

OK



Industria y Comercio
SUPERINTENDENCIA

SS

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT
SOLICITANTE

PATENTE DE INVENCION

07.39669

21. EXPEDIENTE No.

54. TITULO: "USO DE UN INHIBIDOR mTOR EN EL TRATAMIENTO DE LEIOMIOMA UTERINO"

51. CLASIFICACIÓN INTERNACIONAL: A61K 31/00, A61K 31/436, A61K 31/445, A61P 15/00, A61P 35/00

71. SOLICITANTE: WYETH

DOMICILIO: NUEVA JERSEY, ESTADOS UNIDOS

74. APODERADO: ALVARO CORREA ORDOÑEZ
T.P.No.20.281

22. BOGOTA, D.C., Abril 20, 2007

F.W. 28-05-2007
Cecilia

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-039669-00000-0000

Fecha: 2007-04-20 16:45:17 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 79

5n

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

①

SOLICITUD DE :

☒

Patente de Invención

☐

Patente de Modelo de Utilidad

☒

Capítulo I.

☐

Capítulo II.

②

SOLICITANTE
(71)

Nombre: WYETH

Dirección: Five Giralda Farms, Madison, NJ 07940, Estados Unidos de América

Nacionalidad o Domicilio: Nueva Jersey, Estados Unidos de América

Lugar de Constitución: Delaware, Estados Unidos de América

Teléfono:

Fax:

E-Mail

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No.10-62 Piso 6

Teléfono: 634 1500

Fax: 376 2211

E-Mail: office.bogota@bakemet.com

IDENTIFICACION

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

79.143.366 de
Usaquén

TP 20.281

④

INVENTOR (ES)
(72)

Nombre: RUFFOLO, Robert R., Jr.

Dirección: 725 Pughtown Road, Spring City, Pennsylvania 19475, Estados Unidos de América.

Nacionalidad o Domicilio: Estadounidense

⑤ PCT (85)

Solicitud Internacional No. PCT/US2005/039836

Fecha 21-OCT-05

Publicación Internacional No. WO 2006/050461

Fecha 11-MAY-06

⑥

Título (54) USO DE UN INHIBIDOR mTOR EN EL TRATAMIENTO DE LEIOMIOMA UTERINO

⑦

Clasificación Internacional (51) A61K 31/00, A61K 31/436, A61K 31/445, A61P 15/00, A61P 35/00

⑧

Prioridad

SI ☒

NO ☐

(33) País de Origen

US

(32) Fecha

28-OCT-04

(31) Número de Solicitud

60/622,917

⑨

Comprobante de pago No. 07-19714

Fecha 08-MAR-07

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

10

ANEXOS

00002

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso
- ☒ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Extractos, Reporte de búsqueda internacional y opinión escrita y notificación de presentación de documento de prioridad.

11

FIGURA CARATERISTICA

12

Solicito la concesión de la patente,

NOMBRE:

ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de T.P. 20.281

Ucaguan

Instrucciones para la presentación de los anexos, ver reverso de esta página

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 19,714
FECHA : MARZO 8 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-039669-00000-0000
Fecha: 2007-04-20 16:45:17 Dep. 2020 NUECREACIONE
Tra. 11 PATENTE IYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 79

***** CONSIGNACION *****

DEBITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	54689077	08/03/2007	83,306,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

✓
nnnnn

TRADUCCIÓN OFICIAL N° 1104077 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR WYETH

APOSTILLA

1. País: Estados Unidos de América
Este documento público
2. Ha sido firmado por MICHELLE L MC GOWAN
3. Quien actúa en calidad de NOTARIO PÚBLICO DE NUEVA JERSEY
4. Lleva el sello de MICHELLE L MC GOWAN, NOTARIO

Certificado

5. En Trenton, Nueva Jersey
6. El 13 de marzo de 2007
7. Por Bradley Abelow, Tesorero de Nueva Jersey
8. N° A285576
9. Sello (Aparece adherido sello dorado)
10. Firma (firmado) Bradley Abelow


JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

Texto en inglés y en español mediante el cual **WYETH**, domiciliada en los Estados Unidos de América otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**, todos miembros de la firma de abogados Raisbeck, Lara, Rodríguez & Rueda domiciliada en Bogotá, Colombia.

1
nnnn5

Solicitud de Patente en Colombia titulada: **"USO DE UN INHIBIDOR mTOR EN EL TRATAMIENTO DEL LEIOMIOMA UTERINO"**

Dado y firmado el 27 de febrero de 2007

(Firma ilegible)
William H. Calnan, Subsecretario

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito notario certifica el 27 de febrero de 2007, la existencia legal de la sociedad WYETH, así como las funciones y firma de su representante autorizado William H. Calnan, Subsecretario, para efectos de lo cual se basó en lo siguiente:

Acta de Reunión de la Junta Directiva fechada el 27 de abril de 2006

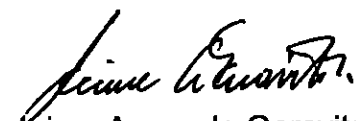
(Firmado) Michelle L. McGowan, Notario Público

(Sello en tinta que dice: "Michelle L. McGowan, Notario Público, Estado de

Nueva Jersey. No. 2108903. Calificado en el Condado de Morris. Comisión vence el 09 de febrero de 2011")

[Sello notarial realizado que dice: "Michelle L. McGowan, Notario Público, Nueva Jersey"]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.


Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 75059

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MICHELLE L MC GOWAN
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
MICHELLE L MC GOWAN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 13TH DAY OF MARCH 2007
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A285576
9. SEAL/STAMP: 10. SIGNATURE



Bradley Abelow

Bradley Abelow, NEW JERSEY TREASURER

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 880.088.840-3
Tel: +57 1 634 1500
Fax: +57 1 378 2211
www.bakernet.com

... 000007

POWER OF ATTORNEY

The undersigned.

WYETH

with offices at

Five Giralda Farms, Madison, NJ 07940,
United States of America

declares that it hereby grants to

**ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA**

all members of the law firm Raisbeck, Lara, Rodríguez & Rueda, with domicile at Av. 82 No. 10 - 62, 6th floor, of Bogotá D. C., Colombia, and for so long as they remain members of the law firm, a full and sufficient power of attorney with respect to Colombian patent application(s) based on PCT/US2005/039836 and entitled "USE OF AN MTOR INHIBITOR IN TREATMENT OF UTERINE LEIOMYOMA" and to obtain patent protection thereof, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of a patent(s) based upon said patent application(s), including filing of assignments, change of name or address, voluntary cancellation; and defending oppositions, cancellations, nullity, writ mandamus, and in general the civil, penal, an administrative processes relating to those rights.

I hereby ratify all lawful actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 27th day of February of 2007

Signature of the person issuing the Power

WYETH


William H. Calnan
Assistant Secretary

PODER DE ABOGADO

La abajo firmada,

WYETH

con oficinas en

Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

declara por el presente que otorga a

**ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA**

Todos miembros de la firma de abogados Raisbeck, Lara, Rodríguez & Rueda, con domicilio en la Av. 82 No. 10 - 62 Piso 6 en Bogotá D. C., Colombia, y hasta tanto ellos continúen siendo miembros de la firma, poder especial amplio y suficiente con respecto a la solicitud(es) de patente en Colombia basada(s) en PCT/US2005/039836 y titulada

“
”,
y para obtener la protección de patente de la misma, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de la(s) patente(s) de invención basada(s) en la mencionada solicitud de patente, incluyendo presentación de traspasos, cambio de nombre o dirección, cancelación voluntaria; y defensa en oposiciones, cancelaciones, nulidades, la tutela, y en general procesos civiles, penales, administrativos relacionados con estos derechos.

Igualmente, ratifico todo lo actuado en derecho hasta el momento en nombre de esta compañía por cualquiera de los mencionados apoderados en los casos mencionados.

Dado y firmado en

A los 27 días del mes de Febrero de 2007

Firma de la persona que firma el Poder

NOTARIAL CERTIFICATION

On this 27 day of February
2007, the undersigned Notary

CERTIFIES

1. That William H. Calnan

of legal age and located at

Five Giralda Farms, Madison, New Jersey 07940 U.S.A.

set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as

Assistant Secretary

of the judicial person WYETH

4. That the judicial person WYETH
having its office in

Five Giralda Farms, Madison, NJ 07940,
United States of America

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source: The minutes from the Board of Directors Meeting dated April 27, 2006.

CERTIFICACION NOTARIAL

A los 27 días del mes de febrero
de 2007, el suscrito Notario

DA FE

- 1 Que WILLIAM H. CALNAN

mayor y domiciliado en

Five Giralda Farms, New Jersey 07940
Estados Unidos de America
suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

- 3 Que el otorgante ha suscrito el referido documento en su carácter de

Subsecretario

de la persona jurídica WYETH

- 4 Que la persona jurídica WYETH
con sede en

Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

- 5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:

Actas de la Junta Directiva de la
reunión de fecha 27 d abril de 2006

Notary Public

Michelle L. McGowan
MICHELLE L. MCGOWAN
Notary Public, State of New Jersey
No. 2108903
Qualified in Morris County
Commission Expires Feb. 9, 2011

El Notario Público

PCT

REQUEST

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

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) AM-101846PCT

Box No. I TITLE OF INVENTION

USE OF AN mTOR INHIBITOR IN TREATMENT OF UTERINE LEIOMYOMA

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Wyeth
Five Giralda Farms
Madison, New Jersey 07940 US

Telephone No.
973-660-5000

Facsimile No.
973-660-7973

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant
for the purposes of:

☐ all designated
States

☒ all designated States except
the United States of America

☐ the United States
of America only

☐ the States indicated in
the Supplemental Box

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

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Ruffolo, Jr., Robert R.
725 Pughtown Road
Spring City, Pennsylvania 19475 US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is
marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant
for the purposes of:

☐ all designated
States

☐ all designated States except
the United States of America

☒ the United States
of America only

☐ the States indicated in
the Supplemental Box

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

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

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

☒ agent

☐ common
representative

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

Kodroff, Cathy A.
Howson and Howson
321 Norristown Road, Suite 200
Spring House Corporate Center
P.O. Box 457
Spring House, Pennsylvania 19477 US

Telephone No.
215-540-9200

Facsimile No.
215-540-5818

Teleprinter No.

Agent's registration No. with the Office
33,980

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

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) if more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If the applicant intends to make an indication of the wish that the international application be treated, in certain designated States, as an application for a patent of addition, certificate of addition, inventor's certificate of addition or utility certificate of addition: in such a case, write the name or two-letter code of each designated State concerned and the indication "patent of addition," "certificate of addition," "inventor's certificate of addition" or "utility certificate of addition," the number of the parent application or parent patent or other parent grant and the date of grant of the parent patent or other patent grant or the date of filing of the parent application (Rules 4.11(a)(iii) and 49bis.1(a) or (b)).

3. If the applicant intends to make an indication of the wish that the international application be treated, in the United States of America, as a continuation or continuation-in-part of an earlier application: in such a case, write "United States of America" or "US" and the indication "continuation" or "continuation-in-part" and the number and the filing date of the parent application (Rules 4.11(a)(iv) and 49bis.1(d)).

"Continuation of Box No. IV"

Kita, Stanley B., Reg. No. 24561
Smith, Jr., George A., Reg. No. 24442
Bak, Mary E., Reg. No. 31215
Bak, William, Reg. No. 37277
Duminiak, Robert J., Reg. No. 51636
Palovich, Tracy, Reg. No. 47840 (patent agent)

Above attorneys are members of the firm of
Howson and Howson.

Address of Howson and Howson is indicated in
Box No. IV.

Barnhard, Elizabeth M., Reg. No. 31088
Barrett, Rebecca R., Reg. No. 35152
Bellon, Christine P., Reg. No. 41611
Bittenbender, Teresa O., Reg. No. 47425
Brazil, Bill T., Reg. No. 50733
Calnan, William H., Reg. No. 29520
Collazo, Diana M., Reg. No. 46635
Flynn, Steven H., Reg. No. 29639
Fontenot, J. Darrell, Reg. No. 46705
Gordon, Alan M., Reg. No. 30637
Goudie, Joy S., Reg. No. 48146
Hild, Kimberly R., Reg. No. 39224
Hogan, John W., Jr., Reg. No. 32703
Hurley, Elizabeth A., Reg. No. 41859
King, William T., Reg. No. 30954
Lences, Barbara L., Reg. No. 41148
Levis, John F., Reg. No. 34210
Lumb, Kathryn M., Reg. No. 46885
Mandel, Adley F., Reg. No. 26942
Manspeizer, David A., Reg. No. 37540
Matthews, Gale F., Reg. No. 32269
Mazzarese, Joseph M., Reg. No. 32803
Milowsky, Arnold S., Reg. No. 35288
Moran, Daniel B., Reg. No. 41204
Nesler, Michael, Reg. No. 55489
Renda, Barbara L., Reg. No. 27626
Rozek, Carol E., Reg. No. 36993
Ryan, Mary Andrea, Reg. No. 28469
Shoarinejad, Fariba, Reg. No. 48182
Ubieta, Albert R., Reg. No. 43212
Webster, Darryl L., Reg. No. 34276

of Wyeth
Patent Law Department
Five Giralda Farms
Madison, New Jersey 07940 US

telephone: 973-660-7676
facsimile: 973-660-7973

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:
 - (i) if more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
 - (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
 - (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
 - (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
 - (v) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.
2. If the applicant intends to make an indication of the wish that the international application be treated, in certain designated States, as an application for a patent of addition, certificate of addition, inventor's certificate of addition or utility certificate of addition: in such a case, write the name or two-letter code of each designated State concerned and the indication "patent of addition," "certificate of addition," "inventor's certificate of addition" or "utility certificate of addition," the number of the parent application or parent patent or other parent grant and the date of grant of the parent patent or other patent grant or the date of filing of the parent application (Rules 4.11(a)(iii) and 49bis.1(a) or (b)).
3. If the applicant intends to make an indication of the wish that the international application be treated, in the United States of America, as a continuation or continuation-in-part of an earlier application: in such a case, write "United States of America" or "US" and the indication "continuation" or "continuation-in-part" and the number and the filing date of the parent application (Rules 4.11(a)(iv) and 49bis.1(d)).

