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DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 444

Referencia : Expediente No. 05-049742
Asunto : Solicitud de patente para: **COMPOSICIÓN FARMACÉUTICA DE LIBERACIÓN PROLONGADA**
Solicitante : INTERVET INTERNATIONAL B.V.
Clase : A61K 031/546, A61P 031/000
Fecha solicitud: 23 de Mayo de 2005

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado me refiero al oficio No. **15576** notificado por fijación en lista del 05 de Diciembre de 2008.

2. Mediante oficio No. **15576** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

2.1 <u>De la solicitud de patente</u>

2.1.1 Reivindicaciones

En primer lugar el Examinador ha señalado que la reivindicación 1 no se encuentra debidamente definida, toda vez que las reivindicaciones independientes referentes a un sistema de entrega farmacéutico, deben indicar la composición cuantitativa del mismo. Se indica además, que las reivindicaciones independientes se destinan solo para definir las modalidades particulares de la invención, de acuerdo con la reivindicación independiente.

De otro lado se ha señalado que se prefieren las denominaciones comunes internacionales sobre los signos distintivos de carácter comercial, en relación con el signo Miglyol®.

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Por último se ha objetado la reivindicación 9, que de acuerdo con el Examinador, define un proceso de práctica convencional de laboratorio y por ende no genera un verdadero salto cualitativo en la regla técnica. 108

2.1.2 Descripción

Señala el Examinador, que la descripción no se acompaña de ensayos experimentales que permitan conocer la superioridad de la fórmula de liberación controlada con respecto a las composiciones del arte previo.

2.1.3 Reivindicaciones relativas a un uso

A este respecto, ha sido objetada la reivindicación 10 por constituir un uso.

2.2 Nivel inventivo

El Examinador considera que el documento D1: WO 0061149 afecta el nivel inventivo de la presente solicitud, argumentando que la única diferencia entre ellos es la selección del componente activo.

Se afirma entonces que un conocedor de la materia podría derivar fácilmente los componentes de un sistema de formulación como el reivindicado, tan solo teniendo en cuenta las enseñanzas del documento D1 y la bibliografía básica sobre la producción de inyectables.

3. Con el fin de subsanar las objeciones expuestas, se presentan las siguientes modificaciones, aclaraciones y argumentos:

3.1 Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 6 reivindicaciones.

Las modificaciones realizadas sobre el pliego reivindicatorio son las siguientes:

- El signo distintivo comercial Miglyol® ha sido modificado por el término químico con el cual se relaciona: ácido caprílico.
- Se han eliminado las reivindicaciones 9 y 10 para superar las objeciones relacionadas con éstas.

Aclaración sobre la reivindicación 1

El Examinador ha considerado que la reivindicación 1 no se encuentra correctamente definida. Sin embargo, disentimos respetuosamente de las apreciaciones del Examinador, ya que la reivindicación 1 es lo suficientemente clara y autosuficiente, encontrándose de acuerdo con los lineamientos del Manual Andino de Patentes. Adicionalmente, es posible establecer que esta reivindicación define todas las características esenciales de la invención, es decir, los elementos que constituyen la composición farmacéutica. Por su parte las reivindicaciones 2 a 8 y dependientes de la reivindicación 1, cumplen la función de referirse a características particulares de los elementos que constituyen la composición farmacéutica definiendo de manera clara y concisa la invención.

De acuerdo con lo anterior, la reivindicación 1 no ha sido modificada. Consideramos que la objeción relacionada con ésta debe tenerse por superada.

3.2 Nivel inventivo

El Manual Andino de Patentes ha definido el método problema-solución que debe seguirse para determinar si una invención tiene o no nivel inventivo y el cual está dirigido a contestar la siguiente pregunta:

> *"la pregunta a contestar es si teniendo en cuenta el estado de la técnica en su conjunto existe alguna indicación que lleve a la persona versada en la materia a modificar o adaptar el estado de la técnica más cercano para resolver el problema técnico, de tal forma que llegue a un resultado que estuviera incluido en el tenor de las reivindicaciones".*

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Por lo tanto, el Manual y el método problema-solución son muy claros en señalar que la conclusión sobre la falta de nivel inventivo de una invención solamente es posible **si existen enseñanzas o sugerencias claras en el estado del arte sobre la invención, esto es, sobre la forma como se soluciona el problema técnico en cuestión.**

Adicionalmente, el mismo Manual indica que algunos de los indicios para identificar la existencia de nivel inventivo son: i) **el hecho de haber superado un prejuicio técnico anterior;** ii) **el hecho de haber superado dificultades técnicas reales** y iii) **el hecho de que la invención responda a una necesidad ya antigua, permanente y aún insatisfecha.**

Ahora bien, con respecto a la anterioridad citada por el Examinador se tiene que:

A partir de la materia revelada por D1, una persona medianamente versada en la materia técnica determina que la lecitina o un fosfolípido son indispensables en la formulación para el ingrediente activo. Por el contrario, la composición de acuerdo con la invención no comprende estos excipientes. La presente solicitud posee entonces diferencias técnicas adicionales no establecidas por el Examinador.

De otro lado, con respecto a las objeciones expuestas por el Examinador sobre la descripción, deseamos poner de presente que en ésta se presenta un número de formulaciones del arte previo que reclaman ser de liberación prolongada, pero que no resultaron en formulaciones deseables con liberaciones prolongadas apropiadas, ya que además requieren ser inyectables y tener reacción local aceptable. Teniendo en cuenta que este problema técnico ha sido resuelto con la presente solicitud y que ésta solución se encuentra debidamente sustentada por medio de los ejemplos, se demuestra que la presente solicitud posee nivel inventivo sobre el arte previo, solucionando una necesidad ya antigua, permanente y aún insatisfecha.

Por lo tanto, D1 no es una anterioridad válida capaz de afectar el nivel inventivo de la presente solicitud y esta objeción se debe tener por superada.

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3.3 Concesión de una solicitud foránea

Por último, aunque compartimos la opinión de su Despacho, en cuanto a que la concesión de una solicitud de patente en otros países, equivalente a la solicitud Colombiana, no obliga a su Despacho a otorgar el privilegio de patente para la misma invención, sí constituye un antecedente favorable para el estudio de patentabilidad que respetuosamente solicitamos tener en cuenta. Por lo tanto informamos a su Despacho que la presente invención fue otorgada por la Oficina de Patentes de Estados Unidos (Patente US 6,911,441) y por la Oficina Europea de Patentes (Patente EP 1558263). Junto con este escrito se presenta copia de las primeras páginas y de las reivindicaciones de estas patentes para su mejor referencia.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación. Sin embargo, en caso de que se considere que existen todavía objeciones sobre la claridad y concisión de la presente solicitud, solicito atentamente y en virtud del artículo 45 de la Decisión 486, expedir una nueva Acción oficial.

5. ANEXOS

- Nuevo pliego reivindicatorio conformado por 8 reivindicaciones.
- Formulario de modificaciones
- Recibo de pago por concepto de modificaciones
- Copia de la primera página y reivindicaciones de las patentes US 6,911,441 y EP 1558263

Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

COLO-04975-843-001-8
COLO-11214-841-028-8
JMS\JMS\ID-145076\WPCL4975
No. M-2009-145076\JMS

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REIVINDICACIONES

1. Una composición farmacéutica inyectable que comprende cefquinona y un vehículo de liberación prolongada caracterizado en que el vehículo de liberación prolongada comprende una mezcla de un aceite y distearato de aluminio.

2. Una composición de acuerdo a la reivindicación 1 caracterizada en que ella comprende el distearato de aluminio en una cantidad de 1.0 a 4 .0 % en peso.

3. Una composición de acuerdo a la reivindicación 2 caracterizada en que ella comprende el distearato de aluminio en una cantidad de 2.5 a 3 .5 % en peso.

4. Una composición de acuerdo a las reivindicaciones 1 a 3 caracterizada en que el aceite es un triglicérido de cadena media o una mezcla de triglicéridos de cadena media.

5. Una composición de acuerdo a la reivindicación 4 caracterizada en que el aceite es ácido caprílico.

6. Una composición de acuerdo a las reivindicaciones 1 a 5 caracterizada en que comprende 2.0 a 20.0 % en peso de cefquinona.

7. Una composición de acuerdo a la reivindicación 6 caracterizada en que el comprende 7.5 % a 10.0 % en peso de cefquinona.

8. Una composición de acuerdo a las reivindicaciones 1 a 7 caracterizada en que la cefquinona es sulfato de cefquinona.

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US006911441B2

(12) **United States Patent**
Schmid et al.

(10) **Patent No.: US 6,911,441 B2**
(45) **Date of Patent: Jun. 28, 2005**

(54) **PROLONGED RELEASE PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Peter Schmid**, Waldbrunn (DE); **Alexander Boettner**, Frankfurt (DE); **Carsten Schmidt**, Mainz (DE); **Mark Allan**, Hofheim (DE); **Carole Barbot**, Boos (FR)

(73) Assignee: **Akzo Nobel N.V.**, Arnhem (NL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 148 days.

(21) Appl. No.: **10/320,250**

(22) Filed: **Dec. 16, 2002**

(65) **Prior Publication Data**

US 2004/0115260 A1 Jun. 17, 2004

(51) **Int. Cl.**[7] **A61K 31/546**
(52) **U.S. Cl.** **514/202**; 514/207
(58) **Field of Search** 514/202, 203, 514/204, 206, 207

(56) **References Cited**

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WO	WO 87/03876	7/1987
WO	WO 00/61149	10/2000
WO	WO 03/063877 A1	8/2003

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Primary Examiner—Barbara P. Badio
(74) *Attorney, Agent, or Firm*—William M. Blackstone

(57) **ABSTRACT**

Novel pharmaceutical compositions of a cephalosporin in a prolonged release vehicle, comprising an oil and aluminium distearate, provide a prolonged duration of effective blood-plasma concentration of the cephalosporin after injection to animals.

12 Claims, 12 Drawing Sheets

of the formulation. The results obtained show that the tested prolonged release formulation maintained therapeutic blood levels only for 12 hours.

Example 10

The pharmacokinetic profile of prolonged release cefquinome formulations, that use various SABER® oil Delivery systems, in cattle (bodyweight 230–345 kg) and pigs (41 to 55 kg) in a dosage of 3 mg or 5 mg/kg bw im and sc to cattle and im 6 and 10 mg/kg bw im to pigs was assessed. The SABER Delivery system uses a high viscosity base compound (sucrose acetate isobutyrate, SAIB) to provide controlled release. Upon addition of a small amount of solvent (Ethanol (EtOH), Ethyl lactate (EtLac), the high viscosity component, SAIB converts to an easily injectable liquid. Once inside the body, the solvent dissipates and a semi-solid, biodegradable implant is formed. The tested prolonged release formulation are Lot 96557, Lot 96558, Lot 96559.

The formulations were administered at a single dose subcutaneous (sc) into the neck or intramuscular (im) in M. triceps brachii. Each animal received each of the preparations once with a 7 days washout period between the administrations.

Blood samples were collected by jugular venipuncture (cattle) and by puncture of the anterior Vena cava (pigs) at times 0, 1, 4, 6, 8, 24, 32, 48, 56 and 72 h after drug administration. The concentration of cefquinome in plasma samples was determined by bioassay. On validation of the method a limit of quantification (LOQ) of 0.04 μg cefquinome/mL plasma was established.

FIG. **10** shows bovine plasma cefquinome concentrations (μg/mL) after im administration of the formulations to cattle. FIG. **11** shows bovine plasma cefquinome concentrations (μg/mL) after sc administration of the formulations to cattle. FIG. **12** shows porcine plasma cefquinome concentrations (μg/mL) after im administration of the formulations to pigs.

