S)-N-[[3-[3-fluoro-4-[4-(hidroxiacetil)-1-piperazinil]-fenil]-2-oxo-5-oxazolidinil]metil]acetamida, que se conoce como eperezolida, el compuesto del Ejemplo 8 de la patente de los Estados Unidos 5,837,870, es conocida y tiene la siguiente fórmula química



La linezolida y la eperezolida pueden producirse mediante los procesos que constan en las patentes de los Estados Unidos 5,688,791 y 5,837,870, así como en la Publicación Internacional WO99/24393 Se producen, preferentemente, mediante el proceso de la patente de los Estados Unidos 5,837,870

Se prefiere que la linezolida producida se utilice en la forma cristalina II, que tiene las características indicadas en el CUADRO A. Una vez que se ha sintetizado la linezolida, se prepara la Forma II cristalina a partir de linezolida de alta pureza enantiomérica Se prefiere que la linezolida tenga una pureza enantiomérica de más de un 98%, se prefiere más que la linezolida tenga una pureza de más de un 99%, y se prefiere aun más que la linezolida tenga una pureza de un 99,5% La linezolida con una pureza enantiomérica superior al 98% a utilizar para preparar la forma cristalina II puede ser una solución o un sólido. El material inicial de linezolida, ya sea sólido o

en solución, se mezcla con un disolvente seleccionado del grupo formado por compuestos de fórmula agua, acetonitrilo, cloroformo, cloruro de metileno, R_1-OH donde R_1 es un grupo alquilo de 1 a 6 átomos de carbono, R_1-CO-R_2, donde R_2 es un grupo alquilo de 1 a 6 átomos de carbono y R_1 se ha definido anteriormente, fenil-sustituido con 1 a 3 R_1, donde R_1 se ha definido anteriormente, R_1-CO-O-R_2, donde R_1 es un grupo alquilo de 1 a 6 átomos de carbono y R_1 se ha definido anteriormente R_1-O-R_2, donde R_1 es un grupo alquilo de 1 a 6 átomos de carbono y R_1 se ha definido anteriormente Se prefiere que el disolvente se seleccione del grupo formado por agua, acetato de etilo, metanol, etanol, propanol, isopropanol, butanol, acetonitrilo, acetona, metil-etil cetona, cloroformo, cloruro de metileno, tolueno, xileno, dietil-éter, o metil-t-butil éter Se prefiere más que el disolvente sea acetato de etilo, acetona, acetonitrilo, propanol, o isopropanol La opción más preferida es que el disolvente sea acetato de etilo La mezcla de linezolida en el disolvente se agita a una temperatura por debajo de los 80° hasta que se formen cristales de Forma II y desaparezcan los cristales de otras formas sólidas, por ejemplo, la Forma I Se prefiere disolver la linezolida en acetato de etilo a una temperatura cercana al punto de ebullición del disolvente Esta mezcla se enfría a una temperatura de aproximadamente 70° La mezcla puede sembrarse con cristales de Forma II a fin de facilitar la cristalización Se prefiere que el producto sólido se enfríe y se agite a una temperatura de aproximadamente 45° a 60° hasta que los sólidos consistan únicamente en cristales de Forma II. La opción más preferida es mantener la suspensión acuosa a una temperatura de aproximadamente 55° Se prefiere mezclar la linezolida y el solvente durante por lo menos 10 minutos, se prefiere aun más mezclar la linezolida y el solvente durante por lo menos 20 minutos, y la opción más preferida es mezclar la linezolida y el solvente durante por lo menos 30 minutos El tiempo y la temperatura variarán según el disolvente seleccionado Cuando se utiliza acetato de etilo, se prefiere mezclar durante un período no inferior a 60 minutos La suspensión acuosa cristalina puede enfriarse más para mejorar el rendimiento, y el producto sólido de la Forma II puede aislarse La mezcla puede enfriarse más y agitarse Otras medidas que se pueden tomar a fin de facilitar la cristalización incluyen, sin limitación alguna, el enfriamiento, la concentración de la solución por evaporación o destilación, o por adición de otros disolventes Los cristales se aíslan mediante procedimientos conocidos por las personas versadas en la técnica.