"Continuation of Box No. IV"

Connelly, Michael John, EPI Reg. No. 52260
Denholm, Anna Marie, EPI Reg. No. 78620
Mannion, Sally Kim, EPI Reg. No. 62230
Talbot, Dawn Jacqueline, EPI Reg. No. 86720
Wileman, David Francis, EPI Reg. No. 46000

c/o Wyeth
Huntercombe Lane South
Taplow, Maidenhead
Berkshire SL6 0PH
United Kingdom

telephone: 1628-604-377
facsimile: 1628-799-098

00012

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents. However,

- ☐ DE Germany is not designated for any kind of national protection
- ☐ KR Republic of Korea is not designated for any kind of national protection
- ☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed: .

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 28 October 2004 (28/10/04)	60/622,917	US		
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)).

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / EP

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

00013

Box No. IX CHECK LIST; LANGUAGE OF FILING		
This international application contains: (a) on paper, the following number of sheets: request (including declaration sheets) : 5 description (excluding sequence listing and/or tables related thereto) : 17 claims : 3 abstract : 1 drawings : Sub-total number of sheets : 26 sequence listing : tables related thereto : (for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below) Total number of sheets : 26 (b) ☐ only in electronic form (Section 801(a)(i)) (i) ☐ sequence listing (ii) ☐ tables related thereto (c) ☐ also in electronic form (Section 801(a)(ii)) (i) ☐ sequence listing (ii) ☐ tables related thereto Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the ☐ sequence listing: ☐ tables related thereto: (additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): 1. ☒ fee calculation sheet : 1 2. ☐ original separate power of attorney : 3. ☐ original general power of attorney : 4. ☒ copy of general power of attorney; reference number, if any: : 1 5. ☐ statement explaining lack of signature : 6. ☐ priority document(s) identified in Box No. VI as item(s): : 7. ☐ translation of international application into (language): : 8. ☐ separate indications concerning deposited microorganism or other biological material : 9. ☐ sequence listing in electronic form (indicate type and number of carriers) (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) : (ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter : (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column : 10. ☐ tables in electronic form related to sequence listing (indicate type and number of carriers) (i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) : (ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) : (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column : 11. ☒ other (specify): transmittal letter to the USRO : 1	Number of items
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English	
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i>		
By: <u>Cathy A. Kodroff</u> Cathy A. Kodroff Attorney for Applicants		

For receiving Office use only	
1. Date of actual receipt of the purported international application: _____	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: _____	
4. Date of timely receipt of the required corrections under PCT Article 11(2): _____	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid
For International Bureau use only	
Date of receipt of the record copy by the International Bureau: _____	

00014

Assignment of Invention

In consideration of the payment by ASSIGNEE to ASSIGNOR of good and valuable consideration, the receipt of which is hereby acknowledged,
ASSIGNOR:

- (1) Full Name of Inventor: Robert R. Ruffolo, Jr.
Residence: 725 Pughtown Road, Spring City, PA 19475
Citizenship: US

hereby sells, assigns and transfers to ASSIGNEE:

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

and the successors, assigns and legal representatives of the ASSIGNEE the entire right, title and interest for the United States and its territorial possessions and in all foreign countries, including all rights to claim priority, in and to the invention entitled:

METHOD OF TREATING UTERINE LEIOMYOMA

and invented by ASSIGNOR and the following additional inventors, if any:

and which is found in U.S. Provisional Application No 60/622,917 filed on: October 28, 2004

[also check if foreign application(s) is(are) also being assigned]

☒ and any legal equivalent thereof in a foreign country,

the date of filing and application number of said U.S. application when known, to be inserted above, including the right to claim priority, including any and all improvements disclosed therein, and in and to all Letters Patent to be obtained for said invention by the above application or any subsequently filed provisional, nonprovisional, continuation, divisional, renewal, or substitute thereof, and as to Letters Patent any reissue or re-examination thereof.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR authorizes ASSIGNEE to make applications for and to receive Letters patent for said invention in any of said countries in its own name, or in ASSIGNOR's name, at its election.

ASSIGNOR covenants and agrees to execute or procure any further necessary assurance of the title to said invention and any Letters Patent which may issue therefore and to, at any time, upon the request and at the expense of ASSIGNEE deliver any testimony in any interference, litigation or proceeding related thereto and execute all papers that may be necessary or desirable to perfect the title to said invention or any Letters Patent which may be granted therefore in ASSIGNEE, its successors, assigns or other legal representatives, and that to, at any time, upon the request and at the expense of ASSIGNEE execute any continuation, continuation-in-part, divisional, renewal or substitute thereof, and as to Letters Patent and reissue or re-examination thereof, or any other additional applications of Letters Patent for said invention or any part thereof, all of which applications and any Letters Patent issuing thereon are hereby assigned to ASSIGNEE, and will make all rightful oaths or declarations, and do all lawful acts requisite for procuring the same therein, without further compensation, but at the expense of ASSIGNEE, its successors, assigns or other legal representatives.

ASSIGNOR authorizes and requests the Commissioner of Patents to issue any and all Letters Patent of the United States for said invention, resulting from any of the aforesaid applications to its ASSIGNEE

Robert R. Ruffolo, Jr. 11/11/04
Robert R. Ruffolo, Jr. Date

ACKNOWLEDGMENT

State of Pennsylvania }
County of Montgomery } ss:

On the 11th day of November, 2004, Robert R. Ruffolo, Jr. personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.



Rubene D. Owens
Notary Public

(19) World Intellectual Property Organization
International Bureau



PCT

(43) International Publication Date
11 May 2006 (11.05.2006)

(10) International Publication Number
WO 2006/050461 A1

(51) International Patent Classification:

A61K 31/00 (2006.01) A61P 15/00 (2006.01)
A61K 31/436 (2006.01) A61P 35/00 (2006.01)
A61K 31/445 (2006.01)

(21) International Application Number:

PCT/US2005/039836

(22) International Filing Date: 21 October 2005 (21.10.2005)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/622,917 28 October 2004 (28.10.2004) US

(71) Applicant (for all designated States except US): WYETH
[US/US]; Five Giralda Farms, Madison, New Jersey 07940
(US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): RUFFOLO, Robert,
R., Jr. [US/US]; 725 Pughtown Road, Spring City, Penn-
sylvania 19475 (US).

(74) Agent: KODROFF, Cathy, A.; Howson and Howson, 321
Norristown Road, Suite 200, Spring House Corporate Cen-
ter, P.O. Box 457, Spring House, Pennsylvania 19477 (US).

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

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

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

(54) Title: USE OF AN MTOR INHIBITOR IN TREATMENT OF UTERINE LEIOMYOMA

(57) Abstract: The invention provides for the use of an mTOR inhibitor in the treatment or inhibition of fibroids.

WO 2006/050461 A1

USE OF AN mTOR INHIBITOR IN TREATMENT OF UTERINE LEIOMYOMA

5

BACKGROUND OF THE INVENTION

This invention relates to the use of an mTOR inhibitor in the treatment or inhibition of uterine leiomyoma (fibroids) in a mammal.

10 mTOR, also known as FKBP12-rapamycin associated protein (FRAP), is a key enzyme in a variety of signal transduction pathways, including cytokine-stimulated cell proliferation, translation of mRNAs for several key proteins that regulate the G1 phase of the cell cycle, and interleukin-2 (IL-2) induced transcription. Inhibition of mTOR leads to the inhibition of the progression of the cell cycle from G1 to S. Rapamycin
15 (commercially available as SirolimusTM), a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus*, has been identified as a key mTOR inhibitor.

Rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is an ester of rapamycin. The preparation and use of hydroxyesters of rapamycin, including CCI-779, are described in U.S. Patent Nos. 5,362,718 and
20 6,277,983. Still another regioselective method for synthesis of CCI-779 is described in U.S. Patent Application No. 10/903,062, filed July 30, 2004 (published February 10, 2005 as U.S. Patent Publication No. US 2005-0033046 A1), and its counterpart, International Patent Application No. PCT/US2004/22860 (published February 24, 2005 as International Patent Publication No. WO 2005/016935 A3). CCI-779 has been described
25 as having an *in vitro* and *in vivo* activity against a number of tumor cell types. CCI-779 binds to and forms a complex with the cytoplasmic protein FKBP, which inhibits mTOR. It is hypothesized that CCI-779 delays the time to progression of tumors or time to tumor recurrence. This mechanism of action is more typical of cytostatic rather than cytotoxic agents and is similar to that of sirolimus.

30 Uterine leiomyoma (fibroids) are benign tumors arising from the myometrium (smooth muscle layer) of the uterus. Leiomyoma are the most common solid pelvic tumor of women and are 2-5 times more likely to occur in black women than white women. Fibroids occur in as many as 75% of reproductive age women, with 25% of

00018

these women symptomatic to the point of seeking treatment. Women with symptomatic fibroids suffer from menorrhagia, pelvic pain and pressure, and are more subject to reproductive dysfunction such as infertility or multiple miscarriages.

5 The primary treatment for patients with fibroids is surgery - either myomectomy for removal of tumor and preservation of childbearing potential, or hysterectomy. Fibroids are the most common indication for hysterectomy and account for approximately 200,000 procedures performed annually in the United States.

Thus, there is a need in the art for more effective methods of treating and inhibiting fibroids.

10

SUMMARY OF THE INVENTION

The invention provides for the use of an mTOR inhibitor in treating or inhibiting, or in the preparation of a medicament useful in treating or inhibiting, uterine leiomyoma (fibroids) in a female mammalian subject. In another aspect, the invention provides for
15 the use of a rapamycin in treating or inhibiting, or in the preparation of a medicament useful in treating or inhibiting, uterine leiomyoma in a female mammalian subject. In one embodiment, the invention provides the use of rapamycin or CCI-779 in treating or inhibiting, or in the preparation of a medicament useful in treating or inhibiting, uterine leiomyoma in a female mammalian subject.

20 In other aspects, the invention provides for pharmaceutical compositions comprising an mTOR inhibitor, and in certain embodiments, a rapamycin, rapamycin, or CCI-779, in unit dosage form in association with a pharmaceutically acceptable carrier, which are useful in treating or inhibiting uterine leiomyoma in a female mammalian subject.

25 In yet another embodiment, the invention provides for pharmaceutical packs containing a course of treatment of uterine leiomyoma for one individual mammal, each pack comprising a container having one unit, one to four units, or more units of an mTOR inhibitor, and in certain embodiments, a rapamycin, rapamycin or CCI-779 in unit dosage form.

30 Other aspects and advantages of the invention will be apparent from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

nnn19

The present invention provides methods of using an effective amount of an mTOR inhibitor in the treatment or inhibition of, or in the preparation of a medicament useful in treating or inhibiting, uterine leiomyoma (fibroids). In one embodiment, an effective amount of rapamycin is useful in methods of treating or inhibiting fibroids. In another embodiment, an effective amount of CCI-779 (rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid) is useful in methods of treating or inhibiting fibroids. Other compounds useful in the methods of the invention in treating or inhibiting fibroids include effective amounts of a rapamycin, such as esters (including 42-esters), ethers (including 42-ethers), oximes, hydrazones, and hydroxylamines of rapamycin. In another embodiment, the invention provides for methods of treating or inhibiting fibroids using an effective amount of 42-O-(2-hydroxy)ethyl rapamycin (CerticanTM (everolimus)).

In another embodiment, FK-506 is useful in methods of treating or inhibiting fibroids. In another embodiment, AP23573 is useful in methods of treating or inhibiting fibroids.

As used herein, the term **fibroid** or **fibroids** shall have the same meaning as uterine leiomyoma, as described above.

As used herein, the term **mTOR inhibitor** means a compound or ligand, or a pharmaceutically acceptable salt thereof, that inhibits cell replication by blocking the progression of the cell cycle from G1 to S. The term includes the neutral tricyclic compound rapamycin (sirolimus) and other rapamycin compounds, including, *e.g.*, rapamycin derivatives, rapamycin analogues, other macrolide compounds that inhibit mTOR activity, and all compounds included within the definition below of the term "a rapamycin".