The formulations a and b provided prolonged release pharmacokinetic profiles on a low level after sc, im administration to cattle and im administration to pigs, but the industrial development was not considered because of residues of the carrier in the animal body at the injection site, that were still detectable 6 months after the administration. The formulation c did not result in prolonged release profiles with activity >32 h in all applications to pigs and cattle.

What is claimed is:

1. An injectable pharmaceutical composition comprising a cefquinome and a prolonged release vehicle, wherein the prolonged release vehicle comprises a mixture of an oil and aluminium distearate.

2. A composition according to claim **1** comprising the aluminium distearate in an amount of 1.0 to 4.0% by weight.

3. A composition according to claim **2** comprising the aluminium distearate in an amount of 2.5 to 3.5% by weight.

4. A composition according to claim **1**, wherein the oil is a medium chain triglyceride or a mixture of medium chain triglycerides.

5. A composition according to claim **4**, wherein the oil is a polyethylene glycol di-ester of saturated fatty acids having a chain length of 8 to 10 carbon atoms.

6. A composition according to claim **1** comprising 2.0 to 20.0% by weight of a cefquinome.

7. A composition according to claim **6** comprising 7.5 to 10.0% by weight of a cefquinome.

8. A composition according to claim **7**, wherein the cefquinome is cefquinome sulphate.

9. A process for preparing a pharmaceutical composition as defined in claim **1**, comprising the steps of mixing the oil and the aluminium distearate to create the prolonged release vehicle and suspending the cefquinome in the prolonged release vehicle.

10. A process according to claim **9**, wherein the aluminium distearate is added to the oil under gentle stirring and heating to form the prolonged release vehicle and the mixture is allowed to cool before adding the cefquinome.

11. A method for treating or preventing an infectious disease in an animal comprising administering an effective amount of a cefquinome in a single dose in a prolonged release vehicle comprising a mixture of an oil and aluminium distearate.

12. A method for treating or preventing a gram positive or grain negative bacterial infection comprising administering an effective amount of a cefquinome in a prolonged release vehicle comprising a mixture of an oil and aluminium distearate.

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

(11) EP 1 558 263 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
31.05.2006 Bulletin 2006/22

(21) Application number: **03772240.2**

(22) Date of filing: **20.10.2003**

(51) Int Cl.:
A61K 31/546 *(2006.01)*

(86) International application number:
PCT/EP2003/011644

(87) International publication number:
WO 2004/037265 (06.05.2004 Gazette 2004/19)

(54) **PROLONGED RELEASE PHARMACEUTICAL COMPOSITION**

PHARMAZEUTISCHE ZUSAMMENSETZUNG MIT VERLÄNGERTER FREISETZUNG

COMPOSITION PHARMACEUTIQUE A LIBERATION PROLONGEE

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR

(30) Priority: **25.10.2002 EP 02079477**

(43) Date of publication of application:
03.08.2005 Bulletin 2005/31

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(56) References cited:
WO-A-00/61149
WO-A-87/03876
WO-A-03/063877
GB-A- 2 087 236

EP 1 558 263 B1

Printed by Jouve, 75001 PARIS (FR)

b) Z2/79 Cefquinome sulphate (237.1 mg) suspended in ethyloleate +starch glycolate sodium (300 mg)
c) Z2/80 Cefquinome naphthoate (271.2 mg) suspended in ethyloleate + hydroxymethylcellulose high viscosity (50 mg)
d) Z2/81 Cefquinome naphthoate (271.2 mg) suspended in ethyloleate + starch glycolate sodium (300 mg)

The formulations were administered at a single dose subcutaneous (sc) into the neck. Each animal received the preparations once with a 7 days washout period between the administrations.
Blood samples were collected by jugular venipuncture at times 0, 0.5, 1, 1.5, 2, 4, 6, 8, 24, 32, 48, 56, 72 and 80 h after drug administration. The concentration of cefquinome in plasma samples was determined by bioassay.

[0078] Figure 8 shows bovine plasma cefquinome concentrations (mean values in µg/mL) after sc administration of the formulations. The results obtained show that the tested formulations can not maintain therapeutic blood levels for more than 24 hours.

Example 9

[0079] The pharmacokinetic profile of a cefquinome sulphate formulation in a dosage of 5 mg/kg bw was assessed in this study by a parallel comparison with cefquinome ethyloleate oily suspension in a group of 3 cattle (bw 340-380 kg). The tested formulation contained cefquinome sulphate -p hydroxybenzoate and Miglyol® 812.
The formulations were administered at a single dose intramuscular (im) into the M. triceps brachii.
Blood samples were collected by jugular venipuncture at times 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 26, 28, 30, 32, 48, 56 and 72h after drug administration. The concentration of cefquinome in plasma samples was determined by bioassay.
Figure 9 shows bovine plasma cefquinome concentrations (individual animals in µg/mL) after single im administration of the formulation. The results obtained show that the tested prolonged release formulation maintained therapeutic blood levels only for 12 hours.

Example 10

[0080] The pharmacokinetic profile of prolonged release cefquinome formulations, that use various SABER® oil Delivery systems, in cattle (bodyweight 230-345 kg) and pigs (41 to 55 kg) in a dosage of 3 mg or 5 mg/kg bw im and sc to cattle and im 6 and 10 mg/kg bw im to pigs was assessed. The SABER Delivery system uses a high viscosity base compound (sucrose acetate isobutyrate, SAIB) to provide controlled release. Upon addition of a small amount of solvent (Ethanol (EtOH), Ethyl lactate (EtLac), the high viscosity component, SAIB converts to an easily injectable liquid. Once inside the body, the solvent dissipates and a semi-solid, biodegradable implant is formed. The tested prolonged release formulation are Lot 96557, Lot 96558, Lot 96559.

[0081] The formulations were administered at a single dose subcutaneous (sc) into the neck or intramuscular (im) in M.triceps brachii. Each animal received each of the preparations once with a 7 days washout period between the administrations.
Blood samples were collected by jugular venipuncture (cattle) and by puncture of the anterior Vena cava (pigs) at times 0, 1, 4, 6, 8, 24, 32, 48, 56 and 72 h after drug administration. The concentration of cefquinome in plasma samples was determined by bioassay. On validation of the method a limit of quantification (LOQ) of 0.04 µg cefquinome /mL plasma was established.
Figure 10 shows bovine plasma cefquinome concentrations (µg/mL) after im administration of the formulations to cattle.
Figure 11 shows bovine plasma cefquinome concentrations (µg/mL) after sc administration of the formulations to cattle.
Figure 12 shows porcine plasma cefquinome concentrations (µg/mL) after im administration of the formulations to pigs.
The formulations a and b provided prolonged release pharmacokinetic profiles on a low level after sc, im administration to cattle and im administration to pigs, but the industrial development was not considered because of residues of the carrier in the animal body at the injection site, that were still detectable 6 months after the administration. The formulation c did not result in prolonged release profiles with activity >32 h in all applications to pigs and cattle.

Claims

1. An injectable pharmaceutical composition comprising cefquinome and a prolonged release vehicle **characterised in that** the prolonged release vehicle comprises a mixture of an oil and aluminium distearate

2. A composition according to claim 1 **characterised in that** it comprises the aluminium distearate in an amount of 1.0 to 4.0% by weight.

3. A composition according to claim 2 **characterised in that** it comprises the aluminium distearate in an amount of 2.5 to 3.5 % by weight.

4. A composition according to claims 1 to 3 **characterised in that** the oil is a medium chain triglyceride or a mixture of medium chain triglycerides

5. A composition according to claim 4 **characterised in that** the oil is Miglyol®, preferably Miglyol® grade 812.

6. A composition according to claims 1 to 5 **characterised in that** it comprises 2.0 to 20.0 % by weight of cefquinome.

7. A composition according to claim 6 **characterised in that** it comprises 7.5 to 10.0 % by weight of cefquinome.

8. A composition according to claims 1 to 7 **characterised in that** the cefquinome is cefquinome sulphate.

9. A process for preparing a pharmaceutical composition as defined in any of the preceding claims comprising the steps of mixing the oil and the aluminium distearate to create the prolonged release vehicle and suspending the cephalosporin in the prolonged release vehicle.

10. Use of cefquinome in a prolonged release vehicle comprising a mixture of an oil and aluminium distearate for the manufacture of a medicament for the treatment or prevention of infectious diseases in animals.

Patentansprüche

1. Eine einspritzbare pharmazeutische Zusammensetzung, umfassend Cefquinom und ein Trägermaterial für verlängerte Freisetzung, **dadurch gekennzeichnet, dass** das Trägermaterial für verlängerte Freisetzung eine Mischung aus einem Öl und Aluminium-Distearat enthält.

2. Zusammensetzung nach Anspruch 1, **dadurch gekennzeichnet, dass** es das Aluminium-Distearat in einer Menge zwischen 1.0 und 4.0 Gewichtsprozent umfasst.

3. Zusammensetzung nach Anspruch 21, **dadurch gekennzeichnet, dass** es das Aluminium-Distearat in einer Menge zwischen 2.5 und 3.5 Gewichtsprozent umfasst.

4. Zusammensetzung nach einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, dass** das Öl ein mittelkettiges Triglycerid oder eine Mischung von mittelkettigen Triglyceriden ist.

5. Zusammensetzung nach Anspruch 4, **dadurch gekennzeichnet, dass** das Öl Miglyol®, bevorzugt Miglyol® Grad 812 ist.

6. Zusammensetzung nach einem der Ansprüche 1 bis 5, **dadurch gekennzeichnet, dass** es 2.0 bis 20.0 Gewichtsprozent Cefquinom umfasst.

7. Zusammensetzung nach Anspruch 6, **dadurch gekennzeichnet, dass** es 7.5 bis 10.0 Gewichtsprozent Cefquinom umfasst.

8. Zusammensetzung nach einem der Ansprüche 1 bis 7, **dadurch gekennzeichnet, dass** das Cefquinom Cefquinom-Sulfat ist.

9. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung wie sie in einem der vorstehenden Ansprüche beschrieben worden ist, umfassend die Schritte des Mischens des Öls und des Aluminium-Distearats, um das Trägermaterial für verlängerte Freisetzung zu erzeugen und Cephalosporin in dem Trägermaterial für verlängerte Freisetzung zu suspendieren.

10. Verwendung von Cefquinom in einem Trägermaterial für verlängerte Freisetzung, umfassend eine Mischung eines Öls und Aluminium-Distearat für die Herstellung eines Medikamentes zur Behandlung oder Vermeidung von Infektionskrankheiten bei Tieren.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 05-049742- -00006-0000
Fecha: 2009-03-03 17:14:36 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 444 RESPUESTAREQUE Folios: 13

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 16,749
FECHA : MARZO 2 DE 2009

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	19779045	02/03/2009	49,796,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	84 FUSION DE SOLICITUD	111,000.00
		TOTAL : $	111,000.00

SON: CIENTO ONCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 04975-843-0018

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1991, p. 14–19
0066-4804/91/010014-06$02.00/0

Vol. 35, No. 1

Antibacterial Activities In Vitro and In Vivo and Pharmacokinetics of Cefquinome (HR 111V), a New Broad-Spectrum Cephalosporin

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Cefquinome is a new injectable aminothiazolyl cephalosporin derivative. It is stable against chromosomally and plasmid-encoded β-lactamases and has a broad antibacterial spectrum. *Staphylococcus aureus*, streptococci, *Pseudomonas aeruginosa*, and members of the family *Enterobacteriaceae* (*Escherichia coli*, *Salmonella* spp., *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., and *Serratia marcescens*) are inhibited at low concentrations. Cefquinome is also active against many strains of methicillin-resistant staphylococci and enterococci. Its in vitro activity against gram-negative anaerobes is very limited. The high in vitro activity of cefquinome is reflected by its high in vivo efficacy against experimental septicemia due to different gram-positive and gram-negative bacteria. We studied the pharmacokinetic properties of cefquinome in mice, dogs, pigs, and calves. After single parenteral administrations, cefquinome displayed high peak levels, declining with half-lives of about 0.5, 0.9, 1.2, and 1.3 h, respectively. The areas under the concentration-time curve determined for dogs and mice showed linear correlations to the given doses. In dogs the urinary recovery was more than 70% within 24 h of dosing.