Como bien saben las personas versadas en la técnica, las oxazolidinonas son útiles como agentes antibacterianos, particularmente contra los organismos gram-positivos La patente de los Estados Unidos 5,688,792 publica que las oxazolidinonas pueden administrarse por vía intravenosa La formulación preferida de la solución intravenosa de linezolida es

Linezolida	2,0 mg/ml
Dihidrato de citrato de sodio (USP)	1,64 mg/ml
Ácido cítrico anhidro (USP)	0,85 mg/ml
Monohidrato de dextrosa (USP)	50,24 mg/ml
Ácido clorhídrico (10%) q s hasta pH 4,8 (pH 4,6 a 5,0)	
Hidróxido de sodio (10%) q s hasta pH 4,8 (pH 4,6 a 5,0)	
Agua para inyección (USP)	q s ad 1,0 ml

La solución intravenosa de linezolida se formula calentando agua para inyección a una temperatura de 50 a 65°, aproximadamente A continuación, se añade el citrato de sodio, el ácido cítrico y la dextrosa y se agita hasta que se disuelvan Se añade una suspensión acuosa de linezolida a la mezcla anterior y se agita hasta que se disuelva La mezcla se enfría a 25° con agitación Se mide el pH y, si es necesario, se ajusta el mismo Por último, si es necesario, se ajusta el volumen de la mezcla con agua para inyección La mezcla se filtra, se vierte en recipientes de infusión, se envuelve y se procede a su esterilización final por calor húmedo

La solución acuosa para la administración por vía intravenosa puede colocarse en un recipiente que se selecciona del grupo formado por una bolsa, una botella, un frasco, un recipiente para administración parenteral de gran volumen, un recipiente para administración parenteral de pequeño volumen, una jeringa prellenada y un cartucho Se sabe que un frasco es una botella. Sin embargo, las personas versadas en la técnica utilizan el término "botella" para referirse a las botellas grandes y "frascos" para referirse a las botellas pequeñas Se prefiere que el recipiente sea una bolsa, una botella, un frasco o una jeringa prellenada Se prefiere más que el recipiente sea una bolsa o botella. La opción más preferida es que el recipiente sea una bolsa. La forma y/o el tamaño del recipiente no tienen importancia Se prefiere que el recipiente sea una bolsa de tamaño suficiente para albergar 25 a 2 000 ml de solución intravenosa Se prefiere que la mezcla de linezolida se coloque en bolsas en cantidades iguales a

100, 200 o 300 ml de solución, no obstante, los volúmenes menores o mayores son aceptables

Como bien saben las personas versadas en la técnica, los agentes farmacéuticos administrados por vía intravenosa deben ser estériles Si bien existen varios métodos para esterilizar una solución intravenosa, se prefiere que la esterilización final de las soluciones intravenosas de oxazolidinonas, incluidas las de linezolida, se lleve a cabo por calor húmedo o por vapor Cuando se usa el término "esterilización final por calor húmedo" , el mismo hace referencia a, e incluye, la esterilización por vapor

En la esterilización final de una solución intravenosa por calor húmedo, la solución se coloca en el recipiente en el cual (1) se va a almacenar y después se va a transferir al recipiente desde el cual se ha de administrar, o (2) se va a guardar y administrar la solución desde el mismo recipiente para suministrar la solución intravenosa al paciente Por consiguiente, es imperativo que el ingrediente farmacéuticamente activo (oxazolidinona, linezolida) no reaccione con el recipiente en el cual se ha de realizar la esterilización final por calor húmedo y donde se guardará, o se guardará y administrará