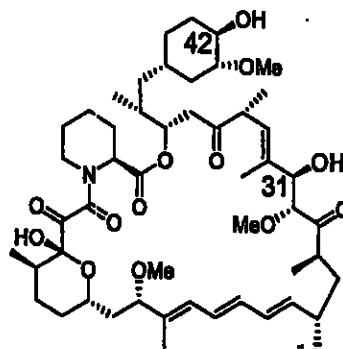
These include compounds with a structural similarity to "a rapamycin", *e.g.*, compounds with a similar macrocyclic structure that have been modified to enhance therapeutic benefit. The term also includes, *e.g.*, rapamycin, 32-deoxorapamycin, 16-pent-2-ynyloxy-32-deoxorapamycin, 16-pent-2-yllyloxy-32(S)-dihydro-rapamycin, 16-pent-2-yllyloxy-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-

20
nnn 20

methylpropionic acid (CCI-779), 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin, or a pharmaceutically acceptable salt thereof, as disclosed in U.S. Patent No. 5,362,718, ABT578, or 40-(tetrazolyl)-rapamycin, 40-epi-(tetrazolyl)-rapamycin, *e.g.*, as disclosed in International Patent Publication No. WO 99/15530, or
5 rapamycin analogs as disclosed in International Patent Publication No. WO 98/02441 and WO 01/14387, *e.g.*, AP23573.

FK-506 can also be used in the method of the invention.

As used herein, the term a rapamycin defines a class of immunosuppressive compounds that contain the basic rapamycin nucleus as shown below.



10

The rapamycins of this invention include compounds that are chemically or biologically modified as derivatives of the rapamycin nucleus, while still retaining immunosuppressive properties. Accordingly, the term a rapamycin includes rapamycin,
15 and esters, ethers, carbamates, oximes, hydrazones, and hydroxylamines of rapamycin, as well as rapamycins in which functional groups on the rapamycin nucleus have been modified, for example through reduction or oxidation. Also included in the term a rapamycin are pharmaceutically acceptable salts of rapamycins.

The term a rapamycin also includes 42- and/or 31-esters and ethers of rapamycin
20 as described in the following patents, which are all hereby incorporated by reference: alkyl esters (U.S. Patent No. 4,316,885); aminoalkyl esters (U.S. Patent No. 4,650,803); fluorinated esters (U.S. Patent No. 5,100,883); amide esters (U.S. Patent No. 5,118,677); carbamate esters (U.S. Patent No. 5,118, 678); silyl esters (U.S. Patent No. 5,120,842); aminodiester (U.S. Patent No. 5,162,333); sulfonate and sulfate esters (U.S. Patent No.
25 5,177,203); esters (U.S. Patent No. 5,221,670); alkoxyesters (U.S. Patent No. 5,233,036);

21
00021

O-aryl, -alkyl, -alkenyl, and -alkynyl ethers (U.S. Patent No. 5,258,389); carbonate esters (U.S. Patent No. 5,260,300); arylcarbonyl and alkoxy carbonyl carbamates (U.S. Patent No. 5,262,423); carbamates (U.S. Patent No. 5,302,584); hydroxyesters (U.S. Patent No. 5,362,718); hindered esters (U.S. Patent No. 5,385,908); heterocyclic esters (U.S. Patent No. 5,385,909); gem-disubstituted esters (U.S. Patent No. 5,385,910); amino alkanolic esters (U.S. Patent No. 5,389,639); phosphorylcarbamate esters (U.S. Patent No. 5,391,730); carbamate esters (U.S. Patent No. 5,411,967); carbamate esters (U.S. Patent No. 5,434,260); amidino carbamate esters (U.S. Patent No. 5,463,048); carbamate esters (U.S. Patent No. 5,480,988); carbamate esters (U.S. Patent No. 5,480,989); carbamate esters (U.S. Patent No. 5,489,680); hindered N-oxide esters (U.S. Patent No. 5,491,231); biotin esters (U.S. Patent No. 5,504,091); O-alkyl ethers (U.S. Patent No. 5,665,772); and PEG esters of rapamycin (U.S. Patent No. 5,780,462). The preparation of these esters and ethers is disclosed in the patents listed above.

Further included within the definition of the term a rapamycin are 27-esters and ethers of rapamycin, which are disclosed in U.S. Patent No. 5,256,790, which is hereby incorporated by reference. Also described are C-27 ketone rapamycins which are reduced to the corresponding alcohol, which is in turn converted to the corresponding ester or ether. The preparation of these esters and ethers is disclosed in the patent listed above. Also included are oximes, hydrazones, and hydroxylamines of rapamycin are disclosed in U.S. Patent Nos. 5,373,014, 5,378,836, 5,023,264, and 5,563,145, which are hereby incorporated by reference. The preparation of these oximes, hydrazones, and hydroxylamines is disclosed in the above-listed patents. The preparation of 42-oxorapamycin is disclosed in 5,023,263, which is hereby incorporated by reference.

As used herein, the term a CCI-779 means rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid, and encompasses prodrugs, derivatives, pharmaceutically acceptable salts, or analogs thereof.

As used herein, the term treatment means treating a mammal having fibroids (uterine leiomyoma) by providing said mammal with an effective amount of a compound or composition for the purpose of inhibiting growth of the fibroid, eradication of the fibroid, or palliation of the fibroid.

nnn22

As used herein, the term **inhibition** means delaying or preventing the onset or progression of fibroids in a mammal having or susceptible to developing such disease by providing said mammal with an effective amount of a compound or composition of the invention.

5 As used herein, the term **providing** means either directly administering a compound or composition of the invention or administering a prodrug, derivative, pharmaceutical salt, or analog of an mTOR inhibitor, which will result in a desired amount of the compound or composition in the body.

10 All terms used herein, whether used in the singular or plural form, shall include both the singular and plural form unless otherwise indicated.

As used herein, the terms **include**, **includes**, and **including** indicates that the subject is open to other items, *i.e.*, an open class.

As used herein, the terms **comprise**, **comprises**, and **comprising** indicates that the subject is open to other items, *i.e.*, an open class.

15 As used herein, the terms **contain**, **contains**, and **containing** indicates that the subject is open to other items, *i.e.*, an open class.

As used herein, the terms **consists of** and **consisting of** indicates that the subject is closed to other items, *i.e.*, a closed class.

20 All other terms used herein shall be defined as expressly or impliedly defined within this specification, and then, if necessary, in accordance with their interpretation by one of ordinary skill in the relevant art.

Compositions/Formulations:

25 Compositions useful in the present invention comprise an active compound (*e.g.*, an mTOR inhibitor) as described herein. In one embodiment, the compound is CCI-779 (rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid)(U.S. Patent No. 5,362,718). The preparation of CCI-779 is disclosed in U.S. Patent No. 5,362,718, which is hereby incorporated by reference. A regioselective preparation of CCI-779 is described in U.S. Patent No. 6,277,983. Still another regiospecific method for
30 synthesis of CCI-779 is described in US Patent Application No. 10/903,062, filed July 30,

2004, and its counterpart, International Patent Application PCT/US2004/22860, filed July 15, 2004. Rapamycin is commercially available as SirolimusTM.

In another embodiment, the compound is AP23573. In another embodiment, the compound is CerticanTM (everolimus). Other compounds useful in the methods, compositions, and pharmaceutical packs of the invention include a rapamycin, such as rapamycin, esters (including 42-esters), ethers (including 42-ethers), oximes, hydrazones, and hydroxylamines of rapamycin. In another embodiment, the rapamycin is 42-O-(2-hydroxy)ethyl rapamycin (everolimus, Novartis, U.S. Patent No. 5,665,772, hereby incorporated by reference). In other embodiments, compositions of the present invention contain other compounds useful in the invention as described herein.

In yet another embodiment, the compound is FK-506.

Administration of the compositions may be oral, intravenous, respiratory (*e.g.*, nasal or intrabronchial), parenteral, intraperitoneal, transdermal (including all administration across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues), and vaginal (including intrauterine administration).

It is projected that the oral dosage of a compound useful in the invention will be 10 mg/ week to 250 mg/week, about 20 mg/week to about 150 mg/week, about 25 mg/week to about 100 mg/week, or about 30 mg/week to about 75 mg/week. For rapamycin, the projected oral dosage will be between 0.1 mg/day to 25 mg/day. Intravenous dosages are generally predicted to be five to tenfold less than oral dosages. Precise dosages will be determined by the administering physician based on experience with the individual subject to be treated.

In one embodiment, the pharmaceutical composition is in unit dosage form, *e.g.*, as tablets, capsules, or pre-filled vials or syringes. In such form, the composition is subdivided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, pre-filled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

24

nonox

Oral formulations containing the compounds of this invention may comprise any conventionally used forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as pharmaceutically acceptable

5 starches (e.g., corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants),

10 suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium laurel sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, dry starches and

15 powdered sugar. Surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine.

20 Oral formulations herein may utilize delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also comprise administering the active compound in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed. Preferred oral formulations for CCI-779 are disclosed in U.S. Published Patent Application No. US 2004-0077677 A1 (also U.S.

25 Patent Application No. 10/663,506). Preferred solid oral formulations for rapamycin are disclosed in US Patent 5,989,591, and preferred oral liquid formulations for rapamycin are disclosed in 5,536,729.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

30 The compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically

acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

5 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of
10 microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. In one embodiment, injectable formulations for CCI-779 are disclosed in U.S. Patent Publication No. US 2004-0167152 (also U.S. Patent Application No. 10/626,943), which is hereby
15 incorporated by reference.

In one embodiment, the injectable formulation useful in the invention provides a compound in a cosolvent concentrate containing a parenterally acceptable solvent and an antioxidant as described above and a parenteral formulation containing a compound
20 useful in the invention, a parenterally acceptable cosolvent, an antioxidant, a diluent solvent, and a surfactant. Any given formulation useful in this invention may contain multiple ingredients of each class of component. For example, a parenterally acceptable solvent can include a nonalcoholic solvent, an alcoholic solvent, or mixtures thereof.

Examples of suitable non-alcoholic solvents include, e.g., dimethylacetamide, dimethylsulfoxide or acetonitrile, or mixtures thereof. An alcoholic solvent may contain
25 one or more alcohols as the alcoholic solvent component of the formulation. Examples of solvents useful in the formulations of the invention include, without limitation, ethanol, propylene glycol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 1000, or mixtures thereof. These cosolvents are particularly desirable because degradation via oxidation and lactone cleavage occurs to a lower extent
30 for these cosolvents. Further, ethanol and propylene glycol can be combined to produce a less flammable product, but larger amounts of ethanol in the mixture generally result in

76

00000

better chemical stability. A concentration of 30 to 100% v/v ethanol in the mixture is preferred.

5 In another embodiment, the stability of a compound useful in the invention in parenterally acceptable alcoholic solvents is enhanced by addition of an antioxidant to the formulation. Acceptable antioxidants include, but are not limited to, citric acid, d,1- α -tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, propyl gallate, and mixtures thereof. Generally, the parenteral formulations useful in this embodiment will contain an antioxidant component(s) in a concentration ranging from 0.001% to 1% w/v, or 0.01% to 0.5% w/v, of the cosolvent concentrate although lower or higher concentrations may be 10 desired. In one embodiment, of the antioxidants, d,1- α -tocopherol is particularly desirable and is used at a concentration of 0.01 to 0.1% w/v with a preferred concentration of 0.075% w/v of the cosolvent concentrate.

15 In other embodiments, the antioxidant component of the formulation of the invention also exhibits chelating activity. Examples of such chelating agents include, e.g., citric acid, acetic acid, and ascorbic acid (which may function as both a classic antioxidant and a chelating agent in the present formulations). Other chelating agents include such materials as are capable of binding metal ions in solution, such as ethylene diamine tetra acetic acid (EDTA), its salts, or amino acids such as glycine are capable of enhancing the stability of a compound useful in the invention. In some embodiments, 20 components with chelating activity are included in the formulations of the invention as the sole antioxidant component. Typically, such metal-binding components, when acting as chelating agents are used in the lower end of the range of concentrations for the antioxidant components provided herein. Higher concentrations yield less stable solutions and thus, less desirable for products to be subject to long-term storage in liquid form. Additionally, such chelating agents may be used in combination with other 25 antioxidants as part of the antioxidant component of the invention. For example, an acceptable formulation may contain both citric acid and d,1- α -tocopherol. Optimal concentrations for the selected antioxidant(s) can be readily determined by one of ordinary skill in the art, based upon the information provided herein.

30 In certain embodiments of the parenteral formulations useful in the invention, surfactants are used in the diluent solution to prevent precipitation of the components of

the formulation. Parenterally acceptable surfactants may be readily selected by one of ordinary skill in the art and include: polysorbate 20, polysorbate 80, salts of bile acids (taurocholate, glycocholate, cholate, deoxycholate, etc.), which are optionally combined with lecithin. Alternatively, ethoxylated vegetable oils, such as a pegylated castor oil (e.g., such as PEG-35 castor oil which is sold, e.g., under the name Cremophor EL, BASF), vitamin E tocopherol propylene glycol succinate (Vitamin E TGPS), and polyoxyethylene-polyoxypropylene block copolymers can be used in the diluent as a surfactant, as well as other members of the polysorbate family such as polysorbate 20 or 60. Other components of the diluent may include water, ethanol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 1000, or blends containing one or more of these polyethylene glycols, propylene glycol and other parenterally acceptable sugars, polyols and electrolytes. It is expected that the surfactant will comprise 2 to 100% w/v, 5 to 80% w/v, 10 to 75% w/v, 15 to 60% w/v, 5% w/v, or 10% w/v, of the diluent solution.