At present cephalosporins are widely used for the treatment of infections in humans. The aminothiazolyl cephalosporins are particularly important because they possess favorable chemotherapeutic properties and are associated with low rates of adverse effects (1, 8). Cefotaxime was the first representative of this group of cephalosporins (11). During our efforts to find new derivatives with even broader antibacterial spectra or better pharmacokinetics, a series of polar cephalosporins was synthesized (3). From these compounds, cefpirome was selected to be developed for use in human medicine (6, 13).

Cefquinome (HR 111V) (Fig. 1) is another representative of this group. Here we report the antibacterial activity of cefquinome in vitro, its therapeutic efficacy in experimental infections, and its pharmacokinetic properties in animals.

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MATERIALS AND METHODS

Antimicrobial agents. Cefquinome, cefotaxime, and cefpirome were synthesized by Hoechst AG, Frankfurt, Federal Republic of Germany. Cefoperazone and cefuroxime are commercially available.

Bacterial strains. The bacterial strains used were clinical isolates obtained from various hospitals in Europe between 1978 and 1988 and strains maintained in our own laboratories. All bacterial strains were stored on agar slants at room temperature or as suspensions in liquid nitrogen.

Antimicrobial susceptibility testing. The susceptibility of aerobic bacteria was tested by means of the agar dilution test on Mueller-Hinton agar (Difco, Detroit, Mich.). When streptococci were tested, the agar was supplemented with 10% horse blood. Plates were inoculated with a multipoint inoculator (Greiner, Nürtingen, Federal Republic of Germany) which delivered 5×10^4 CFU per spot of stationary, freshly diluted cultures of the strains concerned. The MIC was taken as the lowest concentration at which no visible growth could be detected after 24 h at 37°C. The MICs for methicillin-resistant *Staphylococcus aureus* were read after 48 h at 30°C. The MICs for 50 and 90% of the isolates (MIC_{50} and MIC_{90}, respectively) were calculated from the results.

The susceptibility of obligate gram-positive and gram-negative anaerobes was tested by using the agar dilution test on Wilkins-Chalgren agar (Oxoid, Wesel, Federal Republic of Germany). Overnight cultures of the appropriate test strains diluted 1:10 in fresh thioglycolate medium (Oxoid) were used as the inoculum. The MICs of the antibiotics were determined after the plates had been incubated in anaerobic jars (Oxoid) for 48 h at 37°C.

β-Lactamase stability. The enzymes used were released from the bacteria by ultrasonication and partially purified by chromatography on Sephacryl S-200 superfine (Pharmacia, Freiburg, Federal Republic of Germany). For the spectrophotometric UV test (11), 2 ml of a 10^{-3} M solution of cefquinome and 50 μl of enzyme solution were mixed. The A_{255} was monitored for 10 min at room temperature. The relative rates of hydrolysis were compared with the decay of cephaloridine.

Affinity to PBPs. The binding of cefquinome to penicillin-binding proteins (PBPs) of *Escherichia coli* K-12 was determined as previously described (12) by using ^{125}I-ampicillin.

Influence of nutrient medium. The effect of the composition of the culture medium was examined in the serial macrodilution test. Geometrical dilution series of the compound were prepared in different fluid nutrient media and inoculated with suspensions of the test organisms. The following commercial bacterial culture media were used: Mueller-Hinton medium (Difco), ABM III (Difco), standard I (Merck), heart infusion medium (Difco), brain heart infusion medium (Difco), standard bouillon (Oxoid), 1% Tryptone (Difco), Iso-Sensitest broth (Oxoid), and nutrient broth (Oxoid).

The effect of pH on the activity of cefquinome was determined in the serial macrodilution test with Mueller-

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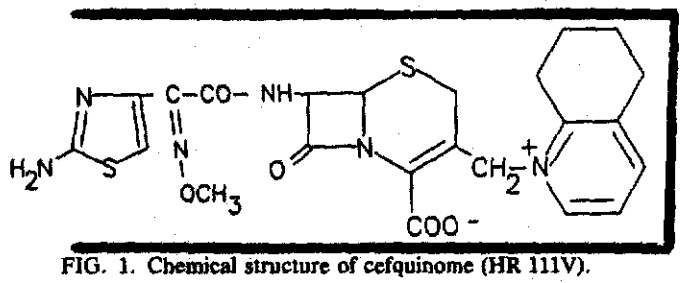

FIG. 1. Chemical structure of cefquinome (HR 111V).

Hinton medium (Difco) which had been adjusted to pH values between 5.5 and 9.

Mouse protection test. NMRI mice of both sexes, weighing 18 to 22 g, were used in the experiments. The mice were kept in groups of 10 in Makrolon cages and were given grain feed (Nestlen KG, Mannheim, Federal Republic of Germany) and tap water ad libitum. The animals were infected intraperitoneally with 0.3 ml of a bacterial suspension in 5% hog gastric mucin adjusted to a multiple lethal dose. Untreated animals died within 6 to 48 h after infection, depending on the bacterial species. The mice were treated subcutaneously (s.c.) immediately and 4 h after infection. They were observed for 10 days, and a daily record of deaths was kept. The median effective doses (ED_{50}s), i.e., the doses required to protect 50% of the animals from death, were calculated by probit analysis (7) from the number of animals surviving on day 10 after the infection.

Pharmacokinetic studies. Groups of NMRI albino mice, weighing 19 ± 1 g, were dosed s.c. with 10 and 40 mg of cefquinome per kg. At defined intervals after dosing, blood samples were obtained from a cut at the tip of the tail by using a 10-μl capillary (wetted with sodium citrate) and kept at 4°C. Urine was collected in metabolism cages. Groups of three male beagle dogs, weighing about 22 kg each, were dosed with 5, 10, and 20 mg/kg intravenously (i.v.) via the cephalic vein. Blood samples were withdrawn from the cephalic vein in the opposite leg. Urine was collected by catheterization. Groups of five or six male and female pigs (Deutsches veredeltes Landschwein), weighing approximately 18 kg each, were injected i.v. with 10 mg of cefquinome via the vena jugularis or s.c. in the base of the left ear. Blood samples were withdrawn from the contralateral jugular vein. Male and female calves weighing between 110 and 140 kg were dosed with 10 mg of cefquinome per kg i.v. via the vera jugularis. Preliminary pharmacokinetic results were obtained after s.c., intramuscular, and intratracheal application.

Bioassay. Blood, serum, plasma, and urine samples were bioassayed by the agar diffusion test with Mueller-Hinton agar supplemented with 10% sheep blood and seeded with *Streptococcus pyogenes* A77 as the assay strain. Standard solutions were prepared from pooled murine blood and urine and from autologous body fluids taken from untreated dogs, pigs, and calves. Cefquinome concentrations were calculated by regression analysis, using the standard curves in which the logarithms of the concentrations were proportional to the areas of the inhibition zones.

Pharmacokinetic calculations. Curve fitting was carried out by nonlinear regression with the computer program PHAKOK. Pharmacokinetic analysis of the concentration-time data after i.v. administration indicated that the best curve fits were usually achieved by using an open two-compartment model. Mean values and standard deviations of the pharmacokinetic parameters were calculated from individual fitted curves.

RESULTS

Antibacterial spectrum. The results of the susceptibility testing of numerous clinical isolates of gram-positive and gram-negative bacteria are summarized in Tables 1 and 2. The data indicate that cefquinome has high antibacterial activity in vitro against nearly all strains tested. The MICs of cefquinome (Table 1) for methicillin-susceptible and methicillin-resistant staphylococci are nearly identical to those of cefpirome, i.e., in the range of 0.195 to 50 μg/ml. Thus, the MIC_{50}s and MIC_{90}s of cefquinome (1.563 and 25 μg/ml, respectively) are slightly lower than those of cefotaxime. The MIC_{90} of cefquinome against streptococci of serogroups A, B, and C is 0.024 μg/ml and is therefore slightly lower than that of cefpirome and cefotaxime. Against enterococci the MIC_{90} of cefquinome was about 32 μg/ml, indicating that against this group of bacteria cefquinome is slightly more active than cefpirome but significantly more active than cefotaxime.

All the species of the *Enterobacteriaceae* tested are usu-

TABLE 1. In vitro activities of cefquinome, cefpirome, and cefotaxime against gram-positive bacteria

Organism (no. tested)	Antimicrobial agent[a]	MIC (μg/ml)		
		Range	50%	90%
Staphylococcus aureus				
Methicillin susceptible (40)	HR 111V	0.195–25	0.781	1.563
	CPO	0.391–25	0.781	1.563
	CTX	0.781–50	1.563	6.25
Methicillin resistant (30)	HR 111V	1.563–50	12.5	25
	CPO	0.781–50	12.5	50
	CTX	3.125–>100	25	100
Streptococcus spp., serogroups A, B, and C (36)	HR 111V	≤0.006–0.781	<0.006	0.024
	CPO	≤0.006–0.781	0.012	0.049
	CTX	≤0.006–3.125	≤0.006	0.049
Enterococci (40)	HR 111V	1.0–64	4.0	32
	CPO	1.0–128	4.0	64
	CTX	2.0–>128	128	>128

[a] HR 111V, Cefquinone; CPO, cefpirome; CTX, cefotaxime.

TABLE 2. In vitro activities of cefquinome, cefpirome, and cefotaxime against gram-negative bacteria

Organism (no. tested)	Antimicrobial agent[a]	MIC (μg/ml)		
		Range	50%	90%
Escherichia coli (40)	HR 111V	<0.006–0.781	0.049	0.391
	CPO	<0.006–0.391	0.049	0.195
	CTX	≤0.006–0.195	0.024	0.049
Salmonella spp. (38)	HR 111V	0.049–0.391	0.098	0.195
	CPO	0.012–0.098	0.024	0.049
	CTX	≤0.006–0.098	0.024	0.049
Klebsiella spp. (40)	HR 111V	0.024–12.5	0.049	0.391
	CPO	0.024–3.125	0.049	0.195
	CTX	≤0.006–3.125	0.049	0.195
Serratia marcescens (40)	HR 111V	0.098–6.25	0.195	0.391
	CPO	0.049–3.125	0.098	0.391
	CTX	0.098–3.125	0.195	0.781
Enterobacter spp. (40)	HR 111V	0.049–6.25	0.098	0.781
	CPO	0.024–6.25	0.098	1.563
	CTX	0.012–100	0.195	25
Citrobacter spp. (40)	HR 111V	0.024–6.25	0.049	0.195
	CPO	0.012–12.5	0.024	0.195
	CTX	0.024–100	0.098	3.125
Proteus mirabilis (27)	HR 111V	0.024–0.391	0.098	0.195
	CPO	0.012–0.391	0.024	0.195
	CTX	≤0.006–0.024	≤0.006	0.012
Proteus spp. (indole positive) (30)	HR 111V	≤0.006–100	0.195	25
	CPO	≤0.006–100	0.195	25
	CTX	≤0.006–100	1.563	12.5
Pseudomonas aeruginosa (100)	HR 111V	0.391–50	6.25	25
	CPO	0.195–50	3.125	12.5
	CTX	0.781–>100	12.5	50

[a] HR 111V, Cefquinome; CPO, cefpirome; CTX, cefotaxime.

ally highly susceptible to cefquinome (Table 2). The MIC_{90}s of this compound against *E. coli*, *Salmonella* spp., *Klebsiella* spp., *Serratia marcescens*, *Enterobacter* spp., *Citrobacter* spp., and *Proteus mirabilis* are below 1 μg/ml. The MIC_{90} of cefquinome against indole-positive *Proteus* spp. is 25 μg/ml. The MIC_{50} and MIC_{90} determined for cefquinome are in the same range as those of cefpirome and cefotaxime.