Se ha hallado que, cuando la superficie de contacto entre el recipiente y la solución se compone de por lo menos un 50% de poliolefina, hay una pérdida significativamente mucho menor de linezolida durante y después de la esterilización final por calor húmedo Lo esencial es que el material de la superficie de contacto entre el recipiente y la solución sea fundamentalmente una poliolefina, el resto del recipiente puede estar hecho de poliolefina o de otros materiales Se prefiere que la superficie de contacto entre el recipiente y la solución se componga de un porcentaje aproximado de un 50 a un 100% de poliolefina. Se prefiere más que la superficie de contacto entre el recipiente y la solución se componga de un porcentaje aproximado de un 70 a un 90% de poliolefina. Se prefiere más que la superficie de contacto entre el recipiente y la solución se componga de un porcentaje aproximado de un 80% de poliolefina. Se prefiere aun más que la superficie de contacto entre el recipiente y la solución se componga de poliolefina.

Entre las poliolefinas se incluyen, por ejemplo, el polietileno, el polipropileno, los polibutenos, los poliisoprenos y los polipentenos y sus polímeros y mezclas Se prefiere que la poliolefina se seleccione del grupo formado por polietileno y

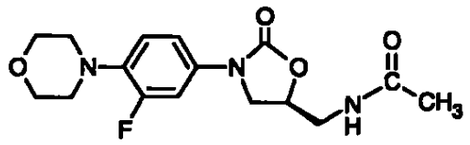
polipropileno Se prefiere más que la poliolefina sea polipropileno o una mezcla de polipropileno y polietileno

DEFINICIONES Y CONVENCIONES

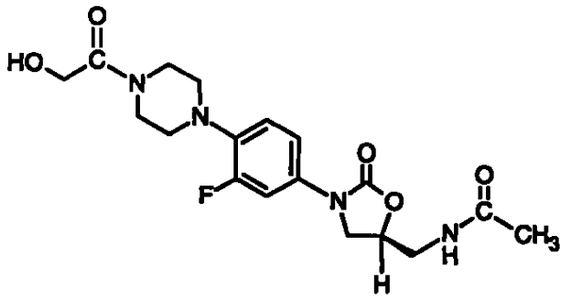
Las definiciones y explicaciones que aparecen a continuación se refieren a los términos utilizados en todo este documento, incluida la especificación y las reivindicaciones

DEFINICIONES

El término *linezolida* se refiere a la (S)-N-[[3-[3-fluoro-4-(4-morfolinil)fenil]-2-oxo-5-oxazolidinil]metil]acetamida, el compuesto de fórmula



El término *eperezolida* se refiere a la (S)-N-[[3-[3-fluoro-4-[4-(hidroxiacetil)-1-piperazinil]-fenil]-2-oxo-5-oxazolidinil]metil]acetamida, el compuesto de fórmula



Todas las temperaturas se expresan en grados centígrados

El término "poliolefinas" (según la definición del Whittington's Dictionary of Plastics, James F Carley, Ed , Technomic Publishing Co , Lancaster, PA, 1993) se refiere a cualquiera de los compuestos pertenecientes al género más amplio de termoplásticos, polímeros de olefinas simples como el etileno, el polipropileno, los butenos, los isoprenos y los pentenos y copolímeros y modificaciones de los mismos

IV significa "intravenoso", o "por vía intravenosa"

"Esterilizar por calor" y "esterilizar por calor húmedo" se refieren a, e incluyen, la esterilización por vapor.

El término "farmacéuticamente aceptable" se refiere a las propiedades y sustancias que son aceptables para el paciente desde el punto de vista fármaco-toxicológico, y al químico farmacéutico fabricante, desde el punto de vista físico-

químico en lo referente a la composición, la formulación, la estabilidad, la aceptación por parte del paciente y la biodisponibilidad

EJEMPLOS

Sin más prolegómenos, se cree que aquellos versados en la técnica estarán en condiciones, utilizando la descripción precedente, de poner en práctica la presente invención en su pleno alcance Los siguientes ejemplos detallados describen cómo preparar los diversos compuestos y/o llevar a cabo los diversos procesos de la invención, debiendo interpretarse como meras ilustraciones, y no como limitaciones en ningún sentido, de la comunicación precedente Las personas versadas en la técnica reconocerán fácilmente variantes apropiadas de los procedimientos, tanto en lo que se refiere a los reactivos como a las condiciones y técnicas de las reacciones