A parenteral formulation useful in the invention can be prepared as a single solution, or can be prepared as a cosolvent concentrate containing a compound useful in the invention, an alcoholic solvent, and an antioxidant, which is subsequently combined with a diluent that contains a diluent solvent and suitable surfactant. Prior to use, the cosolvent concentrate is mixed with a diluent comprising a diluent solvent, and a surfactant. In one embodiment, a compound useful in the invention is prepared as a cosolvent concentrate according to the invention, having concentrations of compound from 0.05 mg/mL, from 2.5 mg/mL, from 5 mg/mL, from 10 mg/mL, or from 25 mg/mL up to approximately 50 mg/mL. The concentrate can be mixed with the diluent up to approximately 25 mg/mL. For example, the concentration of a compound useful in the invention in the parenteral formulation may be from about 2.5 to 10 mg/mL. This invention also covers the use of formulations having lesser concentrations of a compound useful in the invention in the cosolvent concentrate, and formulations in which one part of the concentrate is mixed with greater than 1 part of the diluent, e.g., concentrate:diluent in a ratio of about 1:1.5, 1:2, 1:3, 1:4, 1:5, or 1:9 v/v, and so on, to parenteral formulations having compound concentrations down to the lowest levels of detection.

28

nnnn

In another embodiment, the antioxidant may comprise from about 0.0005 to 0.5% w/v of the formulation. The surfactant may, for example, comprise from about 0.5% to about 10% w/v of the formulation. The alcoholic solvent may be, for example, from about 10% to about 90% w/v of the formulation.

- 5 In other embodiments, the parenteral formulations useful in this invention can be used to produce a dosage form that is suitable for administration by either direct injection or by addition to sterile infusion fluids for intravenous infusion.

- Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. Such administrations may be carried out using the compounds useful in the invention, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal). The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active compound into the blood stream such as a semi-permeable membrane covering a reservoir containing the active compound with or without a carrier, or a matrix containing the active compound. Other occlusive devices are known in the literature and would be readily available to one of skill in the art.
- 10
15
20

- Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.
- 25

In one embodiment, the compositions are delivered vaginally in the form of a conventional suppository, cream, gel, ring, or coated intrauterine device (IUD).

29

mamm

Pharmaceutical Packs/Kits:

The invention includes a product or pharmaceutical pack containing a course of treatment of uterine leiomyoma for one individual mammal comprising one or more container(s) having one, one to four, or more unit(s) of an mTOR inhibitor (e.g., CCI-779) in unit dosage form

In another embodiment, pharmaceutical packs contain a course of treatment of uterine leiomyoma for one individual mammal comprising a container having a unit of a rapamycin in unit dosage form. In other embodiments, the rapamycin is rapamycin, an ester (including a 42-ester, ether (including a 42-ether), oxime, hydrazone, or hydroxylamine of rapamycin. In another embodiment, the rapamycin is 42-O-(2-hydroxy)ethyl rapamycin.

In another embodiment, the rapamycin is CCI-779, and the pack contains one or more container(s) comprising one, one to four, or more unit(s) of CCI-779.

In some embodiments, the compositions of the invention are in packs in a form ready for administration. In other embodiments, the compositions of the invention are in concentrated form in packs, optionally with the diluent required to make a final solution for administration. In still other embodiments, the product contains a compound useful in the invention in solid form and, optionally, a separate container with a suitable solvent or carrier for the compound useful in the invention.

In still other embodiments, the above packs/kits include other components, e.g., instructions for dilution, mixing and/or administration of the product, other containers, syringes, needles, etc. Other such pack/kit components will be readily apparent to one of skill in the art.

The following examples are illustrative of the present invention, but are not a limitation thereof.

EXAMPLES

Example 1: *In vivo* testing of the effectiveness of treatment of fibroids in the Eker rat

5 A. *Background:*

The Eker rat is a well-characterized model system for uterine leiomyoma [Walker, et al., *Genes, Chromosomes, and Cancer*, 38:349-356 (2003); Houston, et al., *Cancer Research*, 63:1221-1227 (2003); and Walker, C.L., *Journal of the Society for Gynecologic Investigation*, 7(4), 249-256 (2000)]. Approximately 65% of virgin female
10 Eker rats spontaneously develop uterine leiomyoma by 12-16 months as a result of mutation of the *Tsc-2* gene.

 B. *Method:*

Eker rats 12-16 months of age are treated with a compound useful in the invention and evaluated for tumor regression via conventional techniques and methods
15 (e.g., ultrasound or laparoscopy). RNA/protein obtained from study animals is obtained and used *in vitro* for characterization of the mechanism(s) of compound effectiveness.

 C. *Results:*

A tested mTOR inhibitor, e.g., CCI-779, is expected to be effective in the treatment of uterine leiomyoma (fibroids) in the dosage range of approximately 10-250
20 mg/week (oral) or approximately 2-50 mg/week (intravenous). A tested rapamycin is expected to be effective at the projected oral dosage of between 0.1 mg/day to 25 mg/day.

Example 2: *In vivo* testing of the effectiveness of treatment of fibroids in the Guinea pig

25 A. *Background:*

Guinea pigs spontaneously develop fibroids as they age. This process may be accelerated by administration of estradiol, all-trans retinoic acid and troglitazone [Tsibris, et al., *J. Soc. Gynecol. Invest.*, 5(suppl1):180 (abstract)(1998); Tsibris, et al., *Cancer Res.*, 59:5737 (1999); and U.S. Patent No. 6,218,594 B1].

31

B. Method:

Fibroids are induced in Guinea pigs by treatment with estradiol, all-trans retinoic acid and troglitazone. Guinea pigs are then treated with a compound useful in the invention and evaluated for tumor regression via conventional techniques and methods (e.g., ultrasound or laparoscopy). RNA/protein obtained from study animals is obtained and used *in vitro* for characterization of the mechanism(s) of compound effectiveness.

C. Results:

A tested mTOR inhibitor, e.g., CCI-779, is expected to be effective in the treatment of uterine leiomyoma (fibroids) in the dosage range of approximately 10-250 mg/week (oral) or approximately 2-50 mg/week (intravenous). A tested rapamycin is expected to be effective at the projected oral dosage of between 0.1 mg/day to 25 mg/day.

Example 3: *In vivo* testing of the effectiveness of inhibition of fibroids in the Eker rat

A. Background:

The Eker rat is a well-characterized model system for uterine leiomyoma [Walker, et al., *Genes, Chromosomes, and Cancer*, 38:349-356 (2003); Houston, et al., *Cancer Research*, 63:1221-1227 (2003); and Walker, C.L., *Journal of the Society for Gynecologic Investigation*, 7(4), 249-256 (2000)]. Approximately 65% of virgin female Eker rats spontaneously develop uterine leiomyoma by 12-16 months as a result of mutation of the *Tsc-2* gene.

B. Method:

Eker rats at approximately 9 months of age are treated with a compound useful in the invention and evaluated for tumor inhibition by comparison with a vehicle-treated control group until following the time in which vehicle-treated rats have developed tumors (about 12-16 months of age). Tumor growth is monitored via conventional techniques and methods (e.g., ultrasound or laparoscopy). RNA/protein obtained from study animals is obtained and used for characterization of compound effectiveness.

32

NAME

C. *Results:*

A tested mTOR inhibitor, *e.g.*, CCI-779, is expected to be effective in the inhibition of uterine leiomyoma (fibroids) in the dosage range of approximately 10-250 mg/week (oral) or approximately 2-50 mg/week (intravenous). A tested rapamycin is
5 expected to be effective at the projected oral dosage of between 0.1 mg/day to 25 mg/day.

Example 4: *In vivo* testing of the effectiveness of inhibition of fibroids in the Guinea pig

A. *Background:*

10 Guinea pigs spontaneously develop fibroids as they age. This process may be accelerated by administration of estradiol, all-trans retinoic acid and troglitazone [Tsibris, et al., *J. Soc. Gynecol. Invest.*, 5(suppl1):180 (abstract)(1998); Tsibris, et al., *Cancer Res.*, 59:5737 (1999); and U.S. Patent No. 6,218,594 B1].

B. *Method:*

15 Healthy Guinea pigs, not having fibroids, are treated with a compound useful in the invention and evaluated for tumor regression via conventional techniques and methods (*e.g.*, ultrasound or laparoscopy). Guinea pigs are then subjected to treatment with estradiol, all-trans retinoic acid and troglitazone, and compared to Guinea pigs not pre-treated with a compound useful in the invention. RNA/protein obtained from
20 study animals is obtained and used *in vitro* for characterization of the mechanism(s) involved in fibroid tumorigenesis.

C. *Results:*

A tested mTOR inhibitor, *e.g.*, CCI-779, is expected to be effective in the inhibition of uterine leiomyoma (fibroids) in the dosage range of approximately 10-250
25 mg/week (oral) or approximately 2-50 mg/week (intravenous). A tested rapamycin is expected to be effective at the projected oral dosage of between 0.1 mg/day to 25 mg/day.

30

33

~~00003~~

- All documents identified herein are incorporated by reference. One of skill in the art will recognize that minor modifications to the conditions and techniques described in the specific embodiments described herein can be varied without departing from the present invention. Such minor modifications and variants are within the scope of the
5. invention as defined by the following claims.

34

CLAIMS:

1. Use of an mTOR inhibitor in the preparation of a medicament useful in the treatment or inhibition of uterine leiomyoma in a mammal.
2. Use of a rapamycin in the preparation of a medicament useful in the treatment or inhibition of uterine leiomyoma in a mammal.
3. Use according to claim 2, wherein the rapamycin is rapamycin.
4. Use according to claim 2, wherein the rapamycin is an ester, ether, oxime, carbamate, hydrazone, or hydroxylamine of rapamycin.
5. Use according to claim 4, wherein the rapamycin is a 42-ester or 42-ether of rapamycin.
6. Use according to claim 5, wherein the rapamycin is 42-O-(2-hydroxy)ethyl rapamycin.
7. Use of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) in the preparation of a medicament useful in the treatment or inhibition of uterine leiomyoma in a mammal.
8. A pharmaceutical composition useful in treating or inhibiting uterine leiomyoma in a mammal, the composition comprising an mTOR inhibitor in unit dosage form in association with a pharmaceutically acceptable carrier.
9. A pharmaceutical composition useful in treating or inhibiting uterine leiomyoma in a mammal, the composition comprising a rapamycin in unit dosage form in association with a pharmaceutically acceptable carrier.

35

10. The pharmaceutical composition according to claim 9, wherein the rapamycin is rapamycin.
11. The pharmaceutical composition according to claim 9, wherein the rapamycin is an ester, ether, carbamate, oxime, hydrazone, or hydroxylamine of rapamycin.
12. The pharmaceutical composition according to claim 11, wherein the rapamycin is a 42-ester or 42-ether of rapamycin.
13. The pharmaceutical composition according to claim 12, wherein the rapamycin is 42-O-(2-hydroxy)ethyl rapamycin.
14. A pharmaceutical composition useful in treating or inhibiting uterine leiomyoma in a mammal, the composition comprising rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) in unit dosage form in association with a pharmaceutically acceptable carrier.
15. A pharmaceutical pack containing a course of treatment of uterine leiomyoma for one individual mammal, said pack comprising a container having a unit of an mTOR inhibitor in unit dosage form.
16. The pharmaceutical pack according to claim 15, wherein said pack contains one to four units of an mTOR inhibitor.
17. A pharmaceutical pack containing a course of treatment of uterine leiomyoma for one individual mammal, said pack comprising a container having a unit of a rapamycin in unit dosage form.
18. The pharmaceutical pack according to claim 17, wherein the rapamycin is rapamycin.

36
~~119999~~

19. The pharmaceutical pack according to claim 17, wherein the rapamycin is an ester, ether, carbamate, oxime, hydrazone, or hydroxylamine of rapamycin.

20. The pharmaceutical pack according to claim 19, wherein the rapamycin is a 42-ester or 42-ether of rapamycin.

21. The pharmaceutical pack according to claim 20, wherein the rapamycin is 42-O-(2-hydroxy)ethyl rapamycin.

22. A pharmaceutical pack containing a course of treatment of uterine leiomyoma for one individual mammal, said pack comprising a container having a unit of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) in unit dosage form.

23. A pharmaceutical pack according to claim 22, wherein said pack contains one to four units of CCI-779.

37

USO DE UN INHIBIDOR mTOR EN EL TRATAMIENTO
DE LEIOMIOMA UTERINO

. n n n 37

ANTECEDENTE DE LA INVENCION

Esta invención se relaciona con el uso de un inhibidor mTOR en el tratamiento o inhibición del leiomioma uterino (fibroides) en un mamífero.

El mTOR, también conocido como proteína asociada a FKBP12-rapamicina (FRAP), es una enzima clave en una variedad de rutas de transducción de señal, que incluyen proliferación celular estimulada por citoquina, traducción de mRNA para varias proteínas clave que regulan la fase G1 del ciclo celular, y la transcripción inducida por interleuquina-2 (IL-2). La inhibición mTOR conduce a la inhibición de la progresión del ciclo celular del G1 a S. La rapamicina (disponible comercialmente de SirolimusTM), un antibiótico trieno macrociclina producido por *Streptomyces hygroscopicus*, que se ha identificado como un inhibidor mTOR clave.

