



Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

06-75262

21. EXPEDIENTE No.

54. TÍTULO "COMPOSICIÓN FARMACÉUTICA DIRECTAMENTE
COMPENSABLE PARA LA ADMINISTRACIÓN ORAL DE CCI-779"

51. CLASIFICACIÓN INTERNACIONAL A61K 9/00 / A61K31/435//
A61P31/04

71. SOLICITANTE WYETH

DOMICILIO NUEVA JERSEY, ESTADOS UNIDOS

74. APODERADO ALVARO CORREA ORDOÑEZ.
T.P. 20.281

22. BOGOTÁ, D. C., Agosto 1, 2006.

SS

PETITORIO

000001


Industria y Comercio
SUPERINTENDENCIA

Espac'

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Rad: 06-075262- 00000-0000

Fec. 2006-08-01 16 11.26 Dep 2020 NUECREACIO

Tra. 11 PATENTEYII

Ene: 376 FASENACIONALI

Act 411 PRESENTACION

Folios: 23

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

08-08-06

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
Lugar de Constitución.

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@bakernet.com

IDENTIFICACION

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

79 143 366 de

Usaquén

TP 20 281

④

INVENTOR (ES)

(72)

Nombre. ASHRAF, Muhammad y BENJAMIN, Eric J

Dirección: 67 Boulevard, Elmwood Park, NJ 07407, Estados Unidos y 3211 Morris Farm Drive, Jamestown, NC 27282, Estados Unidos, respectivamente

Nacionalidad o Domicilio. Estadounidense

⑤ PCT (85)

Solicitud Internacional No PCT/US2004/042178

Fecha 14-DIC-04

Publicación Internacional No WO 2005/070393

Fecha 4-AGO-05

⑥ Título (54)

COMPOSICIÓN FARMACÉUTICA DIRECTAMENTE COMPRESIBLE PARA LA ADMINISTRACIÓN ORAL DE

CCI-779

⑦

Clasificación Internacional (51)

A61K 9/00

A61K31/435 // A61P31/04

⑧

Prioridad

SI

☒

NO

☐

(33) País de Origen

US

(32) Fecha

08-ENE-04

(31) Número de Solicitud

60/534 951

⑨

Comprobante de pago No. 08-52116

Fecha 11-JUL-06

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

10

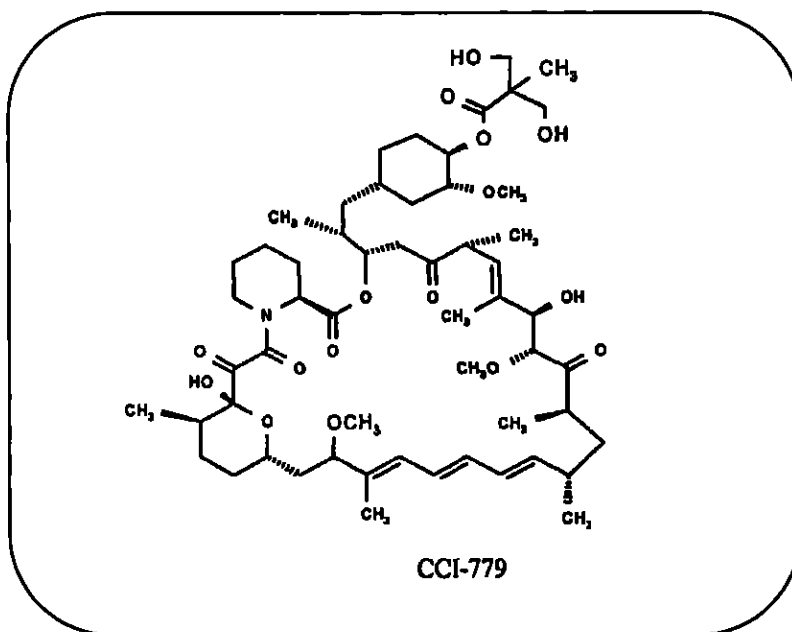
ANEXOS

000002

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite 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

11

FIGURA CARACTERISTICA



12

Solicito la concesión de la patente,

NOMBRE ALVARO CORREA ORDOÑEZ

FIRMA

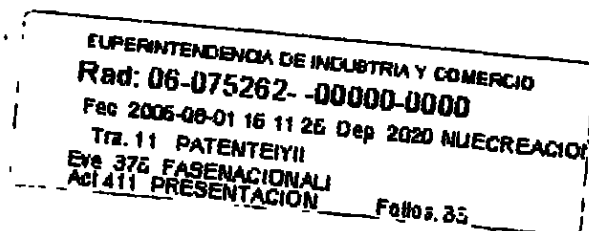
C C 79 143 366 de Usaquén T.P. 20.281

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 52,116
FECHA : JULIO 11 DE 2006



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PGO
SBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	37209761	11/07/2006	53,570,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL :	\$ 463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

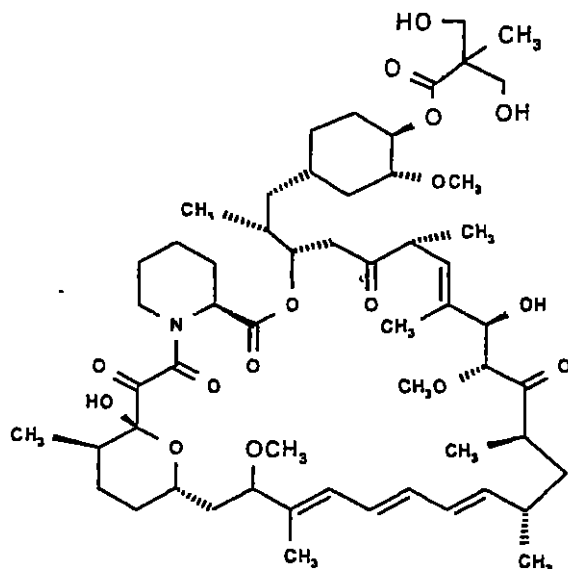
RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIRECTLY COMPRESSIBLE PHARMACEUTICAL COMPOSITION FOR THE ORAL ADMINISTRATION OF CCI-779

BACKGROUND OF THE INVENTION

Rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is an anticancer agent and is characterized by the following structure.



CCI-779

CCI-779 exhibits cytostatic, as opposed to cytotoxic properties, and may delay the progression of tumors or tumor recurrence. The mechanism of action of CCI-779 that results in the G1 to S phase block is novel for an anticancer drug. *In vitro*, CCI-779 has been shown to inhibit the growth of a number of histologically diverse tumor cells. Central nervous system (CNS) cancer, leukemia (T-cell), breast cancer, prostate cancer, and melanoma lines were among the most sensitive to CCI-779. The compound arrested cells in the G1 phase of the cell cycle.

CCI-779 has poor water solubility (less than 1 µg/ml) and high permeability (Log PC ≥ 4.1 in 1-octanol/water system and $P_{eff} = 4.5 \times 10^{-5}$ cm/sec obtained from *in situ* rat intestinal perfusion study using metoprolol tartrate as a marker) and is classified as class II compound according to BCS classification system. One obstacle towards the formulation of CCI-779 is its poor aqueous dissolution and low oral bioavailability.