Against *Pseudomonas aeruginosa* (Table 2), cefquinome

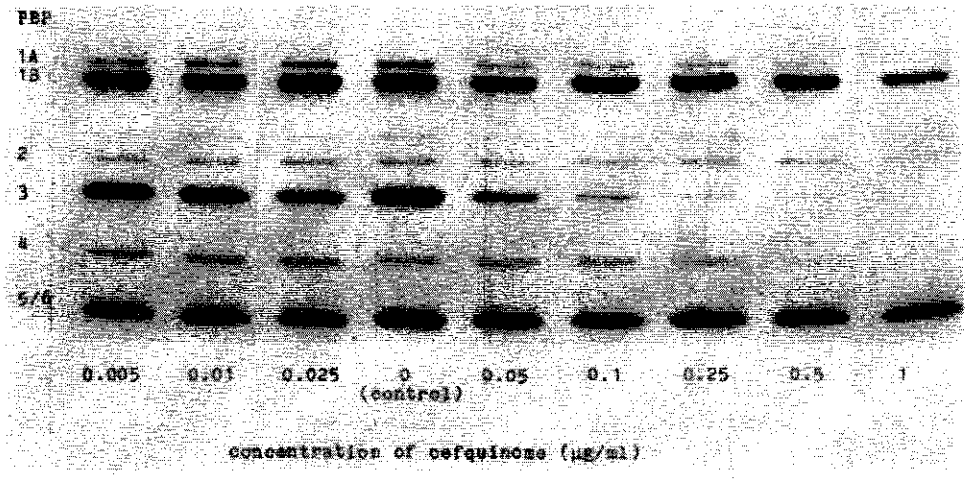

FIG. 2. Autoradiogram showing binding of cefquinome to PBPs of *E. coli* K-12.

TABLE 3. Comparative chemotherapeutic activities of cefquinome, cefotaxime, cefoperazone, and cefuroxime in vitro (MIC) and in vivo (mouse septicemia model)

Organism	Antimicrobial agent[a]	MIC (μg/ml)	ED_{50} (mg/kg) (95% confidence limits)
Staphylococcus aureus Giorgio	HR 111V	0.313	0.96 (–[b])
	CTX	1.56	6.38 (4.62–9.98)
	CPZ	1.56	12.28 (6.25–25)
	CXM	1.25	5.68 (3.56–7.03)
Staphylococcus aureus SG 511	HR 111V	0.391	1.6 (0.78–3.1)
	CTX	1.56	9.6 (6.68–13.82)
	CPZ	0.781	8.84 (6.21–12.56)
	CXM	0.313	4.42 (3.02–6.4)
Streptococcus pyogenes A77	HR 111V	0.002	0.09 (0.05–0.15)
	CTX	0.02	0.21 (0.16–0.28)
	CPZ	0.125	5.4 (4.05–7.21)
	CXM	0.004	0.24 (0.16–0.36)
Streptococcus pneumoniae	HR 111V	0.008	0.17 (0.06–0.51)
	CTX	0.004	1.29 (0.76–2.08)
	CPZ	0.031	4.4 (2.9–6.52)
	CXM	0.031	2.28 (0.91–4.33)
Escherichia coli 078	HR 111V	0.03	0.04 (0.03–0.05)
	CTX	0.08	0.09 (0.07–0.12)
	CPZ	0.313	0.2 (0.1–0.39)
	CXM	2.5	16.48 (12.6–21.62)
Salmonella typhimurium MZ II	HR 111V	0.06	0.07 (0.05–0.1)
	CTX	0.02	0.06 (–)
	CPZ	0.625	1.02 (0.69–1.54)
	CXM	1.25	15.58 (10.71–22.57)
Klebsiella pneumoniae DT-S	HR 111V	0.008	0.39 (0.25–0.6)
	CTX	0.004	0.76 (0.39–1.56)
	CPZ	0.062	1.88 (1.28–2.72)
	CXM	0.5	>12.5 (–)
Proteus mirabilis ATCC 14273	HR 111V	0.078	0.88 (0.57–1.31)
	CTX	0.02	0.78 (0.4–1.6)
	CPZ	0.625	5.22 (3.7–7.38)
	CXM	0.625	8.84 (6.22–12.56)
Pasteurella multocida	HR 111V	0.078	4.52 (–)
	CTX	0.02	1.85 (1.13–3.15)
	CPZ	0.078	1.66 (1.07–2.62)
	CXM	0.5	>5 (–)

[a] HR 111V, Cefquinome; CTX, cefotaxime, CPZ, cefoperazone; CXM, cefuroxime.
[b] –, Not calculable.

proved to be more active than cefotaxime but slightly less active than cefpirome.

In vitro activity against anaerobes. The MICs of cefquinome, cefpirome, cefotaxime, and cefuroxime against single laboratory strains of gram-positive and gram-negative anaerobic bacteria were determined. Against gram-negative species (*Bacteroides* spp. [11 strains], *Fusobacterium* spp. [3 strains]) cefquinome, like cefpirome, has only very limited in vitro activity. Against 11 of the 14 strains tested, MICs of cefquinome were >100 μg/ml. Strains resistant to both cefotaxime and cefuroxime are also resistant to cefquinome. In general, the gram-positive anaerobes (*Peptostreptococcus anaerobius* [MIC, 0.391 μg/ml], *Propionibacterium acnes* [MIC, 0.098 μg/ml], *Clostridium* spp. [MIC, 1.563 μg/ml])

TABLE 4. Pharmacokinetic parameters of cefquinome in mice after s.c. administration[a]

Dose (mg/kg)	n	$t_{1/2}$ (h)	C_{max} (μg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (mg · h/liter)	% UR (0–18 h)
10	8	0.58 ± 0.09	7.5 ± 2.9	0.38 ± 0.16	7.8 ± 1.9	75.8
40	8	0.49 ± 0.19	25.9 ± 5.1	0.45 ± 0.13	26.8 ± 7.7	85.1

[a] $t_{1/2}$, Elimination half-life; C_{max}, peak concentration of drug in serum; T_{max}, time to C_{max}; $AUC_{0-\infty}$, area under the concentration-time curve from 0 h to infinity; UR, urinary recovery.

TABLE 5. Pharmacokinetic parameters of cefquinome in dogs after i.v. administration[a]

Dose (mg/kg)	n	Body wt (kg)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (mg · h/liter)	V_{ss} (liters/kg)	CL_{tot} (ml/min)	UR (%)	
							0–7 h	7–24 h
5	3	21.8 ± 0.8	0.85 ± 0.10	26.6 ± 4.7	0.20 ± 0.06	70.1 ± 13.5	76.8 ± 8.7	1.5 ± 0.2
10	3	21.5 ± 2.2	0.98 ± 0.28	50.4 ± 13.7	0.24 ± 0.09	79.3 ± 27.9	73.8 ± 9.7	2.6 ± 0.2
20	3	21.2 ± 2.6	0.96 ± 0.08	104.6 ± 5.9	0.22 ± 0.04	67.6 ± 5.4	61.5 ± 6.9	1.4 ± 0.5

[a] $t_{1/2}$, Elimination half-life; $AUC_{0-\infty}$, area under the concenration-time curve from 0 h to infinity; V_{ss}, volume of distribution at steady state; CL_{tot}, total body clearance; UR, urinary recovery.

were susceptible to cefquinome and the other cephalosporins tested.

Binding to the PBPs. Figure 2 shows an autoradiogram exhibiting PBP patterns obtained by various dilutions of cefquinome. This compound, as all other aminothiazolyl cephalosporins, binds preferentially to PBP 3 of *E. coli* K-12. Significant binding was found at concentrations as low as 0.1 μg/ml. A concentration of 1 μg/ml results in a further binding to PBP 1A/B.

β-Lactamase stability. The susceptibilities of cefquinome, cefpirome, and cefotaxime to a number of different types of β-lactamases from gram-negative bacteria were tested. By using the susceptibility of cephaloridine as the standard, relative rates of hydrolysis (RRH) were calculated. The data clearly indicate that cefquinome, with one exception (OXA-1, RRH = 100), is highly resistant to hydrolysis (RRH < 2) by plasmid-encoded (TEM-1, TEM-2, OXA-2, OXA-3, SHV-1, PSE-1, PSE-2, PSE-3, PSE-4) β-lactamases from *E. coli*, *Klebsiella pneumoniae*, or *P. aeruginosa* as well as chromosomally encoded β-lactamases from *Citrobacter* spp., *Enterobacter cloacae* and *K. oxytoca*.

The RRHs of cefpirome are greater than 2 with the plasmid-encoded β-lactamases of the types OXA-1 (RRH, 99), PSE-2 (RRH, 20), and PSE-3 (RRH, 3) and from the chromosomally encoded enzyme from *K. oxytoca* (RRH, 3). Cefotaxime was hydrolyzed by β-lactamases OXA-1 (RRH, 32), OXA-2 (RRH, 7), PSE-2 (RRH, 7), and PSE-3 (RRH, 6) and the enzymes from *Citrobacter* spp. (RRH, 8) and *K. oxytoca* (RRH, 6). These results show that cefquinome is more stable than cefpirome or cefotaxime against β-lactamases.

Effect of medium composition and pH on in vitro activity. The MICs of cefquinome for *S. aureus* SG 511 and *E. coli* 1507E in nine commercial culture media (Mueller-Hinton medium, ABM III, standard I, heart infusion medium, brain heart infusion medium, standard bouillon, 1% Tryptone, Iso-Sensitest, and nutrient broth 2) were determined. The MICs of the compound for *S. aureus* SG 511 and *E. coli* 1507E varied only by one dilution step (0.313 to 0.625 and 0.062 to 0.125 μg/ml, respectively). Thus, the antibacterial activity of cefquinome does not depend upon the composition of the culture medium. The antibacterial activity of cefquinome for the same test organisms does not vary markedly in Mueller-Hinton medium adjusted to pH values ranging from 5.5 to 9.0.

In vivo efficacy in mouse septicemia. The high in vitro activity of cefquinome (Table 3) against the pathogens involved was reflected by excellent in vivo activity against the septicemias induced in mice by these strains. Cefquinome has good in vivo activity against *S. aureus*, which is not typical for most other broad-spectrum cephalosporins including cefotaxime. Table 3 clearly demonstrates that cefquinome is superior to cefotaxime, cefoperazone, and cefuroxime as regards protection against the experimental *S. aureus* Giorgio and SG 511 infections in mice. The ED_{50}s of cefquinome for these strains are 0.96 and 1.6 mg/kg, respectively, which is 6 to 12 times more active than the reference compounds. The activity demonstrated by cefquinome against infections due to *Streptococcus pyogenes* A77 was also higher than that of cefotaxime, cefoperazone, and cefuroxime. The *Streptococcus pneumoniae* infection also responded well to cefquinome. The ED_{50} (0.17 mg/kg) of cefquinome was 2 to 15 times lower than those of the reference compounds.