El 42-éster rapamicina con ácido 3-hidroxi-2-(hidroximetil)-2-metilpropiónico (CCI-779) es un éster de rapamicina. La preparación y uso de hidroxiésteres de rapamicina, que incluyen CCI-779, se describen en las Patentes Estadounidenses Nos. 5,362,718 y 6,277,983. Todavía otro método regio selectivo, para la síntesis del CCI-779 se describe en la solicitud de Patente No. 10/903,062, presentada en Julio 30, 2004 (publicada en

Febrero 10, 2005 como la solicitud de Patente Estadounidense No. US 2005-0033046 A1), y su contraparte, la solicitud de Patente Internacional No. PCT/US2004/22860 (publicada en Febrero 24, 2005 como publicación de Patente Internacional No. WO 2005/016935 A3).

El CCI-779 se ha descrito por tener una actividad in vitro e in vivo contra un número de tipos de células de tumor. El CCI-779 se une a y forma un complejo con la proteína citoplásmica FKBP, que inhibe el mTOR. Existe la hipótesis que el CCI-779 retrasa el tiempo de progresión de los tumores o el tiempo de recurrencia del tumor. Este mecanismo de acción es más típico de agentes citostáticos a diferencia de agentes citotóxicos y es similar aquel del sirolimus.

El leiomioma uterino (fibroides) es un tumor benigno que surge del miometrio del útero (capa de músculo liso). El leiomioma es el tumor pélvico sólido más común de la mujer y es 2-5 veces más probable que ocurra en mujeres negras que en mujeres blancas. Los fibroides ocurren en tanto como el 75% de las mujeres en edad reproductiva, con 25% de estas mujeres sintomáticas al punto de buscar tratamiento. Las mujeres con fibroides sintomático sufren de menorragia, dolor pélvico y presión, y están más sujetas a disfunción reproductiva tal como infertilidad o múltiples abortos involuntarios.

El tratamiento primario para pacientes con fibroides es cirugía-miomectomía para remoción de tumor y preservación de la potencial maternidad, o histerectomía. Los fibroides son la indicación más común para histerectomía y cuentan con

39

nnn39

aproximadamente 200,000 procedimientos desarrollados anualmente en los Estados Unidos.

Así, subsiste la necesidad en la técnica para más métodos efectivos de tratamiento e inhibición de las fibroides.

RESUMEN DE LA INVENCION

La invención prevé el uso de un inhibidor mTOR en el tratamiento o inhibición, o en la preparación de un medicamento útil en el tratamiento o inhibición, del leiomioma uterino (fibroides) en un sujeto mamífero hembra. En otro aspecto la invención prevé el uso de una rapamicina en el tratamiento o inhibición, o en la preparación de un medicamento útil en el tratamiento o inhibición, del leiomioma uterino en el sujeto mamífero hembra. En una modalidad. La invención suministra el uso de rapamicina o CCI-779 en el tratamiento o inhibición, o en el tratamiento de un medicamento útil en el tratamiento o inhibición de leiomioma uterino en un sujeto mamífero hembra.

En otros sujetos, la invención prevé composiciones farmacéuticas que comprenden un inhibidor mTOR, y en ciertas modalidades, una rapamicina, rapamicina, o CCI-779, en forma de dosis unitaria en asociación con un portador farmacéuticamente aceptable, que es útil en el tratamiento o inhibición del leiomioma uterino en un sujeto mamífero hembra.

En aún otra modalidad, la invención prevé paquetes farmacéuticos que contienen un curso de tratamiento de leiomioma

uterino para un individuo mamífero, cada paquete comprende un contenedor que tiene una unidad, de uno a cuatro unidades, o más unidades de un inhibidor mTOR, y en ciertas modalidades, una rapamicina, rapamicina o CCI-779 en forma de dosis unitaria.

Otros aspectos y ventajas de la invención serán evidentes a partir de la siguiente descripción detallada de la invención.

DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención prevé métodos de uso de una cantidad efectiva de un inhibidor mTOR en el tratamiento o inhibición de, o en la preparación de un medicamento útil en el tratamiento o inhibición, de leiomioma uterino (fibroides). En una modalidad, una cantidad efectiva de rapamicina es útil en métodos para tratar o inhibir fibroides. En otra modalidad, una cantidad efectiva de CCI-779 (42-éster de rapamicina con ácido 3-hidroxi-2-(hidroximetil)-2-metilpropiónico) es útil en métodos para tratar o inhibir fibroides. Otros compuestos útiles en los métodos de la invención en el tratamiento o inhibición de fibroides incluyen cantidades efectivas de una rapamicina, tal como ésteres (que incluyen 42-ésteres), éteres (que incluyen 42-éteres), oximas, hidrazonas, e hidroxilaminas de rapamicina. En otra modalidad, la invención prevé métodos para tratar o inhibir fibroides utilizando una cantidad efectiva de 42-O-(2-hidroxi)etilo rapamicina (CerticanTM(everolimus)).

" nnnT

En otra modalidad, FK-506 es útil en métodos para tratar o inhibir las fibroides. En otra modalidad el AP23573 es útil en métodos para tratar o inhibir fibroides.

Como se utiliza aquí, el término **fibroide** o **fibroides** debe tener el mismo significado de leiomioma uterino, como se describió anteriormente.

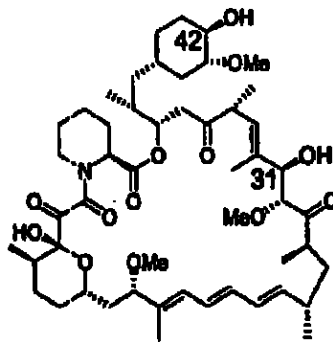
Como se utiliza aquí, el término **inhibidor mTOR**, significa un compuesto o ligando, o una sal farmacéuticamente aceptable de esta, que inhibe la replicación celular al bloquear la progresión del ciclo celular del G1 a S. El término incluye el compuesto tricíclico neutral rapamicina (sirolimus) y otros compuestos rapamicina, que incluyen, por ejemplo, derivados de rapamicina, análogos de rapamicina, otros compuestos macrolida que inhiben la actividad mTOR, y todos los compuestos incluidos dentro de la definición adelante del término "una rapamicina".

Estos compuestos incluyen una similitud estructural con "una rapamicina", por ejemplo, compuestos con una estructura macrocíclica similar que se han modificado para mejorar el beneficio terapéutico. El término también incluye, por ejemplo, rapamicina, 32-deoxorapamicina, 16-pent-2-ililoxi-32-deoxorapamicina, 16-pent-2-ililoxi-32(S)-dihidro-rapamicina, 16-pent-2-ililoxi-32(S)-dihidro-40-O-(2-hidroxietil)-rapamicina, 40-O-(2-hidroxietil)-rapamicina, 42-éster de rapamicina con ácido 3-hidroxi-2-(hidroximetil)-2-metilpropiónico (CCI-779), 40-[3-hidroxi-2-(hidroximetil)-2-metilpropanoato]-rapamicina, o una sal farmacéuticamente aceptable de esta, como se describe en la

Patente Estadounidense No. 5,362,718, ABT578, o 40-(tetrazolil)-rapamicina, 40-epi-(tetrazolil)-rapamicina, por ejemplo, como se describe en la Publicación de Patente Internacional No. WO 99/15530, o análogos de rapamicina como se describe en la Publicación de Patente Internacional No. WO 98/02441 y WO 01/14387, por ejemplo, AP23573.

El FK-506 también se puede utilizar en el método de la invención.

Como se utiliza aquí, el término **una rapamicina** define una clase de compuestos inmunosupresores que contienen el núcleo rapamicina básico como se muestra adelante.



Las rapamicinas de ésta invención incluyen compuestos que son químicamente o biológicamente modificados como derivados del núcleo rapamicina, mientras que retienen todavía las propiedades inmunosupresoras. De acuerdo con esto, el término **una rapamicina** incluye rapamicina, y ésteres, éteres, carbamatos, oximas, hidrazonas, e hidroxilaminas de rapamicina, así como también rapamicinas en las que los grupos funcionales en el núcleo rapamicina se han modificado, por ejemplo a través de reducción u

oxidación. También se incluye en el término una rapamicina sales farmacéuticamente aceptables de rapamicinas.

El término **una rapamicina** también incluye 42- y/o 31 - ésteres y éteres de rapamicina como se describe en las siguientes patentes, que se incorporan todas aquí como referencia: ésteres de alquilo (Patente Estadounidense No. 4,316,885); ésteres de aminoalquilo (Patente Estadounidense No. 4,650,803); ésteres fluorinados (Patente Estadounidense No. 5,100,883); ésteres de amida (Patente Estadounidense No. 5,118,677); ésteres de carbamato (Patente Estadounidense No. 5,118, 678); ésteres de sililo (Patente Estadounidense No. 5,120,842); aminodiésteres (Patente Estadounidense No. 5,162,333); ésteres de sulfato y sulfonato (Patente Estadounidense No. 5,177,203); ésteres (Patente Estadounidense No. 5,221,670); alcoxiésteres (Patente Estadounidense No. 5,233,036); éteres de O-arilo, -alquilo, -alquenilo, y -alquinilo (Patente Estadounidense No. 5,258,389); ésteres de carbonato (Patente Estadounidense No. 5,260,300); carbamatos de arilcarbonilo y alcoxycarbonilo (Patente Estadounidense No. 5,262,423); carbamatos (Patente Estadounidense No. 5,302,584); hidroxíésteres (Patente Estadounidense No. 5,362,718); ésteres ocultos (Patente Estadounidense No. 5,385,908); ésteres heterocíclicos (Patente Estadounidense No. 5,385,909); ésteres gem-disustituidos (Patente Estadounidense No. 5,385,910); ésteres amino alcanóicos (Patente Estadounidense No. 5,389,639); ésteres de fosforilcarbamato (Patente Estadounidense No. 5,391,730); ésteres de carbamato (Patente Estadounidense No. 5,411,967); ésteres de carbamato (Patente Estadounidense No. 5,434,260); ésteres de amidino carbamato (Patente Estadounidense

No. 5,463,048); ésteres de carbamato (Patente Estadounidense No. 5,480,988); ésteres de carbamato (Patente Estadounidense No. 5,480,989); ésteres de carbamato (Patente Estadounidense No. 5,489,680); ésteres N-óxido impedidos (Patente Estadounidense No. 5,491,231); ésteres de biotina (Patente Estadounidense No. 5,504,091); éteres de O-alquilo (Patente Estadounidense No. 5,665,772); y ésteres PEG de rapamicina (Patente Estadounidense No. 5,780,462). La preparación de estos ésteres y éteres se describe en las patentes listadas anteriormente.

Incluido adicionalmente dentro de la definición del término **una rapamicina** están los 27-ésteres y éteres de rapamicina, que se describen en la Patente Estadounidense No. 5,256,790, que se incorpora aquí como referencia. También se describen rapamicinas de cetona C-27 que se reducen al alcohol correspondiente, que a su vez se convierte al éster correspondiente o éter. La preparación de estos ésteres y éteres se describe en la patente listada anteriormente. También se incluyen oximas, hidrazonas, e hidroxilaminas de rapamicina se describen en las Patentes Estadounidenses Nos. 5,373,014, 5,378,836, 5,023,264, y 5,563,145, que se incorporan aquí como referencia. La preparación de estas oximas, hidrazonas, e hidroxilaminas se describe en las patentes listadas anteriormente. La preparación de 42-oxorapamicina se describe en 5,023,263, que se incorpora aquí como referencia.

Como se utiliza aquí, el término un **CCI-779** significa 42-éster de rapamicina con ácido 3-hidroxi-2-(hidroximetil)-2-

metilpropiónico, y abarca prodrogas, derivados, sales farmacéuticamente aceptables, o análogos de éstos.

Como se utiliza aquí, el término **tratamiento** significa tratar a un mamífero que tiene fibroides (leiomioma uterino) al suministrar a dicho mamífero una cantidad efectiva de un compuesto o composición para el propósito de inhibir el crecimiento del fibroide, erradicación del fibroide, o paliación del fibroide.

Como se utiliza aquí, el término **inhibición** significa retrasar o evitar el inicio o progresión de fibroides en un mamífero que tiene o es susceptible de desarrollar tal enfermedad al suministrar a dicho mamífero una cantidad efectiva de un compuesto o composición de la invención.

Como se utiliza aquí, el término **suministrar** significa administrar directamente un compuesto o composición de la invención o administrar una prodroga, derivado, sal farmacéutica o análogo de un inhibidor mTor, que resultará en una cantidad deseada del compuesto o composición en el cuerpo.

Todos los términos utilizados aquí, sean utilizados en singular, plural deben incluir la forma singular y plural a menos que se indique lo contrario.

Como se utiliza aquí, los términos **incluye**, **incluye**, y **que incluye** indican que el sujeto está abierto a otros elementos, es decir, una clase abierta.

Como se utiliza aquí, los términos **comprende**, **comprende**, y **que comprende** indican que el sujeto está abierto a otros elementos, es decir, una clase abierta.

Como se utiliza aquí, los términos **contiene**, **contiene**, y **que contiene** indican que el sujeto está abierto a otros elementos, es decir, una clase abierta.