Additionally, CCI-779 exhibits aqueous instability and has shown its potential to undergo oxidation

A CCI-779 formulation was developed that employed a wet granulation manufacturing process US Published Patent Application, Publication No. US- 2004- 0077677-A1 This process involved preparation of a hydroalcoholic granulation solution of CCI-779 Further, although the resulting tablets were stable and bioavailable, the preparation of the hydroalcoholic solution was very tedious. Further, CCI-779 was thermodynamically unstable, precipitating within one day after its preparation, requiring it to be used immediately after its preparation

In view of this, a simple manufacturing process is required that can produce stable and bioavailable tablets and can be used for commercial manufacturing

SUMMARY OF THE INVENTION

The present invention provides a convenient and effective method to deliver therapeutic levels of CCI-779 to the patient The invention provides pharmaceutical compositions containing a stable and bioavailable form of micronized CCI-779, and optionally, an antioxidant or a chelating agent, or mixtures thereof, in an immediate release dosage form for oral administration The composition is in the form of a tablet or in filled capsules

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

DETAILED DESCRIPTION OF THE INVENTION

The invention provides micronized CCI-779, that can be readily formulated into an oral dosage unit, and is particularly well suited for a directly compressible unit The inventors have found that tablets prepared by direct compression of micronized CCI-779 formulations of the invention exhibited rapid and complete drug release, as compared to nonmicronized CCI-779, even when the nonmicronized CCI-779 was formulated with surfactants See, e g, Example 4 Thus, the compositions of the invention provide fast drug release

Briefly, CCI-779 is micronized under nitrogen and conventional micronizing techniques, for example with a Trost or jet mill, applied to non-micronized CCI-779. The preparation of non-micronized CCI-779 is described in U.S. Patent 5,362,718, which is hereby incorporated by reference. A regioselective preparation of non-micronized CCI-779 is described in US Patent 6,277,983, which is hereby incorporated by reference. However, the invention is not limited to the method by which the non-micronized CCI-779 is produced. Micronized CCI-779 typically has a particle size of about 0.2 to about 30 microns, about 0.5 to 25 microns, or about 0.5 to 20 microns, as described above.

The compositions of the invention contain micronized CCI-779 with a particle size range in which 10% are less than or equal to about 3 microns (μ), 50% are about 10 μ , and 90% are less than or equal to about 20 μ as determined by Malvern method. In one embodiment, the micronized CCI-779 has a particle size range of 10% are less than or equal to about 2 μ , 50% are about 5 μ , and 90% are less than or equal to about 16 μ as determined by Malvern method.

Suitably, the micronized CCI-779 is present in the composition of the invention in an amount from 0.1% w/w to 50% w/w, based on the weight of an uncoated composition of the invention. This amount may be varied, depending upon the amount of micronized CCI-779 to be delivered to a patient. For example, an effective amount of micronized CCI-779 is generally in the range, e.g., about 0.1 to about 50 mg, about 10 mg to about 30 mg, or about 0.5 to about 2 mg micronized CCI-779. The desired therapeutic regimen can be taken into consideration when formulating a composition of the invention. For example, micronized CCI-779 can be in the range of 0.1% w/w to 10% w/w for an uncoated composition of the invention. In another example, micronized CCI-779 can be in the range of 5% w/w to 25% w/w based upon the weight of an uncoated unit dose. In yet another example, micronized CCI-779 can be in the range of 6% w/w to 8% w/w, 15% w/w to 40% w/w, or 20% w/w to 30% w/w based on the weight of an uncoated unit dose.

In addition to containing micronized CCI-779, the composition of the present invention can contain pharmaceutically acceptable additives and/or excipients.

Typically, these additives are biologically inert and useful for manufacture of a dosing

unit. The compositions of the invention may contain one or more filler/binder, disintegrant, a dissolution enhancer (including, *e.g.*, a surfactant), glidant, and lubricant. In certain embodiments, the compositions further contain one or more antioxidants, chelating agents, or pH modifiers. Optionally, the antioxidant, chelating agent, and/or pH modifier may be micronized. Micronized additives and excipients are prepared using conventional techniques, as described.

Examples of pharmaceutically acceptable binders, fillers and disintegrants include sucrose, lactose, magnesium stearate, gum acacia, cholesterol, tragacanth, stearic acid, gelatin, casein, lecithin (phosphatides), carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, cetostearyl alcohol, cetyl alcohol, cetyl esters wax, dextrates, dextrin, lactose, dextrose, glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate, polyoxyethylene alkyl ethers, polyethylene glycols, polyoxyethylene castor oil derivatives, polyoxyethylene stearates, and polyvinyl alcohol, and the like.

In one embodiment, the disintegrant is croscarmellose sodium. Suitably, a composition of the invention contains a total of about 3% w/w to 8% w/w disintegrant, *e.g.*, about 4% to about 6% w/w.

In one embodiment, the binders and fillers are selected from the group consisting of polyvinylpyrrolidone (povidone), lactose (including anhydrous lactose), and microcrystalline cellulose, and mixtures thereof. Suitably, a composition of the invention contains a total of about 75 % w/w to 88% w/w binder/filler, or about 80% w/w to 82% w/w binder/filler, based on the weight of an uncoated composition. For example, a composition of the invention may contain, in addition to the micronized CCI-779 and other components, about a low amount of povidone, *e.g.* about 5 to 7% w/w, and more desirably, about 6% w/w, with the remainder of the filler in the uncoated composition being supplied by other components. In another example, a composition of the invention may contain a high amount of povidone, *e.g.*, about 25 to 35% w/w, and more desirably, about 30 to 32 % w/w povidone, with the remainder of the filler in the uncoated composition being supplied by other components. In yet another example, a composition

of the invention contains a combination of lactose, preferably anhydrous lactose, and microcrystalline cellulose, optionally with povidone or another filler/binder. In such a composition (based on uncoated weight), anhydrous lactose is generally present in an amount of about 30% w/w to about 60% w/w, and more desirably, about 30 % w/w,

5 about 32% w/w, about 50% w/w, or about 55% w/w anhydrous lactose. Suitably, in such an uncoated composition, microcrystalline cellulose is present in an amount of about 15% w/w to about 30% w/w of the uncoated composition, and more desirably, about 16% w/w, about 23% w/w, about 25% w/w, about 28% w/w of the uncoated composition.

Dissolution enhancers may be included in the micronized CCI-779 composition
10 (based on uncoated weight) of the invention. Preferably, one or more dissolution enhancers may optionally be present in the composition in an amount of from about 0.5 % w/w to about 10 % w/w, and preferably, from about 5% w/w to about 8% w/w, about 5.5%, about 6% w/w, or 6.5% w/w, based on the weight of an uncoated composition. Examples of dissolution enhancers include surfactants, chelating agents (*e.g.* EDTA),
15 disintegrants, or combinations thereof.

In one embodiment, the surfactant is about 0.25 % w/w to about 10 % w/w of an uncoated composition, and preferably, about 5% w/w to about 6.5% w/w. In one embodiment, the surfactant is selected from sodium lauryl sulfate (also known as sodium dodecyl sulfate). Other suitable surfactants are well known to those of skill in the art and
20 can be selected including, without limitation, polysorbates including, *e.g.*, polysorbate 80, Polaxamer 188™ surfactant, sodium lauryl sulfate (sodium dodecyl sulfate), salts of bile acids (taurocholate, glycocholate, cholate, deoxycholate, *etc.*) which may be combined with lecithin. Alternatively, ethoxylated vegetable oils, such as Cremophor EL, vitamin E tocopherol propylene glycol succinate (Vitamin E TGPS), polyoxyethylene-
25 polyoxypropylene block copolymers, and poloxamers.