EJEMPLO 1 Solución intravenosa de linezolida (1 ml)

La composición de la solución intravenosa de linezolida es la siguiente

Linezolida	2,0 mg
Dextrosa, USP	50,24 mg
Citrato de sodio, USP	1,64 mg
Ácido cítrico, USP	0,85 mg
Agua para inyección, USP	q s ad 1 ml

La solución intravenosa de linezolida se formula calentando agua para inyección a 60°. A continuación se añade el citrato de sodio, el ácido cítrico y la dextrosa y se agita hasta que se disuelvan Se añade una suspensión acuosa de linezolida a la mezcla anterior y se agita hasta que se disuelva. La mezcla se enfría a 25° con agitación El pH se mide y se ajusta, si es necesario. Por último, si es necesario, se ajusta el volumen de la mezcla con agua para inyección. La mezcla se filtra, se vierte en recipientes de infusión, se envuelve y se procede a su esterilización final por calor húmedo

EJEMPLO 2 Solución intravenosa de linezolida (300 ml)

La solución intravenosa del título se prepara siguiendo el procedimiento general del EJEMPLO 1 y haciendo variantes no esenciales pero utilizando 300 veces la cantidad de cada ingrediente, es decir, 600 mg de linezolida.

CUADRO A

Linezolida, (S)-N-[[3-[3-fluoro-4-(4-morfolinil)fenil]-2-oxo-5-oxazolidinil]metil]acetamida, en la "Forma II" cristalina, tiene el siguiente espectro de difracción de rayos X del polvo cristalino

Distancia interplanar d (Á)	Ángulo 2θ (°)	Intensidad relativa (%)
12,44	7,10	2
9,26	9,54	9
6,37	13,88	6
6,22	14,23	24
5,48	16,18	3
5,28	16,79	100
5,01	17,69	2
4,57	19,41	4
4,50	19,69	2
4,45	19,93	6
4,11	21,61	15
3,97	22,39	23
3,89	22,84	4
3,78	23,52	7
3,68	24,16	1
3,52	25,28	13
3,34	26,66	1
3,30	27,01	3
3,21	27,77	1

y un espectro infrarrojo (IR) (método de aceite mineral) de 3364, 1748, 1675, 1537, 1517, 1445, 1410, 1401, 1358, 1329, 1287, 1274, 1253, 1237, 1221, 1145, 1130, 1123, 1116, 1078, 1066, 1049, 907, 852 y 758 cm^{-1}

REIVINDICACIONES

1 Un recipiente para una solución acuosa intravenosa de un agente gram-positivo de oxazolidinona, en el que el material de la superficie de contacto entre el recipiente y la solución se compone de por lo menos un 50% de poliolefina

2 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 1, donde el recipiente se selecciona del grupo formado por una bolsa, una botella, un frasco, un recipiente para administración parenteral de gran volumen un recipiente para administración parenteral de pequeño volumen, una jeringa prellenada y un cartucho

3 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 2, donde el recipiente es una bolsa, una botella un frasco y una jeringa prellenada

4 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 2, donde el recipiente es una bolsa

5 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 2, donde el recipiente es una botella

6 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 2, donde el recipiente es un frasco

7 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 2, donde el recipiente es una jeringa prellenada

8. Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 1, donde la superficie de contacto entre el recipiente y la solución se compone de poliolefina, o se compone fundamentalmente de poliolefina.