Como se utiliza aquí, los términos **consiste de** y **que consiste de** indican que el sujeto está cerrado a otros elementos, es decir, una clase cerrada.

Todos los otros elementos utilizados aquí se deben definir como implícitamente o expresamente definidos dentro de esta especificación, y luego, si es necesario de acuerdo con su interpretación por un experto en la técnica.

Composiciones/Formulaciones

Las composiciones útiles en la presente invención comprenden un compuesto activo (por ejemplo un inhibidor mTor) como se describe aquí. En una modalidad el compuesto es CCI-779 (42-éster de rapamicina con ácido 3-hidroxi-2-(hidroximetil)-2-metilpropiónico) (Patente Estadounidense 5,362,718). La preparación del CCI-779 se describe en la Patente Estadounidense 5,362,718 que se incorpora aquí como referencia. Una preparación regioselectiva del CCI-779 se describe en la Patente Estadounidense 6,277,983. Todavía otro método regioespecífico

para la síntesis del CCI-779 se describe en la solicitud de Patente Estadounidense No. 10/903,062, presentada en Julio 30, 2004, y su contraparte, la Solicitud de Patente Internacional PCT/US2004/22860, presentada en Julio 15, 2004. La rapamicina está disponible comercialmente como Sirolimus™.

En otra modalidad, el compuesto es AP23573. En otra modalidad, el compuesto es Certican™ (everolimus). Otros compuestos útiles en los métodos, composiciones, y paquetes farmacéuticos de la invención incluyen una rapamicina, tal como rapamicina, ésteres (que incluyen 42-ésteres), éteres (que incluyen 42-éteres), oximas, hidrazonas, e hidroxilaminas de rapamicina. En otra modalidad, la rapamicina es rapamicina 42-O-(2-hidróxi)etilo (everolimus, Novartis, Patente Estadounidense No. 5,665,772, incorporada aquí como referencia). En otras modalidades, las composiciones de la presente invención contienen otros compuestos útiles en la invención como se describe aquí.

En todavía otra modalidad, el compuesto es FK-506.

La administración de las composiciones puede ser oral, intravenosa, respiratoria (por ejemplo, nasal o intrabronquial), parenteral, intraperitoneal, transdérmica (que incluyen todas las administraciones a través de la superficie del cuerpo y las capas internas de los pasajes corpceales que incluyen tejido epitelial y mucosal) y vaginal (que incluye administración intrauterina).

Se proyecta que la dosis oral de un compuesto útil en la invención será de 10 mg/semana a 250 mg/semana, aproximadamente

20 mg/semana a aproximadamente 150 mg/semana, aproximadamente 25 mg/semana a aproximadamente 100 mg/semana, o aproximadamente 30 mg/semana a aproximadamente 75 mg/semana. Para una rapamicina, la dosis oral proyectada estará entre 0.1 mg/día a 25 mg/día. Las dosis intravenosas se predican generalmente de cinco a diez veces menos que las dosis orales. La dosis precisa se determinará por el médico que la administra basado en la experiencia con el sujeto individual a ser tratado.

En una modalidad, la composición farmacéutica está en forma de dosis unitaria, por ejemplo, como tabletas, cápsulas, o frascos o jeringas pre-llenos. En tal forma la composición se subdivide en cantidades apropiadas que contienen dosis unitarias del ingrediente activo; las formas de dosis unitarias pueden ser composiciones empacadas, por ejemplo, polvos empacados, frascos, ampollas, jeringas pre-llenas, o sachets que contienen líquidos. La forma de dosis unitaria puede ser, por ejemplo, una cápsula o tableta en si misma o esta puede ser el número apropiado de cualquiera de tales composiciones en forma de paquete.

Las formulaciones orales que contienen los compuestos de esta invención pueden comprender cualquier forma utilizada convencionalmente, que incluyen tabletas, cápsulas, formas bucales, píldoras, lozenges y soluciones, suspensiones o líquidos orales. Las cápsulas pueden contener mezclas de compuesto activo con llenadores inertes y/o diluyentes tales como almidones farmacéuticamente aceptables (por ejemplo almidón de maíz, papa, o tapioca), azúcares, agentes endulzantes artificiales, celulosa en polvo, tal como celulosa microcristalina y cristalina,

harinas, gelatinas, gomas, etc. Formulaciones de tabletas útiles se pueden hacer por compresión convencional, granulación en húmedo o métodos de granulación en seco y utilizar diluyentes farmacéuticamente aceptables, agentes de unión, lubricantes, desintegrantes, agentes modificadores de superficie (que incluyen tensoactivos), agentes de suspensión o estabilizantes, que incluyen, pero no se limitan a, estearato de magnesio, ácido esteárico, talco, lauril sulfato de sodio, celulosa microcristalina, carboximetil celulosa de calcio, polivinilpirrolidona, gelatina, ácido algínico, goma de acacia, goma xantano, citrato de sodio, silicatos complejos, carbonato de calcio, glicina, dextrina, sucrosa, sorbitol, fosfato de dicalcio, sulfato de calcio, lactosa, caolín, manitol, cloruro de sodio, almidones secos y azúcar en polvo. Agentes modificadores de superficie incluyen agentes modificadores de superficie aniónica y no iónica. Ejemplos representativos de agentes modificadores de superficie incluyen, pero no se limitan a, poloxámero 188, cloruro de benzalconio, estearato de calcio, alcohol cetostearilo, cera emulsificante de cetomacrogol, ésteres de sorbitán, dióxido de silicio coloidal, fosfatos, dodecilsulfato de sodio, silicato de aluminio magnesio, y trietanolamina. Las formulaciones orales aquí pueden utilizar formulaciones de liberación retardada o en el tiempo para alterar la absorción de los compuestos activos. La formulación oral también puede comprender administrar un compuesto activo en agua o en un jugo de fruta, que contiene solubilizantes apropiados o emulsificadores según se necesite. Las formulaciones orales preferidas para CCI-779 se describen en la Solicitud de Patente Publicada Estadounidense No. 2004-0077677 A1, (también la

solicitud de Patente Estadounidense No. 10/663,506).

Formulaciones orales sólidas preferidas para rapamicina se describen en la Patente Estadounidense 5,989,591, y formulaciones líquidas orales preferidas para rapamicina se describen en la 5,536,729.

En algunos casos puede ser deseable administrar los compuestos directamente a las vías aéreas en la forma de un aerosol.

Los compuestos también se pueden administrar parenteral o intraperitonealmente. Las soluciones o suspensiones de éstos compuestos activos como una base libre o como sal farmacológicamente aceptable se pueden preparar en agua mezclada adecuadamente con un tensoactivo tal como hidroxipropilcelulosa. Las dispersiones también se pueden preparar en glicerol polietilenglicoles líquidos y mezclas de éstos en aceites. Bajo condiciones ordinarias de uso y almacenamiento, estas preparaciones contienen un preservativo para evitar el crecimiento de microorganismos.

Las formas farmacéuticas adecuadas para uso inyectable incluyen soluciones acuosas estériles o dispersiones y polvos estériles para la preparación extemporánea de las soluciones inyectables o dispersiones estériles. En todos los casos, la fórmula debe ser estéril y debe ser fluida para que exista fácil grado de liberación desde la jeringa. Esta debe ser estable bajo las condiciones de fabricación y almacenamiento y se debe preservar contra la acción contaminante de microorganismos tales

como bacterias y hongos. El portador puede ser un solvente o medio de dispersión que contiene, por ejemplo, agua, etanol, poliol (por ejemplo glicerol, propilenglicol, y polietilenglicol líquido), mezclas adecuadas de éstos, y aceites vegetales. En una modalidad, las formulaciones inyectables para CCI-779 se describen en la Publicación de Patente Estadounidense No. 2004/0167152 (también solicitud de Patente Estadounidense No 10/626,943), que se incorporan aquí como referencia.

En una modalidad, la formulación inyectable útil en la invención suministra un compuesto en un cosolvente concentrado que contiene un solvente parenteralmente aceptable y un antioxidante como se describió anteriormente y una formulación parenteral contiene un compuesto útil en la invención, un cosolvente parenteralmente aceptable, un antioxidante, un solvente diluyente y un tensioactivo. Cualquier formulación dada útil en esta invención puede contener múltiples ingredientes de cada clase de componente. Por ejemplo, un solvente parenteralmente aceptable puede incluir un solvente no alcohólico, un solvente alcohólico o mezclas de estos.

Ejemplos de solventes no alcohólicos adecuados incluyen, por ejemplo, dimetilacetamida, dimetilsulfóxido o acetonitrilo, o mezclas de estos. Un solvente alcohólico puede contener uno o más alcoholes como el componente solvente alcohólico de la formulación. Ejemplos de solventes útiles en las formulaciones de la invención incluyen, sin limitación, etanol, propilenglicol, polietilenglicol 300, polietilenglicol 400, polietilenglicol 600, polietilenglicol 1000, o mezclas de estos. Estos cosolventes son

52

. nnn51

particularmente deseables debido a que la degradación ocurre por vía de oxidación y clivaje de lactona para un menor alcance de estos cosolventes. Adicionalmente, el etanol y propilenglicol se pueden combinar para producir un producto menos inflamable, pero cantidades mayores de etanol en la mezcla resultan generalmente en mejor estabilidad química. Se prefiere una concentración de 30 a 100% v/v de etanol en la mezcla.

En otra modalidad, la estabilidad de un compuesto útil en la invención en solventes alcohólicos parenteralmente aceptables se mejora por la adición de un antioxidante para la formulación. Antioxidantes aceptables incluyen, pero no se limitan a, ácido cítrico, d,1- α -tocoferol, BHA, BHT, monotioglicerol, ácido ascórbico, propil galato, y mezclas de estos. Generalmente, las formulaciones parenterales útiles en esta modalidad contendrán un componente antioxidante en una concentración que varía de 0.001% a 1% p/v, o 0.01% a 0.5% p/v, del concentrado cosolvente aunque se pueden desear concentraciones mayores o menores. En una modalidad, de los antioxidantes, d,1- α -tocoferol es particularmente deseable y se utiliza en una concentración de 0.01 a 0.1% p/v con una concentración preferida de 0.075% p/v del concentrado cosolvente.

En otras modalidades, el componente antioxidante de la formulación de de la invención también exhibe actividad quelante. Ejemplos de tales agentes quelantes incluyen, por ejemplo, ácido cítrico, ácido acético, y ácido ascórbico (que puede funcionar como un antioxidante clásico y un agente quelante en las formulaciones actuales). Otros agentes quelantes incluyen tales

{

materiales que son capaces de unir iones de metal en solución, tal como ácido etileno diamina tetra acético (EDTA), sus sales, o aminoácidos tales como glicina son capaces de mejorar la estabilidad de un compuesto útil en la invención, en algunas modalidades, los compuestos con actividad quelante se incluyen en las formulaciones de la invención como el único componente antioxidante. Típicamente, tales componentes de unión de metal, cuando actúan como agentes quelantes se utilizan en el extremo inferior del rango de concentraciones para los componentes antioxidantes suministrados aquí. Mayores concentraciones producen menos soluciones estables y así es menos deseable para los productos ser sujetos a almacenamiento a largo plazo en forma líquida. Adicionalmente, tales agentes quelantes se pueden utilizar en combinación con otros antioxidantes como parte del componente antioxidante de la invención. Por ejemplo, una formulación aceptable puede contener ácido cítrico y d,l- α -tocoferol. Concentraciones óptimas para los antioxidantes seleccionados se pueden determinar fácilmente por un experto en la técnica, basado en la información suministrada aquí.

En ciertas modalidades de las formulaciones parenterales útiles en la invención, se utilizan tensoactivos en la solución diluyente para evitar la precipitación de los componentes de la formulación. Tensoactivos parenteralmente aceptables se pueden seleccionar fácilmente por un experto en la técnica e incluyen: polisorbato 20, polisorbato 80, sales de ácido de bilis (taurocolato, glicocolato, colato, deoxicolato, etc.), que se combinan opcionalmente con lecitina. Alternativamente, aceites vegetales etoxilados, tal como un aceite de castor pegilado (por

ejemplo, aceite de castor PEG-35 que se vende, por ejemplo, bajo el nombre comercial Cremophor EL, BASF), succinato de propilenglicol tocoferol vitamina E (Vitamina E TGPS), y copolímeros de bloque de polioxietileno-polioxipropileno que se pueden utilizar en el diluyente como un tensoactivo, así como también otros miembros de la familia polisorbato tal como polisorbato 20 o 60. Otros componentes del diluyente pueden incluir agua, etanol, polietilenglicol 300, polietilenglicol 400, polietilenglicol 600, polietilenglicol 1000, o mezclas que contiene uno o más de éstos polietilenglicoles, propilenglicol y otros azúcares parenteralmente aceptables, polioles y electrolitos. Se espera que el tensoactivo comprenda 2 a 100% p/v, 5 a 80% p/v, 10 a 75% p/v, 15 a 60% p/v, 5% p/v, o 10% p/v, de la solución diluyente.