Acceptable antioxidants include, but are not limited to, citric acid, d,l- α -tocopherol, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), monothioglycerol, ascorbic acid, propyl gallate, and mixtures thereof. It is expected that the total amount of antioxidants in the formulations of this invention will be in
30 concentrations ranging from 0.001% to 3% w/w, and preferably, about 0.01 w/w to about

1% w/w and more preferably, about 0.02 % w/w to 0.1 % w/w, based on the weight of an uncoated composition. In one embodiment, the antioxidant is a combination of BHA and BHT, which may be in nonmicronized form or preferably, in micronized form.

Chelating agents and other materials capable of binding metal ions such as ethylene diamine tetra acetic acid (EDTA) and its salts and hydrates (e.g., EDTA calcium disodium hydrous) are useful in the compositions of the invention. Typically, where present, a chelating agent is present in an amount less than 1 % w/w, e.g., about 0.001 % w/w to about 0.01 % w/w, based on the weight of an uncoated composition. In one embodiment, the chelating agent is present in micronized form.

Acceptable pH modifying agents include, but are not limited to citric acid and salts thereof (e.g., sodium citrate), dilute HCl, and other mild acids or bases capable of buffering a solution containing CCl-779 to a pH of 4 to 6. Where present in a composition of the invention, such pH modifiers are present in an amount up to about 1% w/w, e.g., about 0.001% w/w to about 0.1% w/w, based on the weight of an uncoated composition. Optionally, the pH modifier, can be present in micronized form.

Other suitable components include lubricants and/or glidants. In one embodiment, the lubricant and the glidants can each be present in the composition of the invention in an amount of 0.01 wt% to about 1 wt%, about 0.1 wt% to about 2 wt%, or about 0.2 to about 0.5%, of an uncoated composition. In some embodiments, the lubricant and glidants are present in the composition in amounts of less than 1 wt% of an uncoated composition. An example of a suitable lubricant is magnesium stearate and an example of a suitable glidant is silicone dioxide.

Other suitable inert components of the formulation will be readily apparent to one of skill in the art.

The compositions of the invention are formed into a suitable dosing unit for delivery to a patient. Suitable dosing units include oral dosing units, such as a directly compressible tablet, a capsule, a powder and a suspension. The compositions of the invention can also be formulated for delivery by other suitable routes. These dosing units are readily prepared using the methods described herein and those known to those of skill in the art.

In one embodiment, a composition of the invention is prepared by dry mixing micronized CCI-779 with the other additives in a suitable mixer. The powder mix is then directly compressed into unit dose tablets.

Without limitation as to the method of preparation of a composition of the invention, an example of a suitable micronized CCI-779 formulation includes a low amount of povidone. The following weight percentages are based upon an uncoated composition of the invention.

	CCI-779, Micronized	6% w/w,
	Sodium Lauryl Sulfate	6% w/w,
10	Povidone	6% w/w,
	Lactose Anhydrous	50 % w/w,
	Microcrystalline Cellulose	25% w/w,
	Croscarmellose Sodium	6% w/w;
	Ghdant	0.25% w/w, and
15	Magnesium Stearate	0.25% w/w

Still a further example of a suitable micronized CCI-779 composition contains a high amount of povidone, with weight percentages based upon an uncoated composition of the invention:

	Micronized CCI-779	6 % w/w,
	Sodium Lauryl Sulfate	6% w/w,
	Povidone	31% w/w,
	Lactose Anhydrous	34% w/w,
	Microcrystalline Cellulose	16% w/w,
	Croscarmellose Sodium	6% w/w ;
	Ghdant	0.25% w/w, and
	Magnesium Stearate	0.5% w/w

Yet a further example of a suitable micronized CCI-779 dosing unit, with weight percentages based on total uncoated composition, is:

Micronized CCI-779	6% w/w,
Butylated Hydroxyanisol	0.022% w/w,
Butylated Hydroxytoluene	0.05% w/w,
EDTA	0.011% w/w;
Citric acid	0.08% w/w
Poloxamer 188	6% w/w
Lactose Anhydrous	55% w/w
Microcrystalline Cellulose	28 w/w
Croscarmellose Sodium	4% w/w
Glidant	0.25% w/w, and
Magnesium Stearate	0.5% w/w

Yet another example of a suitable dosing unit, with weight percentages based on
5 total uncoated composition, is

	CCI-779 (Micronized)	6% w/w,
	Butylated Hydroxyanisole (Micronized)	0.022% w/w,
	Butylated Hydroxytoluene (Micronized)	0.05% w/w,
	EDTA Calcium Disodium, Hydrus (Micronized)	0.011% w/w;
10	Citric Acid Anhydrous (Micronized)	1 % w/w,
	Sodium Lauryl Sulfate	6% w/w,
	Povidone K-25	65% w/w,
	Microcrystalline Cellulose	23% w/w,
	Anhydrous Lactose	50% w/w;
15	Croscarmellose Sodium	6 % w/w,
	Colloidal Silicone Dioxide	0.25% w/w, and
	Magnesium Stearate	0.50% w/w

Optionally, the tablets are film-coated. Suitable film-coatings are known to those of skill in the art. For example, the film-coating can be selected from among suitable polymers such as hydroxypropylmethylcellulose, ethyl cellulose, polyvinyl alcohol, and combinations thereof. Such coatings may also contain plasticizers and other desirable components. In one embodiment, the coatings are inert. Other suitable film-coatings can be readily selected by one of skill in the art. Where applied, the weight percent of the film coat is generally in the range of 1 % w/w to 6 % w/w, about 2 % w/w, about 3 % w/w, about 4 % w/w or about 5 % w/w, and more desirably, about 2 % w/w, based on the total weight of the coated composition.

The invention further provides a method of delivering CCI-779 to a patient, said method comprising the step of administering a micronized CCI-779 dosing unit according to the invention.

It is contemplated that when the formulations of this invention are used as an immunosuppressive or anti-inflammatory agent, they can be administered in conjunction with one or more other immunoregulatory agents. Such other antirejection chemotherapeutic agents include, but are not limited to azathioprine, corticosteroids, such as prednisone and methylprednisolone, cyclophosphamide, cyclosporin A, FK-506, OKT-3, and ATG. By combining one or more of the formulations of the present invention with such other drugs or agents for inducing immunosuppression or treating inflammatory conditions, lesser amounts of each of the agents may be required to achieve the desired effect. See, e.g., *Transplantation Proc.* 23: 507 (1991).

The dosage requirements may vary the severity of the symptoms presented and the particular subject being treated. Daily oral dosages of micronized CCI-779 can be 0.05 to 30 mg, about 1 mg to 25 mg, about 5 mg to about 10 mg. In one example, when micronized CCI-779 is used in combination therapy at daily doses in the range of 0.5 to 10 mg. In another example, micronized CCI-779 is used in monotherapy at daily doses in the range of 1 mg to 30 mg. In other embodiments, daily doses are 2 to 5 mg when micronized CCI-779 is used in combination therapy, and 5 to 15 mg when micronized CCI-779 is used as monotherapy.

Treatment can be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages will be determined by the administering physician based on experience with the individual subject treated. In general, the formulations of this invention are most desirably administered at a concentration that will generally afford effective results without causing any unacceptable harmful or deleterious side effects.

The following examples are illustrative of specific embodiments of the invention and are not a limitation on the present invention. The following provide representative examples of the formulations of this invention. These examples are illustrative only, and do not limit the invention.