9 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 8, donde la superficie de contacto entre el recipiente y la solución se compone de un porcentaje aproximado de un 50 a un 100% de poliolefina

10 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 9, donde la superficie de contacto entre el recipiente y la solución se compone de un porcentaje aproximado de un 70 a un 90% de poliolefina

11 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 10, donde la superficie de contacto entre el recipiente y la solución se compone de un porcentaje aproximado de un 80% de poliolefina

12 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 1, donde la superficie de contacto entre el recipiente y la solución se compone de poliolefina

13 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 1, donde la poliolefina se selecciona del grupo formado por polietileno, polipropileno, polibutenos, poliisoprenos y polipentenos y sus polímeros y mezclas

14 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 13, donde la poliolefina se selecciona del grupo formado por polietileno y polipropileno

15 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 14, donde la poliolefina es polipropileno

16 Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 1, donde el agente gram-positivo de oxazolidinona se selecciona del grupo formado por linezolida y eperezolida

17. Un recipiente para una solución acuosa intravenosa, de conformidad con la reivindicación 16, donde el agente gram-positivo de oxazolidinona es linezolida.

18 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona, durante y después de la esterilización final por calor húmedo, en una solución acuosa intravenosa cuya esterilización final se llevará a cabo por calor húmedo, método que comprende

(1) colocar la solucion acuosa intravenosa en un recipiente a esterilizar, donde el material de la superficie de contacto entre el recipiente y la solución se compone de por lo menos un 50% de poliolefina y

(2) esterilizar el recipiente con la solución por calor húmedo

19 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona, de conformidad con la reivindicación 18, donde el recipiente se selecciona del grupo formado por una bolsa, una botella un frasco, un recipiente para administración parenteral de gran volumen, un recipiente para administración parenteral de pequeño volumen, una jeringa prellenada y un cartucho

20 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona, de conformidad con la reivindicación 19, donde el recipiente es una bolsa, una botella, un frasco y una jeringa prellenada

21. Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona, de conformidad con la reivindicación 20, donde el recipiente es una bolsa

22 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona, de conformidad con la reivindicación 18, donde la superficie de contacto entre el recipiente y la solución se compone de poliolefina o se compone fundamentalmente de poliolefina

23 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona, de conformidad con la reivindicación 22, donde la superficie de contacto entre el recipiente y la solución se compone de un porcentaje aproximado de un 50 a un 100% de poliolefina

24 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona, de conformidad con la reivindicación 23, donde la superficie de contacto entre el recipiente y la solución se compone de un porcentaje aproximado de un 70 a un 90% de poliolefina

25 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona de conformidad con la reivindicación 24, donde la superficie de contacto entre el recipiente y la solución se compone de un porcentaje aproximado de un 80% de poliolefina

26 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona de conformidad con la reivindicación 18, donde la superficie de contacto entre el recipiente y la solución se compone de poliolefina

27 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona de conformidad con la reivindicación 18, donde la poliolefina se selecciona del grupo formado por polietileno, polipropileno, polibutenos, poliisoprenos y polipentenos y sus polímeros y mezclas

28. Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona de conformidad con la reivindicación 27, donde la poliolefina se selecciona del grupo formado por polietileno y polipropileno

29 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona de conformidad con la reivindicación 28, donde la poliolefina es polipropileno

30 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona de conformidad con la reivindicación 18, donde el agente gram-positivo de oxazolidinona se selecciona del grupo formado por linezolida y eperezolida.

31 Un método para evitar la pérdida de un agente gram-positivo de oxazolidinona, de conformidad con la reivindicación 30, donde el agente gram-positivo de oxazolidinona es linezolida.

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REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [X] **MODELO DE UTILIDAD** [ ]

- Indicación de que se solicita la concesión de una patente 1
- Datos de identificación del solicitante o de la persona que presenta la solicitud 1
- Descripción de la invención 53
- Dibujos de ser estos pertinentes [ ]
- Comprobante de Pago de las tasas establecidas 3

COMPLETA [X] **INCOMPLETA** [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] **INCOMPLETA** [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema de trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] **INCOMPLETA** [ ]

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Radicacion : 02063632 00000000 Folios: 65
Fecha (AMD): 2002-09-18 15:49:52
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
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