In addition, Table 3 shows the chemotherapeutic efficacies of cefquinome and the three reference compounds in the treatment of infections caused by gram-negative bacteria. Cefquinome showed similar activity to cefotaxime in *E. coli* 078 and *Salmonella typhimurium* MZ II infections, with ED_{50}s of 0.04 and 0.07 mg/kg, respectively. Cefoperazone and, in particular, cefuroxime, however, were distinctly less active against the infections caused by these strains. Similar results were obtained for septicemias induced by *K. pneumoniae* DT-S or *Proteus mirabilis* ATCC 14273. The ED_{50}s of cefquinome for these bacteria were calculated to be 0.39 and 0.88 mg/kg, respectively. Only in the infection due to *Pasteurella multocida* was cefquinome somewhat less active than cefotaxime and cefoperazone.

Pharmacokinetics. The binding of cefquinome to mouse, dog, horse, and calf serum proteins, as measured by a dialysis method, was less than 10% (data not shown). Pharmacokinetic parameters in mice, dogs, pigs, and calves after single parenteral doses of cefquinome are presented in Tables 4 to 7, respectively. Cefquinome was rapidly distributed after parenteral administration and showed high and sustained levels in blood in the species tested. The mean

TABLE 6. Pharmacokinetic parameters of cefquinome in pigs after s.c. and i.v. administration[a]

Dose (mg/kg) and route	n	Body wt (kg)	$t_{1/2}$ (h)	C_{max} (μg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (mg · h/liter)	V_{ss} (liters/kg)	CL_{tot} (ml/min)
10 s.c.	6	17.9 ± 0.7	1.23 ± 0.28	26.1 ± 6.4	0.80 ± 0.16	62.3 ± 17.4		
10 i.v.	5	18.2 ± 0.5	1.32 ± 0.18			66.7 ± 27.2	0.24 ± 0.11	48.5 ± 16.6

[a] $t_{1/2}$, Elimination half-life; C_{max}, peak concentration of drug in serum; T_{max}, time to C_{max}; $AUC_{0-\infty}$, area under the concentration-time curve from 0 h to infinity; V_{ss}, volume of distribution at steady state; CL_{tot}, total body clearance.

TABLE 7. Pharmacokinetic parameters of cefquinome in calves[a]

Dose (mg/kg) and route	n	Body wt (kg)	$t_{1/2}$ (h)	C_{max} (μg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (mg · h/liter)	V_{ss} (liters/kg)	CL_{tot} (ml/min)
10 i.v.	4	118.5 ± 8.9	1.33 ± 0.41			84.7 ± 25.3	0.23 ± 0.13	261 ± 128
10 s.c.	2	138.5		3.6	1.8	19.4		
10 i.m.	1	137.0		4.5	2.0	24.0		
10 i.t.	1	133.0		4.2	1.8	20.8		

[a] i.m., Intramuscular, i.t., intratracheal; $t_{1/2}$, elimination half-life; C_{max}, peak concentration of drug in serum T_{max}, time to C_{max}; $AUC_{0-\infty}$, area under the concentration-time curve from 0 h to ∞; V_{ss}, volume of distribution at steady state; CL_{tot}, total body clearance.

elimination half-lives in dogs (Table 5), pigs (Table 6), and calves (Table 7) after i.v. administration of 10 mg/kg were 0.98, 1.32, and 1.33 h, respectively. The correlation between the doses and the total areas under the concentration-time curves in dogs (Table 5) proved to be linear. Preliminary results in calves indicate little difference between the serum profiles after s.c., intramuscular, or intratracheal administration of cefquinome (Table 7). The calculated volume of distribution at steady state was very similar in all species tested, corresponding to about 25% of the body volume. Cefquinome was excreted mainly via the kidneys. In mice (Table 4) and in dogs (Table 5) about 80% and 63 to 78%, respectively, of the dose was recovered in the urine as antibacterially active substance within 24 h of administration.

DISCUSSION

The introduction of a methoxyimino-aminothiazolyl moiety in the acyl side chain of cephalosporins brought about significant enhancement of activity, extension of the antibacterial spectrum—especially against gram-negative bacteria—and high resistance to inactivation by β-lactamases (3, 9). The introduction of polar C-3′-substituents into a cephem nucleus improves the activity of the aminothiazolyl cephalosporins, especially against staphylococci and *P. aeruginosa*, without loss of activity against members of the *Enterobacteriaceae*. Cefquinome is a representative of this group of cephalosporins, as are cefpirome (5) and cefepime (2). The results of our investigations proved that cefquinome has a broad spectrum of activity. The spectrum includes staphylococci, streptococci, and many strains of methicillin-resistant staphylococci and enterococci. The most important members of the *Enterobacteriaceae* (*E. coli*, *Klebsiella* spp., *Salmonella* spp., *Citrobacter* spp., *Enterobacter* spp., and *Proteus* spp.) are inhibited at low concentrations. Most strains of *P. aeruginosa* are also susceptible to cefquinome. Owing to its resistance to various plasmid-encoded or chromosomally encoded β-lactamases, cefquinome is also active against bacteria that are resistant to earlier cephalosporins. Its action against gram-negative strict anaerobic bacteria (e.g., *Bacteroides fragilis*) is limited, as is that of cefpirome and cefepime (2, 4).

The in vitro activity of cefquinome, similarly to those of other cephalosporins, does not depend on the composition or pH of the test medium.

The broad antibacterial spectrum and the high in vitro activity of cefquinome are reflected by high in vivo efficacy in experimental infections. In mouse models of septicemia induced by both gram-positive and gram-negative bacteria, cefquinome possessed high therapeutic efficacy. All infections were cured by the administration of cefquinome. The ED_{50}s were usually below 1 mg/kg.

The pharmacokinetic properties of cefquinome make a major contribution to its high in vivo activity. After parenteral administration to mice, dogs, pigs, or calves, high and sustained levels were measured in blood. The elimination half-lives are comparable to those of other polar cephalosporins. Cefquinome is excreted mainly by the kidneys: within 24 h of administration, 60 and 80% of the administered dose was recovered in the urine of mice and dogs, respectively.

In conclusion, cefquinome is a new representative of the polar aminothiazolyl cephalosporins. With its broad antibacterial spectrum and favorable pharmacokinetics, it merits further investigation into its chemotherapeutic properties.

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United States Patent [19]

Sieger et al.

[11] **4,016,273**

[45] **Apr. 5, 1977**

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[54] **SUSTAINED RELEASE FORMS OF CERTAIN OXAZEPINES FOR PARENTERAL ADMINISTRATION**

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[52] **U.S. Cl.** **424/250**

[51] **Int. Cl.²** **A11K 31/495**

[58] **Field of Search** ..... 424/250; 260/268 TR

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[57] **ABSTRACT**

A sustained release depot form of the free base or pamoate salt of 2-chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]-oxazepine or 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f]-[1,4]oxazepine in an injectable oil for parenteral administration.

8 Claims, No Drawings

SUSTAINED RELEASE FORMS OF CERTAIN OXAZEPINES FOR PARENTERAL ADMINISTRATION

BACKGROUND OF THE INVENTION

Both 2-chloro-11-(piperazinyl)-dibenz[b,f][1,4]oxazepine and 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine are known compounds having therapeutic effects on the central nervous system.

U.S. Pat. No. 3,546,226 specifically discloses the compound 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, and broadly discloses the compound 2-chloro-11-(piperazinyl)-dibenz[b,f][1,-4]oxazepine, their method of preparation, their non-toxic pharmaceutically acceptable acid addition salts and their utility as central nervous system agents. The '226 patent also discloses the parenteral administration of the above compounds. However, the '226 patent does not disclose sustained release forms of the above compounds as set forth herein.

U.S. Pat. No. 3,663,696 discloses the preparation and treatment of depression with 2-chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepines and the acid addition salts thereof, including the hydrochloride, sulfate, phosphate, citrate, tartrate, maleate, succinate and fumarate. The '696 patent also discloses parenteral administration of the above compounds, and a specific parenteral solution of 2-chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine. However, the '696 patent does not disclose sustained release forms of the above compounds as set forth herein.

U.S. Pat. No. 3,194,733 discloses certain acid esters of phenothiazines useful as tranquilizing or ataractic agents such as the enanthate ester of fluphenazine. The '733 patent discloses the pamoate ester and parenteral formations comprising phenothiazine compounds and aluminum monostearate in vegetable oils or synthetic esters of long chain fatty acids. However, the pamoate of the present invention is not a phenothiazine or an acid ester, but the salt of a base, and is structurally different from the acid ester compounds disclosed in the '733 patent.

Prior to the present invention, there was no prolonged acting central nervous system formulation of 2-chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine or 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, in either the free base or pamoate salt forms. The present invention supplies such formulations. Formulations, capable of prolonged action and consequently less frequent administration, are much desired as they are more convenient and easier to use where continuous and uninterrupted administration is needed.

SUMMARY OF THE INVENTION

[redacted]

methyl-1-piperazinyl)-dibenz[b,f]-[1,4]oxazepine or 2-chloro-11-(1-piperazinyl)-dibenz[b,f]-[1,4]oxazepine in an injectable oil and, optionally, a gelling agent. The invention is also concerned with a method of treating central nervous system disorders in warm-blooded animals which comprises parenterally administering a therapeutically effective amount of the above compounds to mammals.

The compounds of the present invention have a pronounced therapeutic effect on the central nervous system. The compound 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine is particularly active as a neuroplegic, neuroleptic, neuroleptic antidepressant, antimetic, analgesic and sedative. Further information on the central nervous system activity of the later compound can be found in U.S. Pat. No. 3,546,226. It is suitable as an anti-psychotic agent for the treatment of certain psychotic conditions, for example, schizophrenia. The compound 2-chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine also acts upon the central nervous system and is particularly active as an anti-depressant. Further information on the activity of this compound can be found in U.S. Pat. No. 3,663,696.

The compounds of this invention, either in the base form or as the pamoate salts, when incorporated in a formulation containing an injectable oil, with or without a gelling agent such as aluminum monostearate, provide a sustained release (depot) product when administered parenterally. For prolonged action, the compounds are formulated in an injectable oil, preferably a vegetable oil, as for example sesame oil, peanut oil, cottonseed oil, corn oil or soybean oil, or mixtures of these oils, or synthetic oils such as the glycerol or propylene glycol esters of long chain fatty acids. The active component is formulated at a concentration of about 50 mg./ml. to about 400 mg./ml. A gelling agent such as aluminum monostearate may be added to the oil to provide a final concentration of about 10 mg./ml. to about 100 mg./ml., the mixture may then be gelled by appropriate heat treatment. Other suitable gelling agents include aluminum distearate, aluminum tristearate and mixtures thereof; and the aluminum laurate, myristate, palmitate, and oleate salts, and mixtures thereof. The preferred parenteral mode of administration of these compositions is either intramuscular or subcutaneous.

DETAILED DESCRIPTION OF THE INVENTION

The following will illustrate the invention in more detail.

EXAMPLE 1

Preparation of a Parenteral Suspension of 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,-4]oxazepine Base in Gelled [redacted]

A solution phase is prepared by dissolving 2.0 g. of 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,-4]oxazepine base in 30.6 ml. of gelled sesame oil containing 2% aluminum monostearate at 60° C., and then cooling.

The final suspension is prepared by placing 7.0 g. of 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,-4]oxazepine base is a mortar and gradually adding 15.3 ml. of the above solution phase while grinding with a pestle. The result is a thixotropic, but mobile suspension which may be drawn into a syringe and then filled in vials and sterilized.

Since 7.0 gm. of 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine base occupies 4.7 cc, the final volume is 20 cc, giving a final concen-

tration of 8 gm. of active component per 20 cc of the finished preparation. A 2 cc dose then delivers 800 mg.

In the same manner, 13.0 g. of the oxazepine base is mixed in a motar with 40.0 ml. of a 5.0% w/v solution of oxazepine base in gelled sesame oil to yield 50.0 ml. of a mixture containing 30.0% 2/v of oxazepine overall.