EXAMPLE 1: Directly Compressible Tablet Formulations Prepared By Employing Non-Micronized CCI-779

The compositions included in this example employed non-micronized CCI-779 and were prepared with or without a surfactant. The tableting was carried out by dry blending and direct compression method.

Table 1 Quantitative Composition of CCI-779 Tablets, 5mg
Containing Non-Micronized CCI-779 without Surfactant

Ingredients	Percent Wt/Wt	Mg/tablet	Function
CCI-779, non-micronized	1.44	5.00	Active
Butylated Hydroxyanisole, NF	0.1	0.35	Antioxidant
Butylated Hydroxytoluene, NF	0.05	0.18	Antioxidant
EDTA, USP	0.01	0.04	Chelating agent
Sodium Citrate Anhydrous	0.75	2.62	pH modifier
Citric acid, Anhydrous USP	0.25	0.87	pH modifier
Povidone, K17, USP	7.14	24.99	Filler/ Binder
Lactose Anhydrous, NF	34.30	120.05	Filler

Microcrystalline Cellulose,NF (Avicel PH 112)	51.46	180.11	Filler/ Binder
Croscarmellose Sodium, NF	4.00	14.0	Disintegrant
Magnesium Stearate, NF	0.50	1.75	Lubricant
Total	0.05	350	

Table 2: Quantitative Composition of CCI-779 Tablets, 25 mg
Containing Non-Micronized CCI-779 and Surfactant

Ingredients	Percent Wt/Wt	mg/tablet	Function
CCI-779, non-micronized	6.25	25.00	Active
Sodium Lauryl Sulfate, NF	5.625	22.50	Surfactant
Povidone, K17, USP	31.25	125.00	Filler/ Binder
Lactose Anhydrous, NF	33.75	135.00	Filler
Microcrystalline Cellulose,NF (Avicel PH 112)	16.375	65.50	Filler/ Binder
Croscarmellose Sodium, NF	6.0	24.00	Disintegrant
Silicone dioxide (Aerosil 200)	0.25	1.00	Glidant
Magnesium Stearate, NF	0.50	2.00	Lubricant
Total	100	400	

CCI-779 tablets prepared by direct compression of nonmicronized CCI-779 with standard excipients and fillers. in the presence or absence of surfactants yielded tablets that did not exhibit rapid and complete drug release, and thereby resulted in an unsuitable formulation for CCI-779.

EXAMPLE 2 Directly Compressible Tablet Formulations Prepared By Employing Micronized CCI-779, Sodium Lauryl Sulphate And Povidone

The tablet formulations for this example are manufactured using the following protocol

- 5 Microcrystalline cellulose (Avicel PH-112) and povidone K-25 are passed through a screen and transferred to a V-blender of suitable size. Micronized CCI-779 is preblended with a portion of lactose anhydrous separately, then passed through a screen and added to the V-blender. Sodium lauryl sulfate, croscarmellose sodium, silicone dioxide and a portion of lactose anhydrous are passed through a screen and transferred to 10 the V blender. The remaining lactose anhydrous is passed through a screen and transferred it to V-blender and the lids are closed. The material is blended without activation of intensifier bar. Magnesium stearate is passed through a screen, premixed with a weight equivalent portion of powder, blended from V-blender, transferred to the lubricant premix to V-blender and blended without activation of intensifier bar. The final 15 blend is compressed using a tablet press with suitable tooling.

Table 3 Quantitative Composition of CCI-779 Tablets, 25 mg
Containing Low level of Povidone

Ingredients	Percent Wt/Wt	Mg / tablet	Function
CCI-779, Micronized	6.250	25.00	Active
Sodium Lauryl Sulfate, NF	5.625	22.50	Surfactant
Povidone, USP K25	6.250	25.00	Filler/ Binder
Lactose Anhydrous, NF	50.583	202.33	Filler
Microcrystalline Cellulose, NF (Avicel PH 112)	24.543	98.172	Filler/ Binder
Croscarmellose Sodium, NF	6.000	24.00	Disintegrant
Aerosil 200, NF	0.250	1.00	Glidant
Magnesium Stearate, NF	0.500	2.00	Lubricant

Total	100	400	
-------	-----	-----	--

Table 4 Quantitative Composition of CCI-779 Tablets, 25 mg
Containing High Level of Povidone

Ingredients	Percent Wt/Wt	Mg / tablet	Function
CCI-779, Micronized	6.250	25.00	Active
Sodium Lauryl Sulfate, NF	5.625	22.50	Surfactant
Povidone, USP K-25	31.250	125.00	Filler/ Binder
Lactose Anhydrous, NF	33.750	135.00	Filler
Microcrystalline Cellulose, NF (Avicel PH 112)	16.375	65.50	Filler/ Binder
Croscarmellose Sodium, NF	6.000	24.00	Disintegrant
Silicone dioxide (Aerosil 200), NF	0.250	1.00	Glidant
Magnesium Stearate, NF	0.500	2.00	Lubricant
Total	100	400	

5

EXAMPLE 3 Directly Compressible Tablet Formulations Prepared By Employing
Micronized CCI-779 And Poloxamer As Surfactant

The table formulations for this example are manufactured according to the
following protocol

- 10 Pass the poloxamer 188, microcrystalline cellulose (Avicel PH-112) and a portion
of anhydrous lactose through a screen and blend. Mill the blend containing poloxamer
with the help of a Fitz mill and transfer it to a V-blender of suitable size.

- Preblend a portion of anhydrous lactose with micronized butylated
hydroxyanisole, butylated hydroxytoluene, EDTA calcium disodium, hydrous, and citric
15 acid anhydrous. Then add CCI-779 to this preblend, mix and add to the V-blender.

Take a portion of anhydrous lactose, croscarmellose sodium, and colloidal silicon dioxide (Aerosil 200) and pass through a screen, blend and transfer it to V-blender. Pass the remaining anhydrous lactose through a screen and transfer it to V-blender. Close the lids and blend the material without activation of the intensifier bar. Pass magnesium stearate through a screen, premix with a weight equivalent portion of powder, blend and transfer the lubricant premix to V-blender and blend without the activation of the intensifier bar. Compress the final blend using a tablet press equipped with suitable tooling.

Table 5 Quantitative Composition of CCI-779 Tablets, 25 mg
Containing Poloxamer

Ingredients:	Percent wt/wt	Mg / tablet	Function
CCI-779, Micronized	6.250	25.00	Active
Butylated Hydroxyanisole, NF	0.022	0.088	Antioxidant
Butylated Hydroxytoluene, NF	0.050	0.20	Antioxidant
EDTA calcium disodium hydrous, USP	0.011	0.044	Chelating agent
Citric acid, Anhydrous USP	0.080	0.32	pH modifier
Poloxamer 188, NF	6.250	25.00	Surfactant
Lactose Anhydrous, NF	55.060	220.24	Filler
Microcrystalline Cellulose, NF (Avicel PH 112)	27.527	108.58	Filler/ Binder
Croscarmellose Sodium, NF	4.000	16.00	Disintegrant
Aerosil 200, NF	0.250	1.00	Glidant
Magnesium Stearate, NF	0.500	2.00	Lubricant
Total	100	400	

EXAMPLE 4 - Dissolution of CCI-779 Tablets

All the CCI-779 tablet formulations were evaluated by dissolution test. Dissolution test was performed using USP method II in 500 ml of 0.4% sodium lauryl sulfate at 75 RPM paddle speed. Table 6 summarizes the dissolution characteristics of the neat CCI-779 API and various tablet formulations of CCI-779

Table 6 Dissolution Data of CCI-779 Tablet Formulations

	Percent CCI-779 Dissolved					
Time (min)	CCI-779 (API) L21296-119*	Batch Table 1	Batch Table 2	Batch Table 4	Batch Table 3	Batch Table 5
10	4	31	30	56	87	90
20	9	42	58	87	96	94
30	14	50	74	95	98	95
45	21	56	86	97	99	97
60	---	---	93	98	100	97

* Pure CCI-779 was filled in hard gelatin capsules to test its dissolution

Dissolution results in Table 6 show that the tablets prepared by direct compression method (Table 1) did not exhibit rapid and complete drug release. Even the addition of a surfactant (Table 2) did not enhance dissolution of CCI-779 from these tablets. However, the directly compressible compositions of the invention containing micronized CCI-779 (Tables 3, 4, 5) exhibited fast and complete drug release.