Una formulación parenteral útil en la invención se puede preparar como una solución única, o se puede preparar como un concentrado cosolvente que contiene un compuesto útil en la invención, un solvente alcohólico, y un antioxidante, que se combina posteriormente con un diluyente que contiene un solvente diluyente y tensoactivo adecuado. Antes de uso, el concentrado cosolvente se mezcla con un diluyente que comprende un solvente diluyente y un tensoactivo. En una modalidad, un compuesto útil en la invención se prepara como un concentrado cosolvente de acuerdo con la invención, que tiene concentraciones de compuesto de 0.05 mg/mL, de 2.5 mg/mL, de 5mg/mL, de 10 mg/mL, o de 25 mg/mL hasta aproximadamente 50 mg/mL. El concentrado se puede mezclar con el diluyente hasta aproximadamente 25 mg/mL. Por ejemplo, la concentración de un compuesto útil en la invención en

55

nonex

la formulación parenteral puede ser de aproximadamente 2.5 a 10 mg/mL. Esta invención también cubre el uso de formulaciones que tienen concentraciones menores de un compuesto útil en la invención en el concentrado cosolvente, y formulaciones en las que una parte del concentrado se mezcla con más de 1 parte del diluyente, por ejemplo, concentrado: diluyente en una proporción de aproximadamente 1:1.5, 1:2, 1:3, 1:4, 1:5, o 1:9 v/v, y así sucesivamente, a formulaciones parenterales que tienen concentraciones de compuesto bajas a los niveles más bajos de detección.

En otra modalidad, el antioxidante puede comprender de aproximadamente 0.0005 a 0.5% p/v de la formulación. El tensoactivo puede, por ejemplo, comprender de aproximadamente 0.5% a aproximadamente 10% p/v de la formulación. El solvente alcohólico puede ser, por ejemplo, de aproximadamente 10% a aproximadamente 90% p/v de la formulación.

En otras modalidades, las formulaciones parenterales útiles en ésta invención, se pueden utilizar para producir una forma de dosis que es adecuada para administración ya sea inyección directa o por adición de fluidos de infusión estéril para infusión intravenosa.

La administración transdérmica se puede lograr a través del uso de un parche transdérmico que contiene el compuesto activo y un portador que es inerte al compuesto activo, no es tóxico a la piel, y permite el suministro del agente para absorción sistémica en el torrente sanguíneo por vía de la piel. Tales

56

administraciones se pueden llevar a cabo utilizando los compuestos útiles en la invención, o sales farmacéuticamente aceptables de éstos, en lociones, cremas, espumas, parches, suspensiones, soluciones, y supositorios (rectales y vaginales). El portador puede tomar cualquier número de formas tales como cremas y ungüentos, pastas, geles, y dispositivos oclusivos. Las cremas y ungüentos pueden ser líquidos viscosos o emulsiones semisólidas del tipo aceite en agua o agua en aceite. Pastas comprimidas de polvos absorbentes dispersos en petróleo o petróleo hidrofílico que contiene el ingrediente activo en el torrente sanguíneo tal como membrana semipermeable que cubre un reservorio que contiene el compuesto activo en el torrente sanguíneo tal como una membrana semi-permeable que cubre un reservorio que contiene el compuesto activo con o sin un portador, o una mezcla que contiene el compuesto activo. Otros dispositivos oclusivos se conocen en la literatura y pueden ser fácilmente disponibles para un experto en la técnica.

Las formulaciones de supositorio se pueden hacer de materiales tradicionales, que incluyen manteca de coco, con o sin la adición de ceras para alterar el punto de fusión del supositorio, y glicerina. Bases de supositorios solubles en agua, tal como polietilenglicoles de varios pesos moleculares, también se pueden utilizar.

En una modalidad, las composiciones se suministran vaginalmente en la forma de un supositorio convencional, crema, gel, anillo, o dispositivo intrauterino recubierto (IUD).

Paquetes farmacéuticos/Kits:

.. 00056

La invención incluye un producto o paquete farmacéutico que contiene un curso de tratamiento de leiomioma uterino para un individuo mamífero que comprende uno o más contenedores que tiene uno, uno a cuatro, o más unidades de un inhibidor mTOR (por ejemplo, CCI- 779) en forma de dosis unitaria.

En otra modalidad, los paquetes farmacéuticos contienen un curso de tratamiento de leiomioma uterino para un individuo mamífero que comprende un contenedor que tiene una unidad de rapamicina en forma de dosis unitaria. En otras modalidades, la rapamicina es rapamicina, un éster (que incluye un 42-éster, éter (que incluye un 42-éter), oxima, hidrazona, o hidroxilamina de rapamicina. En otra modalidad, la rapamicina es 42-O-(2-hidroxi)etil rapamicina.

En otra modalidad, la rapamicina es CCI-779, y el paquete contiene uno o más contenedores que comprende uno, uno a cuatro, o más unidades de CCI-779.

En algunas modalidades, las composiciones de la invención están en paquetes en una forma lista para administración. En otras modalidades, las composiciones de la invención están en forma concentrada en paquetes, opcionalmente con el diluyente requerido para hacer una solución final para administración. En todavía otras modalidades, el producto contiene un compuesto útil en la invención en forma sólida y, opcionalmente, un contenedor

separado con un solvente adecuado o portador para el compuesto útil en la invención.

En todavía otras modalidades, el anterior paquete/kit incluye otros componentes, por ejemplo, instrucciones para dilución, mezclas y/o administración del producto, otros contenedores, jeringas, agujas, etc. Otro de tales componentes de paquete/kit serán fácilmente evidentes para un experto en la técnica.

Los siguientes ejemplos son ilustrativos de la presente invención, pero no una limitación de ésta.

EJEMPLOS

Ejemplo 1: Prueba *in vivo* de la efectividad de tratamiento de fibroides en la rata Eker

A. Antecedentes:

La rata Eker es un sistema modelo bien caracterizado para leiomioma uterino [Walker, et al., *Genes, Chromosomes, and Cancer*, 38:349-356 (2003); Houston, et al., *Cancer Research*, 63:1221-1227 (2003); and Walker, C.L., *Journal of the Society for Gynecologic Investigation*, 7(4), 249-256 (2000)]. Aproximadamente 65% de ratas Eker hembras vírgenes desarrollan espontáneamente leiomioma uterino durante 12-16 meses como un resultado de la mutación de los genes Tsc-2.

00058

B. Método:

Se tratan ratas Eker de 12-16 meses de edad con un compuesto útil en la invención y se evalúan para regresión de tumor por vía de técnicas y métodos convencionales (por ejemplo, ultrasonido o laparoscopia). La ARN/proteína obtenida de animales de estudio se obtiene y se utiliza *in vitro* para caracterización de los mecanismos de efectividad del compuesto.

C. Resultados:

Un inhibidor mTor probado, por ejemplo, CCI-779, se espera que sea efectivo en el tratamiento de leiomioma uterino (fibroides) en el rango de dosis de aproximadamente 10-250 mg/semana (oral) o aproximadamente 2-50 mg/semana (intravenosa). Una rapamicina probada se espera que sea efectiva en la dosis oral proyectada de entre 0.1 mg/día a 25 mg/día.

Ejemplo 2: Prueba *in vivo* de la efectividad de tratamiento de fibroides en el conejillo de Indias

A. Antecedentes:

Los conejillos de indias desarrollan espontáneamente fibroides cuando ellos envejecen. Este proceso se puede acelerar mediante la administración de estradiol, todos los ácidos trans retinóicos y troglitazona [Tsibris, et al., J. Soc. Gynecol. Invest, 5(suppl1):180 (resumen)(1998); Tsibris, et al., Cancer Res., 59:5737 (1999); y Patente Estadounidense No. 6,218,594 B1].

... ~~nnnsg~~

B. Método:

Se inducen fibroides en los conejillos de indias por tratamiento con estradiol, todos los ácidos trans retinóicos y troglitazona. Los conejillos de indias luego se tratan con un compuesto útil en la invención y se evalúan para regresión de tumor por vía de técnicas y métodos convencionales (por ejemplo ultrasonido o laparoscopia). La ARN/proteína obtenida de animales de estudio se obtiene y se utiliza *in vitro* para caracterización de los mecanismos de efectividad del compuesto.

C. Resultados:

Un inhibidor mTor probado, por ejemplo, CCI-779, se espera que sea efectivo en el tratamiento de leiomioma uterino (fibroides) en el rango de dosis de aproximadamente 10-250 mg/semana (oral) o aproximadamente 2-50 mg/semana (intravenosa).

Una rapamicina probada se espera que sea efectiva en la dosis oral proyectada de entre 0.1 mg/día a 25 mg/día.

Ejemplo 3: Prueba *in vivo* de la efectividad de inhibición de fibroides en la rata Eker

A. Antecedentes:

La rata Eker es un sistema modelo bien caracterizado para leiomioma uterino [Walker, et al., *Genes, Chromosomes, and Cancer*, 38:349-356 (2003); Houston, et al., *Cancer Research*,

63:1221-1227 (2003); and Walker, C.L., *Journal de the Society for Gynecologic Investigation*, 7(4), 249-256 (2000)]. Aproximadamente 65% de ratas Eker hembras vírgenes desarrollan espontáneamente leiomioma uterino durante 12-16 meses como un resultado de la mutación del gen Tsc-2.

B. Método:

Se tratan ratas Eker de aproximadamente 9 meses de edad con un compuesto útil en la invención y se evalúan para inhibición de tumor por comparación con un grupo de control tratado con vehículo hasta el tiempo en el que las ratas tratadas con vehículo han desarrollado tumores (aproximadamente 12-16 meses de edad). Se monitorea el crecimiento de tumor por vía de técnicas y métodos convencionales (por ejemplo, ultrasonido o laparoscopia). La ARN/proteína obtenida de animales de estudio se obtiene y se utiliza para caracterización efectividad del compuesto.

C. Resultados:

Un inhibidor mTor probado, por ejemplo, CCI-779, se espera que sea efectivo en la inhibición de leiomioma uterino (fibroides) en el rango de dosis de aproximadamente 10-250 mg/semana (oral) o aproximadamente 2-50 mg/semana (intravenosa). Una rapamicina probada se espera que sea efectiva en la dosis oral proyectada de entre 0.1 mg/día a 25 mg/día.

Ejemplo 4: Prueba *in vivo* de la efectividad de inhibición de fibroides en el conejillo de Indias

~~non~~

A. Antecedentes:

Los conejillos de indias desarrollan espontáneamente fibroides cuando ellos envejecen. Este proceso se puede acelerar mediante la administración de estradiol, todos los ácidos trans retinóicos y troglitazona [Tsibris, et al., *J. Soc. Gynecol. Invest.*, 5(suppl1):180 (resumen)(1998); Tsibris, et al., *Cancer Res.*, 59:5737 (1999); y Patente Estadounidense No. 6,218,594 B1].

B. Método:

Se tratan conejillos de indias sanos, que no tienen fibroides, con un compuesto útil en la invención y se evalúan para regresión de tumor por vía de técnicas y métodos convencionales (por ejemplo, ultrasonido o laparoscopia). Los conejillos de indias luego se sometan a tratamiento con estradiol, todos los ácidos trans retinóicos y troglitazona, y se comparan con los conejillos de indias no pre-tratados con un compuesto útil en la invención. La ARN/proteína obtenida de animales de estudio se obtiene y se utiliza *in vitro* para caracterización de los mecanismos involucrados en una tumorigénesis fibroide.

C. Resultados:

Un inhibidor mTor probado, por ejemplo, CCI-779, se espera que sea efectivo en la inhibición de leiomioma uterino (fibroides) en el rango de dosis de aproximadamente 10-250

mg/semana (oral) o aproximadamente 2-50 mg/semana (intravenosa).

Una rapamicina probada se espera que sea efectiva en la dosis oral proyectada de entre 0.1 mg/día a 25 mg/día.

Todos los documentos que se identifican aquí se incorporan como referencia. Un experto en la técnica reconocerá que modificaciones menores a estas condiciones y técnicas descritas en las modalidades específicas descritas aquí se pueden variar sin apartarse de la presente invención. Tales modificaciones y variaciones menores están dentro del alcance de la invención como se define por las siguientes reivindicaciones.

REIVINDICACIONES

1. El uso de un inhibidor mTOR en la preparación de un medicamento útil en el tratamiento o inhibición de leiomioma uterino en un mamífero.
2. El uso de una rapamicina en la preparación de un medicamento útil en el tratamiento o inhibición de leiomioma uterino en un mamífero.
3. El uso de acuerdo con la reivindicación 2, en donde la rapamicina es rapamicina.
4. El uso de acuerdo con la reivindicación 2, en donde la rapamicina es un éster, éter, oxima, carbamato, hidrazona, o hidroxilamina de rapamicina.
5. El uso de acuerdo con la reivindicación 4, en donde la rapamicina es un 42-éster o 42-éter de rapamicina.
6. El uso de acuerdo con la reivindicación 5, en donde la rapamicina es rapamicina 42-O-(2-hidroxi)etilo.
7. El uso de 42-éster de rapamicina con ácido 3-hidroxi-2-(hidroximetil)-2-metilpropiónico (CCI-779) en la preparación de un medicamento útil en el tratamiento o inhibición de leiomioma uterino en un mamífero.

8. Una composición farmacéutica útil en el tratamiento o inhibición de leiomioma uterino en un mamífero, la composición comprende un inhibidor mTor en forma de dosis unitaria en asociación con un portador farmacéuticamente aceptable.