EXAMPLE 2

Preparation of a Parenteral Suspension of 2-Chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine Base in Gelled Peanut Oil Containing Aluminum Monostearate

2-Chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine base is placed in a mortar. Sufficient peanut oil, gelled with 2.5% aluminum monostearate, is added gradually, while thoroughly mixing and dispersing the solid in the liquid with a pestle, to make a suspension of the desired concentration (e.g. 40% w/v). The resulting suspension is viscous but mobile. The suspension may be loaded in syringes or vials and sterilized.

EXAMPLE 3

Preparation of a Parenteral Suspension of 2-Chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine, Salt with 4,4'-Methylenebis[3-hydroxy-2-naphthoic Acid] (2:1) in Gelled [redacted]

2-Chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine salt with 4,4'-methylenebis[3-hydroxy-2-naphthoic acid] (2:1) is added to sesame oil gelled with 1.5% aluminum monostearate to make a final concentration of 20% 2/v as the base. The suspension is thoroughly dispersed by ultrasonic agitation for 5 minutes. The suspension may be loaded into syringes or vials and sterilized.

EXAMPLE 4

Preparation of a Parenteral Suspension of 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, Salt with 4,4'-Methylenebis[3-hydroxy-2-naphthoic acid] (2:1) is Gelled Cotton Seed Oil Containing Aluminum [redacted] Monostearate

2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, salt with 4,4'-methyelnebis[3-hydroxy-2-naphthoic acid] (2:1) is added to cotton seed oil gelled with 1.5% aluminum monostearate to make a final concentration of 10% w/v as base. The suspension is thoroughly mixed by ultrasonic agitation. The thixotropic suspension may be loaded into syringes or vials and sterilized.

EXAMPLE 5

Preparation of a Parenteral Suspension of 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, Salt with 4,4'Methylenebis[3-hydroxy-2-naphthoic acid] (2:1) in Sesame oil

2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, salt with 4,4'-methylenebis[3-hydroxy-2-naphthoic acid] (2:1) is added to sesame oil to make a final concentration of 20% w/v as base. The suspension is thoroughly mixed and dispensed by ultrasonic agitation for 5 minutes, or until the mixture becomes warm. The suspension is loaded into vials and sterilized.

EXAMPLE 6

Preparation of a Parenteral Suspension of 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, Salt with 4,4'-Methylenebis[3-hydroxy-2-naphthoic acid] (2:1) in Gelled Peanut Oil Containing Aluminum Monostearate

2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, salt with 4,4'-methylenebis[3-hydroxy-2-naphthoic acid] (2:1) is added to peanut oil gelled with 2.5% aluminum monostearate to make a final concentration of 10% w/v as base. The suspension is thoroughly mixed by ultrasonic agitation. The thixotropic suspension may be loaded into syringes or vials and sterilized.

EXAMPLE 7

Preparation of a Parenteral Suspension of 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, Salt with 4,4'-Methylenebis[3-hydroxy-2-naphthoic acid] (2:1) in Gelled Sesame Oil Containing Aluminum Monostearate

2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, salt with 4,4'-methylenebis[3-hydroxy-2-naphthoic acid] (2:1) is added to sesame oil gelled with 1.0% aluminum monostearate to make a final concentration of 20% w/v as base. The suspension is dispersed by ultrasonic agitation for 5 minutes, or until the mixture becomes warm. The suspension is loaded into vials and sterilized.

EXAMPLE 8

Preparation of a Parenteral Suspension of 2-Chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine Base in Corn Oil

2-Chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine base is placed in a mortar. Sufficient corn oil is added gradually, while thoroughly mixing and dispersing the solid in the liquid with a pestle, to make a suspension of the desired concentration (e.g. 30% w/v). The resulting suspension is viscous but mobile. The suspension may be loaded in syringes or vials and sterilized.

EXAMPLE 9

Preparation of a Parenteral Suspension of 2-Chloro-11-(1-piperazinyl-dibenz[b,f][1,4]oxazepine, Salt with 4,4'-methylenebis[3-hydroxy-2-naphthoic acid] (2:1) in Sesame Oil

2-Chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine, salt with 4,4'-methylenebis[3-hydroxy-2-naphthoic acid] (2:1) is added to sesame oil to make a final concentration of 20% w/v as base. The suspension is dispersed by ultrasonic agitation for 5 minutes, or until the mixture becomes warm. The suspension is loaded into vials and sterilized.

EXAMPLE 10

Preparation of a Parenteral Suspension of 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,-4]oxazepine base, 10% in Sesame Oil

Sesame oil is sterilized at 150° C. for 30 minutes and cooled aseptically. Benzyl alcohol (1.5%) is added aseptically to the sterile oil. 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine base is sterilized with ethylene oxide and added aspetically to the sterile sesame oil to give a final concentration of 10.5% w/v. The suspension is aspetically mixed, keeping the temperature of the suspension below 35° C., and aseptically filled into vials.

EXAMPLE 11

Preparation of a Parenteral Suspension of 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,-4]oxazepine, Salt with Hydrochloric Acid [1,1] in Cottonseed Oil

2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f]-[1,4]oxazepine, salt with hydrochloric acid [1,1] is added to cottonseed oil to make a final concentration of 35% w/v as base. The suspension is dispersed by ultrasonic agitation for 5 minutes, or until the mixture becomes warm. The resulting suspension can readily by discharged through a 21-gauge needle.

EXAMPLE 12

Preparation of a Parenteral Suspension of 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,-4]oxazepine, Salt with Succinic Acid [1,1], in Gelled Corn Oil Containing Aluminum Monostearate

2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f]-[1,4]oxazepine, salt with succinic acid [1,1] is added to corn oil gelled with 2.5% aluminum monostearate to make a final concentration of 25% 2/v as base. The suspension is thoroughly mixed by ultrasonic agitation for 5 minutes, or until the mixture becomes warm. The thixotropic suspension may be loaded into syringes or vials and sterilized.

In order to show the effectiveness of the sustained release formulations of the present invention the following tests were performed:

Formulations:

I 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,-4]oxazepine base in solution at a concentration of 2% in a 70% solution of propylene glycol in water, as a control.

II 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine pamoate in suspension at a concentration of 2.5% (as base) is gelled sesame oil containing 2% aluminum monostearate.

III 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]-oxazepine pamoate in suspension at a concentration of 2.5% (as base) in sesame oil.

IV Prolixin®[1] enanthate [4-{3-[2-(trifluoromethyl)-phenothiazin-10-yl]propyl}-1-piperazine-ethanol heptanoate (enanthate)], hereinafter fluphenazine enanthate, in solution at a concentration of 2.5% in sesame oil.

[1]Trademark E. R. Squibb & Sons.

The above formulations were administered to dogs, intramuscularly, at a concentration of 10 mg./kg. All of the dogs showed marked sedation (arousable), dlight ptosis and a cataleptic-like state on standing. The onset of these effects was about ½ hour for the preparations containing 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine and 1½ hours for fluphenazine enanthate. The dogs appeared to be symptom free in 2 days. After 4 days all the dogs were challenged with apomorphine, subcutaneously, at a concentration of 0.25 mg./kg., to determine any residual drug effect (anti-emetic) not grossly observable. At this time (4 days post administration) only formulations II and IV gave complete protection against emesis.

Another experiment was done in Cebus monkeys, using the same formulations. The symptoms observed were marked sedation, catalepsy (arousable), calming, loss of agressiveness and loss of the flight reaction. The onset of effect was less than ½ hour for the formulations containing 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine and about 1 hour for fluphenazine enanthate. The duration of effect was 3 days for Formula I, 5 days for II, and 4 days for III. The monkey given fluphenazine enanthate was markedly sedated on the fifth day.

The above tests show the prolonged action of Formula II and III containing an active compound of this invention in sesame oil, with and without aluminum monostearate.

The results shown in Table I compare the duration of action of 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f]-[1,4]oxazepine base and pamoate in gelled and ungelled formulations and indicate that the gelling process caused a prolonged effect (P=0.05) for the low dose (5 mg./kg.) of 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine base and for the high dose (10 mg./kg.) of 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine pamoate. There was no significant differences between 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine base and pamoate in the ungelled formulations given in equivalent doses.

It is concluded that the durations of action for both 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]-oxazepine base and pamoate are slightly, but significantly, prolonged when formulated in gelled sesame oil. 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine base and 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,-4]oxazepine pamoate appear to be equal in duration of action. The pamoate formulation has an advantage over 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine base, but only when gelled.

TABLE I

Duration of Catalepsy in Rats (ET_{50} = time for 50% of the rats to remain cataleptic

Parenteral Formulations of 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz-(b,f)[1,4]oxazepine base vs. Pamoate	I.M. mg./kg.	ET_{50} (95% C.L.), Hours
Base	5	56 (44–66)++
(2% solu. - oil)	10	79 (64–104)
Base	5	93 (71–116)*

TABLE I-continued

Duration of Catalepsy in Rats (ET_{50} = time for 50% of the rats to remain cataleptic		
Parenteral Formulations of 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz-(b,f][1,4]oxazepine base vs. Pamoate	I.M. mg./kg.	ET_{50} (95% C.L.), Hours
(2% solu. - gelled oil)	10	70 (estimated)+
Pamoate	10	76 (52–89)+
(2% susp. - oil)	20	82 (60–96)
Pamoate	5	88 (55–315)
(2% susp. - gelled oil)	10	135 (110–188)**

Statistical comparison of the above data showed that 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine pamoate suspended in gelled oil (10 mg./kg.)** produced the longest duration of catalepsy (P=0.05) with the exception of 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine base (5 mg./kg.)* solubilized in gelled oil. ++Significantly (P=0.05) lower than other ET_{50}'s except+.

Other Formulations Studied:		
2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine Pamoate	5	69 (44–86)
(5% susp. - oil)	10	75 (52–92)
Stearate	5	56 (38–67)
(2% solu. - oil)	10	78 (50–120)
Stearate	5	53 (26–70)
(2% solu. - gelled oil)	10	67 (estimated)
Succinate	5	70 (estimated)
(2% susp. - oil)	10	70 (estimated)
Enanthate	5	53 (26–70)
(2% solu. - oil)	10	62 (40–82)
(10% solu. - oil)	10	72 (51–85)
Prolixin	5	87 (74–102)
(2.5% solu. - oil	10	114 (94–158)

We claim:

1. A pharmaceutical composition for parenteral administration characterized by prolonged duration of activity, which comprises as the main active ingredient therein at a concentration of about 50 mg./ml. to about 400 mg./ml. the pamoate salt of 2-chloro-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine or the pamoate salt of 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine, in an injectable oil containing a gelling agent at a concentration of from about 10 mg./ml. to about 100 mg./ml.

2. A composition according to claim 1 wherein the main active ingredient is 2-chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine pamoate and the injectable oil is sesame oil.

3. A composition according to claim 1 wherein the main active ingredient is 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine pamoate and the injectable oil is sesame oil.

4. A composition according to claim 1 wherein the main active ingredient is 2-chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine pamoate, the injectable oil is sesame oil and the gelling agent is aluminum monostearate.

5. A composition according to claim 1 wherein the main active ingredient is 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine pamoate, the injectable oil is sesame oil and the gelling agent is aluminum monostearate.

6. A method of treating central nervous system disorders in a warm-blooded animal which comprises parenterally administering to said animal a therapeutically effective amount of a pharmaceutical composition for parenteral administration containing as the main active ingredient therein at a concentration of about 50 mg./ml. to about 400 mg./ml. the pamoate salt of 2-chloro-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine or the pamoate salt of 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine, in an injectable oil and a gelling agent at a concentration of about 10 mg/ml.