EXAMPLE 5 Bioavailability of CCI-779 in Human - Evaluation of Oral Dosage Forms

The three prototype tablet formulations containing micronized CCI-779 (Tables 3, 4 and 5) were further evaluated for absorption in human volunteers. A

previously used clinical formulation prepared by wet granulation process was used as a control. The results of this biostudy are shown in Table 7 below.

The following chart relates the treatments of the bio-study to the compositions in this document and respective batch numbers of clinical batches.

Treatment	Composition in
High Povidone	Table 3
Low Povidone	Table 4
Poloxamer	Table 5
Control	—

Table 7. Pharmacokinetic Parameters ($\pm$ S D) Following Oral Administration of CCI-779 Tablet, 25 mg to Human Volunteers

Treatment	$t_{1/2}$ (hr)	C_{max} (ng/ml)	T_{max} (hr)	$AUC_{0-\infty}$ (ng.hr/ml)
Low Povidone	79.5 (17.0)	17.06 (8.07)	2.16 (0.9)	554.6 (187.7)
High Povidone	81.8 (23.7)	18.7 (9.6)	2.86 (2.1)	575.4 (190)
Poloxamer	77.9 (18.7)	11.36 (7.0)	4.08 (2.12)	544.0 (150.4)
Control	81.8 (17.2)	27.458 (12.4)	1.39 (0.637)	664.1 (217.5)

EXAMPLE 6 CCI-779 10 mg Film Coated Tablet Formulation Prepared By Employing Micronized CCI-779

5

Table 8 Quantitative Composition of CCI-779 Tablets, 10 mg

Ingredients:	Percent Wt/Wt	mg / tablet	Function
CCI-779, Micronized	6.25	10.00	Active
Butylated Hydroxyanisole, Micronized	0.022	0.035	Antioxidant
Butylated Hydroxytoluene, Micronized	0.050	0.080	Antioxidant
EDTA, Calcium Disodium, Hydrous, Micronized	0.011	0.044	Chelating agent
Citric acid, Anhydrous, Micronized	1.038	1.661	pH modifier
Sodium Lauryl Sulfate	5.625	9.00	Surfactant
Povidone K-25	6.25	10.00	Filler/Binder
Microcrystalline Cellulose (Avicel PH 112)	23.483	37.573	Filler/ Binder
Anhydrous Lactose	50.521	80.833	Filler
Croscarmellose Sodium	6.00	9.60	Disintegrant
Colloidal Silicon Dioxide (Aerosil 200)	0.25	0.40	Glidant
Magnesium Stearate (Vegetable Extract)	0.50	0.80	Lubricant
Total (Core Tablet Weight)	100	160.00	
Opadry II® White 85F18422, HPMC and other inert components	3.00	4.95	

000022

EXAMPLE 7 CCI-779 30 mg Film Coated Tablet Formulation Prepared By Employing Micronized CCI-779

Table 9 Quantitative Composition of CCI-779 Tablets. 30 mg

Ingredients:	Percent Wt/Wt	mg / tablet	Function
CCI-779, Micronized	6.25	30 000	Active
Butylated Hydroxyanisol, Micronized	0 022	0 105	Antioxidant
Butylated Hydroxytoluene, Micronized	0 050	0 240	Antioxidant
EDTA, Calcium Disodium, Hydrous, Micronized	0.011	0 054	Chelating agent
Citric acid, Anhydrous, Micronized	1.038	4 983	pH modifier
Sodium Lauryl Sulfate	5.625	27 00	Surfactant
Povidone K-25	6.25	30 000	Filler/Binder
Microcrystalline Cellulose (Avicel PH 112)	23 483	112 718	Filler/ Binder
Anhydrous Lactose	50.521	242.501	Filler
Croscarmellose Sodium	6.00	28.800	Disintegrant
Colloidal Silicon Dioxide (Aerosil 200)	0.25	1.200	Glidant
Magnesium Stearate (Vegetable Extract)	0 50	2.400	Lubricant
Total (Core Tablet Weight)	100	480.00	
Opadry II® White 85F18422, HPMC and other inert components	2.00	9 796	

5

The documents cited throughout this specification are hereby incorporated by reference. Minor variations and modifications to the methods and materials set forth in the foregoing detailed description and illustrative examples will be readily apparent to those of skill in the art and are encompassed within the scope of the invention.

CLAIMS

- 1 A pharmaceutical composition comprising micronized CCI-779
2. A pharmaceutical composition according to claim 1, wherein the micronized CCI-779 has a particle size range of 10% are less than or equal to about 3 μ , 50% are about 10 μ , and 90% are less than or equal to about 20 μ as determined by Malvern method
- 3 A pharmaceutical composition according to claim 1, wherein the micronized CCI has a particle size range of 10% are less than or equal to about 2 μ , 50% are about 5 μ , and 90% are less than or equal to about 16 μ as determined by Malvern method
- 4 A pharmaceutical composition according to any one of claims 1 to 3 which is an immediate release solid dosage form
- 5 A composition according to any one of claims 1 to 3 selected from the group consisting of a directly compressible tablet, a capsule, a powder and a suspension
- 6 A pharmaceutical composition according to any one of claims 1 to 5, wherein the micronized CCI-779 is present in an amount from 5 % w/w to 10% w/w of the composition
7. A pharmaceutical composition according to any one of claims 1 to 6, further comprising
 - about 5% w/w to about 6.5% w/w surfactant,
 - about 75 % w/w to about 85% w/w filler/binder,
 - about 4% w/w to about 6% w/w disintegrant
- 8 A pharmaceutical composition according to claim 7, wherein the surfactant is sodium lauryl sulfate

9 A pharmaceutical composition according to claim 7 or claim 8, wherein the filler/binder is selected from the group consisting of povidone, lactose, and microcrystalline cellulose, and mixtures thereof

10 A pharmaceutical composition according to any one of claims 7 to 9, wherein the disintegrant is croscarmellose sodium

11 A pharmaceutical composition according to any one of claims 1 to 11, further comprising one or more antioxidants, a chelating agent, and/or a pH modifier

12 A pharmaceutical composition according to claim 11, wherein any one of the one or more antioxidants, a chelating agent and/or pH modifier is micronized.

13 An oral CCI-779 dosing unit comprising micronized CCI-779, a surfactant, a filler/binder, a disintegrant, a glidant, and a lubricant.