9. Una composición farmacéutica útil en el tratamiento o inhibición de leiomioma uterino en un mamífero, la composición comprende una rapamicina en forma de dosis unitaria en asociación con un portador farmacéuticamente aceptable.

10. La composición farmacéutica de acuerdo con la reivindicación 9, en donde la rapamicina es rapamicina.

11. La composición farmacéutica de acuerdo con la reivindicación 9, en donde la rapamicina es un éster, éter, carbamato, oxima, hidrazona, o hidroxilamina de rapamicina.

12. La composición farmacéutica de acuerdo con la reivindicación 11, en donde la rapamicina es un 42-éster o 42-éter de rapamicina.

13. La composición farmacéutica de acuerdo con la reivindicación 12, en donde la rapamicina es rapamicina 42-O-(2-hidroxi)etilo.

14. Una composición farmacéutica útil en el tratamiento o inhibición de leiomioma uterino en un mamífero, la composición comprende 42-éster de rapamicina con ácido 3-hidroxi-2-(hidroximetil)-2-metilpropiónico (CCI-779) en forma de dosis

unitaria en asociación con un portador farmacéuticamente ~~aceptable~~ ^{nnaccj} aceptable.

15. Un paquete farmacéutico que contiene un curso de tratamiento de leiomioma uterino para un individuo mamífero, dicho paquete comprende un contenedor que tiene una unidad de un inhibidor mTor en forma de dosis unitaria.

16. El paquete farmacéutico de acuerdo con la reivindicación 15, en donde dicho paquete contiene una a cuatro unidades de un inhibidor mTor.

17. Un paquete farmacéutico que contiene un curso de tratamiento de leiomioma uterino para un individuo mamífero, dicho paquete comprende un contenedor que tiene una unidad de una rapamicina en forma de dosis unitaria.

18. El paquete farmacéutico de acuerdo con la reivindicación 17, en donde la rapamicina es rapamicina.

19. El paquete farmacéutico de acuerdo con la reivindicación 17, en donde la rapamicina es un éster, éter, carbamato, oxima, hidrazona, o hidroxilamina de rapamicina.

20. El paquete farmacéutico de acuerdo con la reivindicación 19, en donde la rapamicina es un 42-éster o 42-éter de rapamicina.

21. El paquete farmacéutico de acuerdo con la reivindicación 20, en donde la rapamicina es rapamicina 42-O-(2-hidroxi)etilo.

... ~~nnos~~

22. Un paquete farmacéutico que contiene un curso de tratamiento de leiomioma uterino para un individuo mamífero, dicho paquete comprende un contenedor que tiene una unidad de 42-éster de rapamicina con ácido 3-hidroxi-2-(hidroximetil)-2-metilpropiónico (CCI- 779) en forma de dosis unitaria.

23. Un paquete farmacéutico de acuerdo con la reivindicación 22, en donde dicho paquete contiene una a cuatro unidades de CCI-779.

~~000027~~**RESUMEN**

La invención prevé el uso de un inhibidor mTOR en el tratamiento o inhibición de fibroides.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM-101846PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/039836	International filing date (day/month/year) 21/10/2005	(Earliest) Priority Date (day/month/year) 28/10/2004
Applicant WYETH		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

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

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/03983670
nnns

A. CLASSIFICATION OF SUBJECT MATTER

A61K31/00 A61K31/436 A61K31/445 A61P15/00 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/106637 A1 (GUAN KUN-LIANG) 3 June 2004 (2004-06-03) paragraphs '0011! - '0017!, '0025!, '0037!, '0091!, '0100!, '0140!, '0150! - '0154!, '0163!; claims 10,13,18	8-23
Y		1-23
Y	WALKER CHERYL LYN ET AL: "Uterine leiomyoma in the Eker rat: A unique model for important diseases of women." GENES CHROMOSOMES & CANCER, vol. 38, no. 4, December 2003 (2003-12), pages 349-356, XP009062056 ISSN: 1045-2257 the whole document	1-23
	----- -/--	

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

17 February 2006

Date of mailing of the international search report

28/02/2006

Name and mailing address of the ISA/

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

Authorized officer

Paul Soto, R

INTERNATIONAL SEARCH REPORT

Inteonal application No

PCT/US2005/039836

71
00070

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/144204 A1 (SPENCER DAVID) 31 July 2003 (2003-07-31) paragraphs '0016!, '0029!, '0030!, '0061!, '0071!, '0073!, '0172!, '0173!; claims 35-38	8-23
A	-----	1-7
X	WO 99/01118 A (ATHEROGENICS, INC; CHINERY, REBECCA; BEAUCHAMP, R., DANIEL; COFFEY, RO) 14 January 1999 (1999-01-14) page 46, lines 8,10,22 claims 23,27	8-23
A	-----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l application No

PCT/US2005/039836

72
0007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004106637	A1	03-06-2004	AU 2003259803 A1 25-02-2004
		US 2005070567 A1	31-03-2005
US 2003144204	A1	31-07-2003	NONE
WO 9901118	A	14-01-1999	AU 8282798 A 25-01-1999
		CA 2294247 A1	14-01-1999
		CN 1261803 A	02-08-2000
		EP 1019034 A2	19-07-2000
		JP 2002511878 T	16-04-2002

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/US2005/039836	International filing date (day/month/year) 21.10.2005	Priority date (day/month/year) 28.10.2004
--	--	--

International Patent Classification (IPC) or both national classification and IPC
A61K31/00, A61K31/436, A61K31/445, A61P15/00, A61P35/00

Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

 European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Paul Soto, R

Telephone No. +49 89 2399-7346



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/039836

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

75
non

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-7
	No: Claims	8-23
Inventive step (IS)	Yes: Claims	
	No: Claims	1-23
Industrial applicability (IA)	Yes: Claims	1-23
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Reference is made to the following documents:

D1: US 2004/106637 A1 (GUAN KUN-LIANG) 3 June 2004

D2: WALKER CHERYL LYN ET AL: "Uterine leiomyoma in the Eker rat: A unique model for important diseases of women." GENES CHROMOSOMES & CANCER, vol. 38, no. 4 (2003-12), pages 349-356, XP009062056 ISSN: 1045-2257

D3: US 2003/144204 A1 (SPENCER DAVID) 31 July 2003

D4: WO 99/01118 A (ATHEROGENICS, INC; CHINERY, REBECCA; BEAUCHAMP, R., DANIEL; COFFEY, RO) 14 January 1999

2. The present application relates to *the use* of an mTOR inhibitor (**claim 1**), of a rapamycin (**claim 2**) and of the rapamycin 42-ester CCI-779 (**claim 7**) *in the preparation of a medicament useful in the treatment or inhibition of uterine leiomyoma in a mammal*.

The present application further relates to a *pharmaceutical composition* useful in treating or inhibiting uterine leiomyoma in a mammal comprising an mTOR inhibitor (**claim 8**), or a rapamycin (**claim 9**) or the compound CCI-779 (**claim 14**) in unit dosage form in association with a pharmaceutically acceptable carrier; and to a *pharmaceutical pack* containing a course or treatment of uterine leiomyoma for one individual mammal, said pack comprising a container having a unit of an mTOR inhibitor (**claim 15**), a rapamycin (**claim 17**) or the compound CCI-779 (**claim 22**) in unit dosage form.

- 3.1. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33(2)) for the following reasons.

mTOR inhibitors in general but also rapamycins and in particular rapamycin (Sirolimus), 42-O-(2-hydroxy)ethyl rapamycin (Certican, Everolimus) and the 42-ester CCI-779 (Temsirolimus) are well known in the pharmaceutical field and have been extensively used as antifungal, antineoplastic, macrolide, and immunosuppressive agents, whereby

74
00026

neither the pharmaceutical compositions according to present claims 8-14 nor the pharmaceutical packs according to present claims 17-23 are novel. It should be noted that the technical features referring to the medical indication intended for the compositions or the packs, namely the treatment of uterine leiomyoma in a mammal, do not limit in any way the scope of present claims 8-23 because a pharmaceutical composition or pack is defined by its active pharmaceutical components and not by the medical indication intended for it.

- 3.2. Present claims 1-7 are novel over the prior art. In particular **D1** discloses methods to treat disorders which are caused by mutations in the TSC1 or TSC2 genes, such as tuberous sclerosis, the methods comprising the administration of S6K or mTOR inhibitors, such as rapamycin or rapamycin derivatives. However, the document does not explicitly mention the treatment of uterine leiomyoma, whereby it is not novelty destroying for present claims 1-7.

- 4.1. No inventive step (Art. 33(3) PCT) is recognised for that subject-matter which is not novel, namely for claims 8-23.
- 4.2. The subject-matter of present claims 1-7 does also not involve an inventive step for the following reasons.

D1, which is regarded as the closest prior art, discloses the use of S6K or mTOR inhibitors, and in particular rapamycin and derivatives thereof, for the treatment of disorders which are caused by mutations in the TSC1 or TSC2 genes. The present application differs from **D1** in that mTOR inhibitors are used specifically for the treatment of uterine leiomyoma.

Thus, the *problem* to be solved by the present application is regarded in the provision of further medical utilities for rapamycins and other mTOR inhibitors. The *solution* provided by the present application is rendered obvious by **D2**. This document (see the abstract) discloses that Eker rats carry a defect in the TSC-2 tumour suppressor gene and that female Eker rats develop uterine leiomyoma with a high frequency (see also page 14, lines 1-11 of the application). Thus, the skilled person would consider uterine

leiomyoma as one of the disorders caused by mutation in the TSC2 gene contemplated in D1 and would apply the therapeutic treatment disclosed therein, namely the administration of mTOR inhibitors such as rapamycins.

- 5.1. **Present claims 8-23** meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.
- 5.2. For the assessment of the present **claims 1-7** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment, as it is the case of present claims 1-7.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

KODROFF, Cathy, A.
Howson and Howson
321 Norristown Road, Suite 200
Spring House Corporate Center, P.O. Box 457
Spring House, Pennsylvania 19477
ETATS-UNIS D'AMERIQUE

Date of mailing (day month year) 17 March 2006 (17.03.2006)	
Applicant's or agent's file reference AM-101846PCT	IMPORTANT NOTIFICATION
International application No. PCT/US2005/039836	International filing date (day month year) 21 October 2005 (21.10.2005)
International publication date (day month year) Not yet published	Priority date (day month year) 28 October 2004 (28.10.2004)
Applicant WYETH et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR" in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
28 October 2004 (28.10.2004)	60/622,917	US	16 January 2006 (16.01.2006)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Form PCT/IB/304 (October 2005)

Authorized officer

Carlos Roy - Gijsbertus Beijer

Facsimile No. +41 22 740 14 35

Telephone No. +41 22 338 95 61

CSAQQM7E

 Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT		nnn29	
(21) N° de solicitud:			(51) Int Cl: A61K 31/00, A61K 31/436, A61K 31/445, A61P 15/00, A61P 35/00		
22) Fecha de solicitud:			(71) Solicitante(s) WYETH		
(30) Prioridad	(31) No.	32) Fecha	(33) País	(72) Inventor(es)	
	60/622,917	28/10/04	US	RUFFOLO, Robert R. Jr.	
			(74) Apoderado: ALVARO CORREA ORDOÑEZ		
(85) Fecha limite inicio fase nacional: 28/05/07			(87) Publicación internacional		
(86) Datos relativos a la presentación de la solicitud PCT			Fecha: 11/05/06		
Fecha de presentación de la solicitud: 21/10/05			N° publicación: WO 2006/050461		
No. de solicitud PCT/US2005/039836					
(54) Título: USO DE UN INHIBIDOR mTOR EN EL TRATAMIENTO DE LEIOMIOMA UTERINO					

Reivindicación(es):

1. El uso de un inhibidor mTOR en la preparación de un medicamento útil en el tratamiento o inhibición de leiomioma uterino en un mamífero.
8. Una composición farmacéutica útil en el tratamiento o inhibición de leiomioma uterino en un mamífero, la composición comprende un inhibidor mTor en forma de dosis unitaria en asociación con un portador farmacéuticamente aceptable.
15. Un paquete farmacéutico que contiene un curso de tratamiento de leiomioma uterino para un individuo mamífero, dicho paquete comprende un contenedor que tiene una unidad de un inhibidor mTor en forma de dosis unitaria.

Retiro folios 80 y 81
- Tojetas

81

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-039669- -00000-0000

Fecha: 2007-04-20 16:45:17 Dep. 2020 NUECREACION
Tra. 11 PATENTE IYII Ene: 378 FASENACIONAL
Act. 411 PRESENTACION Folios: 79

io
A

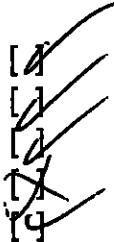
REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION



MODELO DE UTILIDAD []

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



COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

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

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

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

COMPLETA []

INCOMPLETA []

Firma Responsable

Fecha 20 ABR. 2007

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

82

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
WYETH

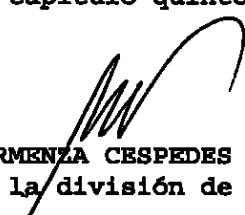
REFERENCIA	Radicación No.	7 39669
	Solicitud internacional	PCT/US2005/039836
	Fecha inicio fase nacional	28/05/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	9881

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486. Cuando se trate de documentos otorgados en el extranjero, deben legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha 19-7-AGO 2007
adpall