7. A method according to claim 6 wherein the main active ingredient is 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine pamoate, the injectable oil is sesame oil and the gelling agent is aluminum monostearate.

8. A method according to claim 6 wherein the main active ingredient is 2-chloro-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine pamoate, the injectable oil is sesame oil and the gelling agent is aluminum monostearate.

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(54) Title: TYLOSIN CONTAINING SUSTAINED RELEASE VETERINARY COMPOSITIONS

(57) Abstract

A sustained release veterinary composition, for intra-muscular and subcutaneous administration comprises Tylosin and an oily vehicle containing a gelling agent, wherein the gelling agent may be an aluminium salt of a fatty acid such as stearic acid and the oily vehicle may be a low viscosity polyol diester of a short chain naturally derived fatty acid such as propylene glycol dicaprylate/dicaprate.

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TYLOSIN CONTAINING SUSTAINED RELEASE VETERINARY COMPOSITIONS

This invention relates to a pharmaceutical preparation and in particular to a veterinary preparation for intramuscular and subcutaneous administration of Tylosin.

Tylosin is a member of the macrolide group of antibiotics which is indicated clinically for the treatment of many bacterial infections in beef cattle, non-lactating dairy cattle and swine.

Tylosin is available as a parenteral product containing 50 mg/ml or 200 mg/ml active ingredient typically administered once daily for a three day period. However such preparations provide quick onset and short duration of action and are associated with irritancy at the site of injection. Thus there is a clinical need for a Tylosin preparation which provides a sustained release of Tylosin over a period of days and may be administered with minimal adverse tissue reactions. An object of this invention is to obviate or mitigate the aforesaid disadvantages.

Accordingly this invention aims to provide a veterinary preparation for intramuscular and subcutaneous administration comprising Tylosin in a system which promotes sustained release of the active ingredient.

According to this invention there is provided a sustained release composition, comprising Tylosin and an oily vehicle containing a gelling agent, e.g. an aluminium salt of a fatty acid. Preferably the oily vehicle is a low viscosity polyol diester of a short chain naturally derived fatty acid, typically propylene glycol dicaprylate/dicaprate. Preferably this vehicle is that which is obtainable under the trade name Neobee Oil. The oily vehicle is preferably present in an amount of from 70-90%, most preferably 84% by weight of the composition.

The gelling agent present is typically aluminium distearate. The aluminium distearate may be present in an

amount of from 0.75-1.25%, but most preferably 0.94%, by weight. Other stearates may also be used to replace aluminium distearate, namely aluminium monostearate or aluminium tristearate. Preferably the aluminium monostearate is present in an amount of from 1-3% but most preferably about 1.8% by weight. Alternatively, an equivalent amount of aluminium tristearate should be present.

This invention further provides a method for incorporation of an active ingredient such as Tylosin into the oily vehicle.

Preferably, Tylosin is present in an amount from 3-30% but most preferably approximately 15% by weight per unit volume. The particle range of the active ingredient is preferably controlled so that 90% of particles have a major dimension of less than 25 μm as measured using the Coulter Counter technique or an equivalent dimension when measured using alternative methods. More preferably the particle size should be less than 10 μm.

The invention also provides a process for preparing a veterinary preparation for intramuscular and subcutaneous administration as hereinbefore defined comprising the steps of:-

Mixing a pharmaceutically acceptable (sterile) vehicle and an agent for sustained release and applying sufficient heat to permit adequate mixing, allowing the mixture to cool to form a gel base, and adding Tylosin to form a suspension thereof in the gel base.

The invention may be more clearly understood from the following description of a formulation thereof given by way of example only:

FORMULATION	**QUANTITY (g/l)**
Tylosin	150.00
Aluminium distearate	9.35
Neobee Oil M20	840.65

The Neobee Oil is placed in a stainless steel pressure vessel in an aseptic area. The contents of the vessel are then heated to 160°C and the temperature is maintained for one hour to sterilise the contents of the vessel. This is allowed to cool and, when the temperature reaches 120°C, the aluminium distearate is added with gentle stirring until dissolution has occurred. The solution is then allowed to cool without further stirring until ambient temperature is reached. At this stage Tylosin is added and suspended aseptically. To achieve the required particle size of Tylosin, the product may be passed through a conventional milling device. Preferably this milling device is a bead mill e.g. that sold under the name Dyno Mill. The final product is a stable off-white/cream suspension which can be used for the prophylaxis and treatment of cattle and pigs infected by micro-organisms sensitive to Tylosin. In general, the product is best administered by intramuscular injection.

The optimal concentration of Tylosin is 150 mg/ml. This has been chosen after consideration of the dose required to produce the required therapeutic effect after a single administration.

In the selection of appropriate oily vehicles, several candidates were initially examined for their suitability in this preparation. Resultant from this a polyol diester of short chain naturally derived fatty acids, propylene glycol dicaprylate/dicaprate was chosen. This oil has low viscosity, low setting point, and is therefore a useful vehicle for parenteral products.

Aluminium distearate is used to gel oily vehicles and, in so doing, to promote sustained release of Tylosin at the site of injection. The process of heating the vehicle, addition of aluminium stearate and allowing the product to cool results in a stable thixotropic gel which both ensures the retention of Tylosin in suspension and accuracy of dosage. The amount of aluminium distearate used is chosen such that there is facilitation of formation of suspension and syringeability.

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Claims

1. A sustained release composition, comprising Tylosin and an oily vehicle containing a gelling agent.

2. A sustained release composition according to claim 1 wherein the gelling agent is an aluminium salt of a fatty acid.

3. A sustained release composition according to claim 2 wherein the fatty acid is stearic acid.

4. A sustained release composition according to claim 1 or claim 2 wherein the oily vehicle is a low viscosity polyol diester of a short chain naturally derived fatty acid.

5. A sustained release composition according to claim 4 wherein the oily vehicle is propylene glycol dicaprylate/dicaprate.

6. A sustained release composition according to claim 1 wherein the oily vehicle is that which is obtainable under the trade name "Neobee Oil".

7. A sustained release composition according to claim 1 or claim 2 wherein the oily vehicle is present in an amount of from 70-90% by weight of the composition.

8. A sustained release composition according to claim 1 or claim 2 wherein the oily vehicle is present in an amount of 84% by weight of the composition.

9. A sustained release composition according to claim 3 wherein the gelling agent is aluminium distearate.

10. A sustained release composition according to claim 9 wherein the aluminium distearate is present in an amount of from 0.75-1.25% by weight of the composition.

11. A sustained release composition according to claim 9 wherein the aluminium distearate is present in an amount of from 0.94% by weight of the composition.

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12. A sustained release composition according to claim 3 wherein the gelling agent is selected from the group consisting of aluminium monostearate, aluminium distearate and aluminium tristearate.

13. A sustained release composition according to claim 12 wherein aluminium monostearate is present in an amount of from 1-3% by weight.

14. A sustained release composition according to claim 12 wherein aluminium monostearate is present in an amount of about 1.8% by weight.

15. A method for incorporation of an active ingredient such as a macrolide antibiotic, e.g. Tylosin into an oily vehicle comprising the steps of controlling the particle size of said active ingredient so that 90% of particles have a major dimension of less than 25 μm as measured using the Coulter Counter technique and mixing said active ingredient into said oily vehicle.

16. A method according to claim 15 wherein the active ingredient is Tylosin which is present in an amount from 3-30% by weight per unit volume.

17. A method according to claim 15 wherein the particle range of the active ingredient is controlled so that 90% of particles have a major dimension less than 10 μm.

18. A process for preparing a veterinary preparation for intramuscular and subcutaneous administration comprising the steps of:-

(i) mixing a pharmaceutically acceptable vehicle and an agent for conferring sustained release properties and applying sufficient heat to permit adequate mixing,
(ii) allowing the mixture to cool to form a gel base, and
(iii) adding Tylosin to form a suspension thereof in the gel base.

19. A process according to claim 18 wherein the concentration of Tylosin is 150 mg/ml.

20. A method of treating livestock for the purposes of countering infection by micro-organisms sensitive to Tylosin comprising the intramuscular or subcutaneous administration thereto of a sustained release composition, comprising Tylosin and an oily vehicle containing a gelling agent, in an amount of from 20 to 30 mg/kg (body weight) administered on a single occasion.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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2020
Bogotá, D.C., 14/04/2009

Abogado
Emilio Ferrero
(Apoderado)

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	Oficio	№ 4662
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Patente de Invención	[X]	Patente de Modelo de Utilidad	[ ]	
Vía Nacional	[ ]			
Vía PCT (fase nacional)	[X]	Cap. I	[ ]	Cap. II [X]

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 40 a 62

1.2. Reivindicaciones: Folios: 63 y 64
Folio: 113 Memorial de 03/03/2009

1.3. Datos PCT:

Solicitud Internacional:	PCT/EP03/011644
Capítulo II	
Fecha Sol. Internacional:	20/12/2003
Publicación. Internacional:	WO04/037265
Fecha Pub. Internacional:	06/05/2004
Fecha Inicio Fase Nacional:	25/05/2005
Fecha Sol. Nacional:	23/05/2005

1.4. Prioridad: EP02079477.2 de 25/10/2002

1.5. Respuesta del solicitante: Folios: 107 a 119 Memorial de 03/03/2009

2. Objeto de la invención

Título de la solicitud

Composición farmacéutica de liberación prolongada

Reivindicaciones

Reivindicaciones 1 a 8: Se reivindica una composición farmacéutica inyectable que comprende: cefquinona y un vehículo de liberación prolongada caracterizado porque:

El vehículo de liberación prolongada comprende una mezcla de un aceite tipo triglicérido de cadena media o una mezcla de triglicéridos de cadena media, tal es el caso del ácido caprílico y diestearato de aluminio en proporción del 1.0 al 4.0% en peso y específicamente en proporciones del 2.5 al 3.5% en peso

Se caracteriza además porque contiene 2.0 a 20% en peso de cefquinona y se formula como sulfato de cefquinona.

Sustento Descriptivo

La invención se relaciona con una composición farmacéutica inyectable que comprende Cefquinona en un vehículo de liberación prolongada, un proceso para preparar la composición y el uso.

Si bien existen diversos sistemas para formular antibióticos, en especial en la forma de suspensiones inyectables para administración por vía intramuscular o subcutánea, no se había desarrollado un sistema basado en aceite y un agente espesante para formular cefquinona, una moderna cefalosporina de tercera y cuarta generación con un amplio espectro.

En general las inyecciones intramusculares o subcutáneas de este producto en dosis de 1mg/kg redundan en una concentración eficaz en el plasma por un periodo de 8 a 12 horas y se recomienda un tratamiento por un periodo de 3 a 5 días consecutivos, por tal razón se requería diseñar una formulación inyectable con un nivel aceptable de efectos secundarios que permita la liberación del compuesto por un periodo prolongado.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K $^{31}/_{546}$ // A 61 P $^{31}/_{00}$** de la **Clasificación Internacional de Patentes**.

3. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 25/10/2002, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	WO0061149	"Long-acting antibacterial composition"	19/10/2000
D2	US4016273	"Sustained release forms of certain oxazepines for parenteral administration"	05/04/1977

D3	WO9421267	"Tylosin containing sustained release veterinary compositions"	29/09/1994

Anterioridad **D1** en los folios 97 a 100 y anterioridades **D2** a **D3** en los folios 126 a 138

4. **Análisis de patentabilidad** (*artículo 14 D. 486*)

4.1 Nivel inventivo *(artículo18 D. 486)*

El nivel inventivo se evaluó mediante comparación técnica entre los elementos característicos de las composiciones reivindicadas y las enseñanzas del estado de la técnica.