14 An oral CCI-779 dosing unit according to claim 13, wherein the micronized CCI-779 has a particle size range of 10% are less than or equal to about 2 μ , 50% are about 5 μ , and 90% are less than or equal to about 16 μ as determined by Malvern method

15. An oral CCI-779 dosing unit according to claim 13 or claim 14, wherein the micronized CCI-779 is present in an amount from 0.1 % w/w to 10% w/w of the dosing unit, based on total uncoated weight.

16 An oral CCI-779 dosing unit according to any one of claims 13 to 15, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate and Polaxamer 188 surfactant

17 An oral CCI-779 dosing unit according to any one of claims 13 to 16, wherein the filler is selected from the group consisting of microcrystalline cellulose anhydrous lactose, povidone, and mixtures thereof

18 An oral CCI-779 dosing unit according to any one of claims 13 to 17, wherein the disintegrant is croscarmellose sodium

19 An oral CCI-779 dosing unit according to any one of claims 13 to 18, wherein the lubricant is magnesium stearate

20 An oral CCI-779 dosing unit according to claim 15, comprising
6 to 7 % w/w micronized CCI-779;
5 to 7% w/w surfactant,
50 to 90% w/w filler,
3 to 8% w/w disintegrant,
less than 1% w/w glidant, and
less than 1% w/w lubricant

21 An oral CCI-779 dosing unit according to claim 20 comprising.

CCI-779, Micronized	6.25% w/w,
Sodium Lauryl Sulfate	5.6% w/w,
Povidone	6.25% w/w,
Lactose Anhydrous	50 % w/w,
Microcrystalline Cellulose	25% w/w,
Croscarmellose Sodium	6% w/w,
Glidant	0.25% w/w, and
Magnesium Stearate	0.25% w/w

22 An oral CCI-779 dosing unit according to claim 20 comprising

Micronized CCI-779	6 % w/w,
Sodium Lauryl Sulfate	6% w/w,

Povidone	31% w/w,
Lactose Anhydrous	34% w/w,
Microcrystalline Cellulose	16% w/w,
Croscarmellose Sodium	6% w/w ,
Ghdant	0.25% w/w, and
Magnesium Stearate	0.5% w/w

23 An oral CCI-779 dosing unit according to claim 20 comprising

Micronized CCI-779	6% w/w,
Butylated Hydroxyanisol	0.022% w/w,
Butylated Hydroxytoluene	0.05% w/w,
EDTA	0.011% w/w,
Citric acid	0.08% w/w
Poloxamer 188	6% w/w
Lactose Anhydrous	55% w/w
Microcrystalline Cellulose	28 w/w
Croscarmellose Sodium	4% w/w
Ghdant	0.25% w/w, and
Magnesium Stearate	0.5% w/w

24 An oral CCI-779 dosing unit according to claim 20 comprising:

CCI-779 (Micronized)	6% w/w;
Butylated Hydroxyanisole (Micronized)	0.022% w/w,
Butylated Hydroxytoluene (Micronized)	0.050% w/w,
EDTA Calcium Disodium, Hydrous (Micronized)	0.011% w/w,
Citric Acid Anhydrous (Micronized)	1% w/w,
Sodium Lauryl Sulfate	6% w/w,
Povidone	6% w/w,
Microcrystalline Cellulose	24% w/w,

Anhydrous Lactose	51% w/w,
Croscarmellose Sodium	6% w/w,
Colloidal Silicone Dioxide	0.25% w/w, and
Magnesium Stearate	0.5% w/w

25 An oral CCI-779 dosing unit according to any of claims 13 to 24, wherein said dosing unit further comprises a seal coat

26 An oral CCI-779 dosing unit according to claim 25, wherein said seal comprises about 2% w/w hydroxypropylmethylcellulose of the coated composition.

27 An oral CCI-779 dosing unit according to any of claims 13 to 26, wherein said dosing unit is selected from the group consisting of a tablet and a capsule.

28 A method of delivering CCI-779 to a patient, said method comprising the step of administering an oral CCI-779 dosing unit according to any of claims 13 to 27

29 Use of micronized CCI-779 in preparing a medicament

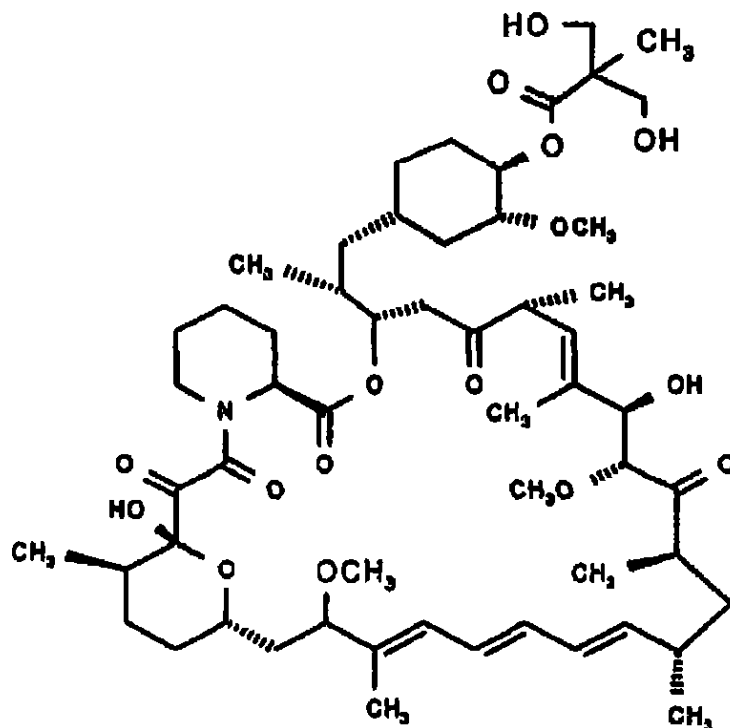
30 Use according to claim 29, wherein said micronized CCI-779 is directly compressed to form the medicament

31 Use of micronized CCI-779 in preparing an oral dosing unit according to any of claims 13 to 27

COMPOSICIÓN FARMACÉUTICA DIRECTAMENTE COMPRESIBLE PARA LA
ADMINISTRACIÓN ORAL DE CCI-779

ANTECEDENTES DE LA INVENCION

El éster 42 de rapamicina con ácido 3-hidroxi-2-(hidroximetil)-2-metilpropiónico (CCI-779) es un agente anticancerígeno y se caracteriza por la siguiente estructura.



CCI-779

Propiedades citostáticas, opuestas a las propiedades citotóxicas, y puede retrasar la progresión de tumores o recurrencia de tumor. El mecanismo de acción del CCI-779 que da como resultado el bloque de fase G1 a S es novedoso para una droga anticancerígena. *In vitro*, el CCI-779 ha mostrado que inhibe el crecimiento de un número de células tumorales histológicamente diversas. El cáncer del sistema nervioso central

(CNS), la leucemia (célula T), el cáncer de mama, el cáncer de próstata, y las líneas de melanoma estuvieron entre las más sensibles al CCI-779. El compuesto disminuyó las células en la fase G1 del ciclo celular.

El CCI-779 tiene pobre solubilidad en agua (menos de 1 µg/ml) y alta permeabilidad ($\text{Log PC} \geq 4.1$ en 1-octano/sistema de agua y $P_{\text{eff}} = 4-5 \times 10^{-5}$ cm/seg obtenida de un estudio de perfusión intestinal de rata *in situ* utilizando tartrato de metoprolol como marcador) y se clasificó como un compuesto clase II de acuerdo al sistema de clasificación BCS. Un obstáculo hacia la formulación del CCI-779 es su pobre disolución acuosa y su baja biodisponibilidad oral.

Adicionalmente, el CCI-779 exhibe inestabilidad acuosa y ha mostrado su potencial para sufrir oxidación.

Una formulación de CCI-779 se desarrolló la cual emplea un proceso de elaboración de granulación en húmedo. La solicitud de patente publicada estadounidense, publicación No. US-2004-0077677-A1. Este proceso involucró la preparación de una solución de granulación hidroalcohólica de CCI-779. Además, aunque las tabletas resultantes fueron estables y biodisponibles, la preparación de la solución hidroalcohólica fue muy tediosa. Además, el CCI-779 fue termodinámicamente inestable, precipitándose un día después de su preparación, requiriendo ser utilizado inmediatamente después de su preparación. En vista de esto, se requiere un simple proceso de elaboración que puede

producir tabletas estables y biodisponibles y se pueden utilizar para elaboración comercial.

RESUMEN DE LA INVENCION

La presente invención suministra un método conveniente y efectivo para suministrar niveles terapéuticos de CCI-779 al paciente. La invención suministra composiciones farmacéuticas que contienen una forma estable y biodisponible de V micronizado, y opcionalmente un antioxidante o un agente quelante, o mezclas de éstos, en una forma de dosis de liberación inmediata para la administración oral. La composición está en la forma de una tableta o en cápsulas rellenas.

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

DESCRIPCION DETALLADA DE LA INVENCION

La invención suministra CCI-779, micronizado que puede ser fácilmente formulado en una unidad de dosis oral, y es particularmente bien adecuado para una unidad directamente compresible. Los inventores han encontrado que las tabletas preparadas mediante compresión directa de formulaciones de CCI-779 micronizada de la invención exhibieron rápida y completa liberación de la droga, comparada con el CCI-779 no micronizado, Aún cuando el CCI-779 no micronizado se formuló con tensoactivos. Ver, por ejemplo, ejemplo 4. Así, las composiciones de la invención suministraron una liberación de droga rápida.

En resumen, el CCI-779 es micronizado bajo nitrógeno y técnicas de micronización convencionales, por ejemplo con un Trost o un molino de chorro, aplicado a un CCI-779 no micronizado. La preparación del CCI-779 no micronizado se describe en la Patente U.S. 5,362,718, que se incorpora aquí como referencia. Una preparación regioselectiva de un CCI-779 no micronizado se describe en la Patente U.S. 6,277,983, que se incorpora aquí como referencia. Sin embargo, la invención no está limitada al método por medio del cual se produce el CCI-779 no micronizado. El CCI-779 no micronizado típicamente tiene un tamaño de partícula de aproximadamente 0.2 a aproximadamente 30 micrómetros, aproximadamente 0.5 a 25 micrómetros o aproximadamente 0.5 a 20 micrómetros como se describió anteriormente.

Las composiciones de la invención contienen CCI-779 micronizado con un rango de tamaño de partícula en el cual el 10% son menores o iguales a aproximadamente 3 micrómetros (μ), 50% son de aproximadamente 10 μ , y 90% son menores o iguales a aproximadamente 20 μ determinadas por el método Malvern. En una modalidad, La CCI-779 micronizada tiene un rango de tamaño de partícula de 10% son menores o iguales a aproximadamente 2 μ , 50% son de aproximadamente 5 μ , y 90% son menores o iguales a aproximadamente 16 μ determinado por el método Malvern.

Adecuadamente el CCI-779 micronizado está presente en la composición de la invención en una cantidad de 0.1% p/p a 50% p/p, con base en el peso de una composición no recubierta de la

invención. Esta cantidad se puede variar, dependiendo de la cantidad de CCI-779 micronizado a ser suministrada a un paciente. Por ejemplo, una cantidad efectiva de CCI-779 micronizada está generalmente en el rango, por ejemplo, de aproximadamente 0.1 a aproximadamente 50 mg, aproximadamente 10 mg a aproximadamente 30 mg, o aproximadamente 0.5 a aproximadamente 2 mg de CCI-779 micronizado. El régimen terapéutico deseado puede ser tomado en consideración cuando se formula una composición de la invención. Por ejemplo, el CCI-779 micronizado puede estar en el rango de 0.1% p/p a 10% p/p para una composición no recubierta de la invención. En otro ejemplo, el CCI-779 micronizado puede estar en el rango de 5% p/p a 25% p/p con base en el peso de una dosis unitaria no recubierta. En aún otro ejemplo el CCI-779 micronizado puede estar en el rango de 6% p/p a 8% p/p, 15% p/p a 40% p/p, o 20% p/p a 30% p/p con base en el peso de una dosis unitaria no recubierta.

Además de contener CCI-779 micronizado, la composición de la presente invención puede contener aditivos farmacéuticamente aceptables y/o excipientes. Típicamente, estos aditivos son biológicamente inertes y útiles para elaborar una unidad dosificante. Las composiciones de la invención pueden contener uno o más llenadores, ligantes, desintegrantes, un mejorador de disolución (incluyendo, por ejemplo un tensoactivo), deslizantes, y lubricantes. En ciertas modalidades, las composiciones contienen además uno o más antioxidantes, agentes quelantes, o modificadores de pH. Opcionalmente, el antioxidante, agente quelante, y/o modificador de pH puede ser micronizado. Los

aditivos y excipientes micronizados son preparados utilizando técnicas convencionales, como se describió.

Ejemplos de ligadores, y desintegrantes farmacéuticamente aceptables incluyen sucrosa, lactosa, estearato de magnesio, goma de acacia, colesterol, tragacanto, ácido esteárico, gelatina, caseína, lecitina (fosfátidos), carboximetilcelulosa calcio, carboximetilcelulosa sodio, metilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa, eftalato de hidroxipropilmetilcelulosa, celulosa no cristalina, cetostearil alcohol, cetil alcohol, cera de cetil ésteres, dextratos, dextrina, lactosa, dextrosa, gliceril monooleato, gliceril monoestearato, gliceril palmitoestearato, polioxietilen alquil éteres, polietilenglicoles, derivados de aceite de castor polioxietileno, estearato de polioxietileno, y polivinil alcohol, y similares.

En una modalidad, el desintegrante es croscarmelosa sodio. Adecuadamente, una composición de la invención que tiene un total de aproximadamente 3% p/p a 8% p/p de desintegrante, por ejemplo, aproximadamente 4% a aproximadamente 6% p/p.

En una modalidad, los ligadores y llenadores de seleccionan del grupo que consiste de polivinil pirrolidona (povidona), lactosa, (incluyendo lactosa anhidra), y celulosa microcristalina, y mezclas de éstas. Adecuadamente, una composición de la invención contiene un total de aproximadamente 75% p/p a 88% p/p de ligante, llenador o aproximadamente 80% p/p a 82% p/p de ligador/llenate, con base en el peso de la composición no recubierta. Por ejemplo, una composición de la

invención puede contener, además del CCI-779 micronizado y otros componentes, aproximadamente una cantidad baja de povidona, por ejemplo aproximadamente 5 a 7% p/p, y más deseablemente aproximadamente 6% p/p, con el resto del llenador en la composición no recubierta que es suministrado por otros componentes. En otro ejemplo, una composición de la invención puede contener una cantidad alta de povidona, por ejemplo, aproximadamente 25 a 35% p/p, y más deseablemente, aproximadamente 30 a 32% p/p de povidona, con el resto del llenador en la composición no recubierta que es suministrada por otros componentes. En aún otro ejemplo, una composición de la invención contiene una combinación de lactosa, preferiblemente lactosa anhidra, y celulosa microcristalina, opcionalmente con povidona u otro llenador/ligador. En tal composición (con base en el peso no recubierto), la lactosa anhidra está generalmente presente en una cantidad de aproximadamente 30% p/p a aproximadamente 60% p/p, y más deseablemente, aproximadamente 30% p/p, aproximadamente 32% p/p, aproximadamente 50% p/p, o aproximadamente 55% p/p de lactosa anhidra. Adecuadamente, en tal composición no recubierta, la celulosa microcristalina está presente en una cantidad de aproximadamente 15% p/p a aproximadamente 30% p/p de la composición no recubierta, y más deseablemente, aproximadamente 16% p/p, aproximadamente 23% p/p, aproximadamente 25% p/p, aproximadamente 28% p/p, de la composición no recubierta.