- **En las cláusulas 1 a 8 del folio 113 se reivindican formulaciones inyectables de liberación prolongada que contienen Cefquinona caracterizadas porque:**

El vehículo de liberación prolongada comprende una mezcla de un aceite tipo triglicérido de cadena media o una mezcla de triglicéridos de cadena media, tal es el caso del ácido caprílico y diestearato de aluminio en proporción del 1.0 al 4.0% en peso y específicamente en proporciones del 2.5 al 3.5% en peso

Se caracteriza además porque contiene 2.0 a 20% en peso de cefquinona y se formula como sulfato de cefquinona.

- **El estado del arte previo a la invención presenta los siguientes documentos:**

Anterioridad D1:
La publicación hace referencia a una composición antibacterial de liberación prolongada que comprende como agente activo la sustancia:

Ácido 7β-[2-(2-aminotiazol-4-il)-(Z)-2-hidroxiiminoacetamido]-3-[(5-metil-1,3,4-tiadiazol-2-il)tiometil]-3-cefem-4-carboxílico que comprende un agente gelificante tal es el caso de una sal de aluminio de un ácido graso, el agente gelificante es diestearato de aluminio y el portador farmacéutico está compuesto en su gran mayoría por un aceite mineral o un aceite vegetal o un triglicérido de un ácido graso de cadena media o un diéster de propilenglicol de un ácido graso de cadena media.

Las composiciones de liberación prolongada pueden comprender de manera adicional lecitina o fosfolípidos.

Anterioridad D2:
La publicación revela formas farmacéuticas de liberación sostenida de una sal pamoato de la base libre del compuesto 2-cloro-11-(1-piperazinil)-dibenz[b,f][1,4]-oxazepina o del compuesto 2-cloro-11-(4-metil-1-piperazinil)-dibenz[b,f]-[1,4]oxazepina en excipientes oleosos para obtener sistemas de administración parenteral.

Las formas específicas de realización reveladas en el documento **D2** comprenden

formulaciones que contienen uno de los agentes activos señalados en combinación con un aceite de sésamo y monoestearato de aluminio con el fin de obtener una suspensión para administración por vía parenteral.

Anterioridad D3:
El documento **D3** hace referencia a composiciones veterinarias que contienen el antibiótico macrocíclico Tylosin en formas de administración intramuscular o subcutánea que permiten la liberación sostenida del principio activo.

Las composiciones comprenden una sal de ácido graso, específicamente del ácido esteárico y un vehículo oleoso (aceite) que presente baja viscosidad, tal es el caso de un diéster de poliol de cadena corta derivado de un ácido graso como propilgenglicol dicaprilato o dicaprato.

En general, la sal del ácido graso se utiliza como agente gelificante de la formulación y para tal fin se adiciona diestearato de aluminio en cantidades entre 0,75 y 1,25% y como vehículo aceitoso se usa aceite vegetal neutro de Noebee® [1].

Tabla 1. Comparación de elementos técnicos:

Materia Reivindicada (Cláusula independiente 1)	**Anterioridad D1**	**Anterioridad D2**	**Anterioridad D3**
Formulaciones inyectables de liberación prolongada de Cefquinona 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-tiazolil)-(metoxilmino)acetil]amino]-2-carboxi-8-oxo-5-tia-1-azabiciclo[4.2.0-oct-2-en-3-il]metil]-5,6,7,8-tetrahidroquinolina	Formulación Antibacterial de liberación prolongada de 7β-[2-(2-aminotiazol-4-il)-(Z)-2-hidroxiiminoacetamido]-3-[(5-metil-1,3,4-tiadiazol-2-il)tiometil]-3-cefem-4-carboxílico	Formulación de liberación sostenida para administración parenteral de una Oxazepina	Formulación veterinaria para administración intramuscular o subcutánea de liberación sostenida del antibiótico Tylosin
Aceite	Aceite mineral o vegetal, triglicérido de un ácido graso o de cadena media	Aceite de sésamo	Aceite
Diestearato de aluminio	Diestearato de aluminio	Monoestearato de Aluminio	Diestearato de aluminio

Evaluación de Diferencias:

De esta manera, al evaluar los elementos característicos de las formulaciones reivindicadas en concordancia con las anticipaciones reveladas por el estado del arte es posible establecer que la única diferencia entre ellos estriba en la selección del componente activo, ya que mientras en la solicitud se determina que se trata de Cefquinona en el antecedente **D1** se indica que se trata del antibacteriano Ácido 7β-[2-(2-aminotiazol-4-il)-(Z)-2-hidroxiiminoacetamido]-3-[(5-metil-1,3,4-tiadiazol-2-il)tiometil]-3-cefem-4-carboxílico, en el antecedente **D2** se indica que se trata de una Oxazepina y en el antecedente **D3** se indica que se trata del antibiótico Tylosin.

No obstante, el vehículo indicado en el antecedente es de común utilización para la formulación de antibacterianos de uso veterinario, no en vano la bibliografía técnica

[1] Aceite vegetal neutro Neobee ® (mct's): Triglicérido de cadena media obtenido del aceite fraccionado de coco. Se utiliza en la elaboración de emulsiones para bebidas y turbios neutros emulsionados. Se emplea como dispersante de la resina esterificada (Ester Gum 8/RE) y contribuye a la turbidez de la bebida final. Se utiliza como vehículo en sabores y aceites esenciales.

relacionada con la producción de soluciones no acuosas para inyección contempla el uso de aceites grasos, en especial cuando el principio activo no muestra suficiente solubilidad en agua, se descompone fácilmente por efecto del agua o se desea un efecto de liberación modificada o retardada[2].

De esta manera, un conocedor de la materia podría derivar fácilmente los componentes de un sistema de formulación como el reivindicado, teniendo en cuenta las enseñanzas del conjunto de documentos **[D1 y D2]** o **[D2 y D3]** porque logran combinar efectivamente un vehículo oleoso con un agente gelificante tipo diestearato de aluminio para la administración de sustancias activas bien sea de tipo antibiótico o con actividad sobre el sistema nervioso central (SNC), con el fin de conseguir un efecto de liberación prolongada en el tiempo de las composiciones farmacéuticas líquidas para administración parenteral, bien sea por vía IM o subcutánea.

Del efecto técnico y el problema técnico objetivo:

Por otra parte, los documentos **D1** y **D3** señalan las ventajas de formular agentes antibióticos en esta clase de vehículo, ventaja derivada precisamente de la liberación sostenida del principio activo y por ende, de la disminución en el número de dosis que se deben administrar al animal y la consiguiente permanencia de las concentraciones plasmáticas de los agentes activos por periodos más prolongados.

El problema técnico estriba precisamente en la dificultad que conlleva la administración de antibióticos a los animales, especialmente al ganado vacuno y a los cerdos, por el nivel de estrés que se genera y la consecuente pérdida de peso, así como las frecuentes visitas del veterinario. Este problema fue resuelto por las investigaciones que revelan las publicaciones **D1** y **D3** cada una de manera independiente, toda vez que consiguen administrar agentes antibióticos en vehículos que permiten la liberación prolongada y sostenida en el tiempo de los principios activos.

Y dado que un indicio de falta de altura inventiva se deriva del intercambio de material por otro análogo conocido, en el caso particular el uso de diferentes agentes antibióticos o sustancias activas y además, el uso de equivalentes técnicos sin que se genere un efecto inesperado, es claro que la materia objeto de estudio se encuentra afectada por el conjunto de las publicaciones en comento **[D1 y D2]** o **[D2 y D3]** porque se derivan sus características esenciales a partir de las enseñanzas que revelan los documentos del estado de la técnica y el efecto técnico había sido previsto por ellas, es decir, la liberación prolongada en el tiempo del agente activo.

Por las razones expuestas anteriormente esta dependencia encuentra que el arte previo afecta la altura inventiva de la materia reclamada y por consiguiente considera que existe incumplimiento de las disposiciones contempladas en el artículo 18 del ordenamiento jurídico andino (D. 486).

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[2] Aceites Grasos:
Un gran número de medicamentos inyectables se elaboran como soluciones oleosas o como suspensiones oleosas. Con este fin en algunas farmacopeas se prescriben diversos aceites vegetales. Ocupan el primer lugar los aceites de cacahuete, oliva, almendras, girasol, soya y sésamo. El aceite de ricino muestra generalmente una capacidad disolvente de medicamentos muy favorable.

VOIGHT, R. Lehrbuch der pharmazeutischen technologie. Editorial Acribia. España. Página 428

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5. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO0061149	1 a 8	Nivel Inventivo
D2	US4016273	1 a 8	Nivel Inventivo
D3	WO9421267	1 a 8	Nivel Inventivo

6. Respuesta a los argumentos del solicitante:

- El señor solicitante señala en su memorial de fecha 03/03/2009 lo siguiente: *"A partir de la materia revelada por D1, una persona medianamente versada en la materia técnica determina que la lecitina o un fosfolípido son indispensables en la formulación para el ingrediente activo. Por el contrario, la composición de acuerdo con la invención no comprende estos excipientes. La presente solicitud posee entonces diferencias técnicas adicionales no establecidas por el Examinador".*

De conformidad con los argumentos del señor solicitante la materia reivindicada por él se diferencia del contenido del documento D1 en que en este documento se indica la adición indispensable de lecitina o de un fosfolípido. Sin embargo, esta lectura de las características más representativas de las composiciones reveladas por la publicación D1 no tiene en cuenta que a partir de la reivindicación 5 se están revelando modalidades alternativas de la materia allí descrita, es decir, aquellas composiciones que ADEMÁS pueden contener fosfolípidos o lecitina *(ver el significado gramatical de la palabra further en el contexto de la cláusula dependiente 5).*

Así, el contenido de la reivindicación 5 de la publicación WO0061149 señala una situación eventual para una modalidad particular de la invención allí revelada, no en vano esta cláusula se presenta en la forma de reivindicación dependiente, es decir, como una modalidad alternativa de la invención.

En consecuencia, una lectura acorde con lo revelado en el documento claramente le permite ver al conocedor de la materia que se trata, según la cláusula independiente 1, de composiciones antibacteriales de liberación prolongada que contienen como agente activo: *1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-tiazolil)-(metoxiimino)acetil]amino]-2-carboxi-8-oxo-5-tia-1-azabiciclo[4.2.0-oct-2-en-3-il]metil]-5,6,7,8-tetrahidroquinolina* en combinación con un agente gelificante y un portador farmacéuticamente aceptable.

Según la cláusula dependiente 2 dentro del género farmacotécnico de los gelificantes se prefiere una sal de aluminio de un ácido graso y según la cláusula 3 de manera particular se elige al diestearato de aluminio. Ahora bien, el contenido de la cláusula 4 de la publicación D1 señala que el portador corresponde a uno o más componentes seleccionados entre: aceite mineral, aceite vegetal, triglicéridos de ácidos grasos de cadena media y diésteres de ácidos grasos de cadena media de propilenglicol.

Así las cosas, se aleja de la verdad técnica el señor solicitante cuando afirma que el examinador no tuvo en cuenta todas las características de las composiciones que

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revela el documento **D1**, ya que allí se presentan dos modalidades de composición aquéllas que sólo contienen el principio activo más el agente gelificante diestearato de aluminio en un vehículo oleoso y aquellas que eventualmente contienen además de los excipientes señalados lecitina o un fosfolípido.

Por las razones señaladas, el documento **D1** si constituye una anterioridad válida y certera al momento de anticipar las características esenciales de las composiciones que reivindica el señor solicitante en el folio 113 de la solicitud.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 24 ABR. 2009

CONCEPTO TÉCNICO No. 1158	**EXAMINADOR TÉCNICO** Código No. **202044**