Los mejoradores de disolución pueden estar incluidos en la composición de CCI-779 micronizada (con base en el peso no recubierto) de la invención. Preferiblemente, uno o más

mejoradores de disolución pueden estar opcionalmente presentes en la composición en una cantidad de desde aproximadamente 0.5% p/p a aproximadamente 10% p/p, y preferiblemente, desde aproximadamente 5% p/p a aproximadamente 8% p/p, aproximadamente 5.5%, aproximadamente 6% p/p, o 6.5% p/p, con base en el peso sobre una composición no recubierta. Ejemplos de mejoradores de disolución incluyen tensoactivos, agentes quelantes (por ejemplo EDTA), desintegrantes, o combinaciones de éstos.

En una modalidad, el tensoactivo es aproximadamente 0.25% p/p a aproximadamente 10% p/p de una composición no recubierta, y preferiblemente, aproximadamente 5% p/p a aproximadamente 6.5% p/p. En una modalidad, el tensoactivo se selecciona de lauril sulfato de sodio (también conocido como dodecil sulfato de sodio). Otros tensoactivos adecuados son bien conocidos por aquellos expertos en la técnica y se pueden seleccionar incluyendo, sin limitación, polisorbato que incluyen, por ejemplo, polisorbato 80, tensoactivo de poloxámero 188TM, lauril sulfato de sodio (dodecil sulfato de sodio), sales de ácidos de bilis (taurocolato, glicocolato, colato, desoxicolato, etc.) que pueden ser combinados con lecitina. Alternativamente, los aceites vegetales etoxilados, tal como el Cremofor EL, vitamina E tocoferol propilenglicol succinato (vitamina E TGPS), copolímeros de bloque de plioxietileno-polioxipropileno, y poloxámeros.

Los antioxidantes aceptables incluyen, pero no están limitados a, ácido cítrico, d,l- α -tocoferol, hidroxianisol butilado (BHA), hidroxitolueno butilado (BHT), monotioglicerol, ácido ascórbico, propil galato, y mezclas de éstos. Se espera que

la cantidad total de antioxidantes en las formulaciones de esta invención estarán en concentraciones que varían desde 0.001% a 3% p/p, y preferiblemente, aproximadamente 0.01 p/p a aproximadamente 1% p/p, y más preferiblemente, aproximadamente 0.025 P/P A 0.1% P/P, con base en el peso de una composición no recubierta. En una modalidad, el antioxidante es una combinación de BHA BHT, que pueden estar en forma no micronizada o preferiblemente en forma micronizada.

Los agentes quelantes y otros materiales capaces de unir iones metálicos tal como ácido etileno diamina tetra acético (EDTA) y sus sales e hidratos (por ejemplo EDTA calcio disodio hidratado) son útiles en las composiciones de la invención. Típicamente, donde están presentes, un agente quelante está presente en una cantidad menor de 1% p/p, por ejemplo aproximadamente 0.001% p/p a aproximadamente 0.01% p/p, con base en el peso de una composición no recubierta. En una modalidad, el agente quelante está presente en forma micronizada.

Los agentes de modificación de pH aceptables incluyen, pero no están limitados a ácidos cítricos y sales de estos (por ejemplo citrato de sodio), HCL diluido, y otros ácidos o bases medias capaces de amortiguar una solución que contiene CCI-779 a un pH de 4 a 6. Donde está presente en una composición de la invención, tales modificadores de pH están presentes en una cantidad hasta de aproximadamente 1% p/p, por ejemplo, aproximadamente 0.001% p/p a aproximadamente 0.1% p/p, con base en el peso de una composición no recubierta. Opcionalmente, el modificador de pH puede estar presente en forma micronizada.

Otros componentes adecuados incluyen lubricantes y/o deslizantes. En una modalidad, el lubricante y los deslizantes pueden cada uno estar presentes en la composición de la invención en una cantidad de 0.01% en peso a aproximadamente 1% en peso, aproximadamente 0.1% en peso a aproximadamente 2% en peso o aproximadamente 0.2 a aproximadamente 0.5% de una composición no recubierta. En algunas modalidades, el lubricante y los deslizantes están presentes en la composición en cantidades de menos de 1% en peso de una composición no recubierta. Un ejemplo de un lubricante adecuado es estearato de magnesio y un ejemplo de deslizantes adecuados es e dióxido de silicio.

Otros componentes inertes adecuados de la formulación serán fácilmente evidentes para un experto en la técnica.

Las composiciones de la invención están formadas en una unidad de dosis adecuada para suministro a un paciente. Las unidades de dosis adecuadas incluyen unidades de dosis orales, tales como tableta directamente compresible, una cápsula, un polvo y una suspensión. Las composiciones de la invención también se pueden formular para suministro por otras rutas adecuadas. Estas unidades de dosificación son fácilmente preparadas utilizando los métodos descritos aquí y aquellos conocidos por los expertos en la técnica.

En una modalidad, una composición de la invención se prepara al mezclar en seco CCI-779 micronizado con los otros aditivos en

un mezclador adecuado. Una mezcla de polvo es luego directamente comprimida en tabletas de dosis unitaria.

Sin limitación para el método de preparación de una composición de la invención, un ejemplo de una formulación de CCI-779 micronizada adecuada incluye una cantidad baja de povidona. Los siguientes porcentajes en peso están basados en una composición no recubierta de la invención.

CCI-779 micronizado	6% P/P;
Lauril Sulfato de sodio	6% p/p;
Povidona	6% p/p;
Lactosa Anhidra	50% p/p;
Celulosa Microcristalina	25% p/p;
Croscarmelosa Sodio	6% p/p;
Deslizante	0.25% p/p; y
Estearato de Magnesio	0.25% p/p;

Aún un ejemplo adicional de una composición de CCI-779 micronizada adecuada contiene una alta cantidad de povidona, con porcentajes en peso basados en una composición no recubierta de la invención.

CCI-779 micronizado	6% P/P;
Lauril Sulfato de sodio	6% p/p;
Povidona	31% p/p;
Lactosa Anhidra	34% p/p;
Celulosa Microcristalina	16% p/p;
Croscarmelosa Sodio	6% p/p;

Deslizante	0.25% p/p; y
Estearato de Magnesio	0.5% p/p;

Aún un ejemplo adicional de una dosis de dosificación de CCI-779 micronizada adecuada, con porcentajes en peso basados en la composición no recubierta total, es:

CCI-779 micronizada	6% p/p;
Hidroxianizol Butilado	0.022% p/p;
Hidroxitolueno Butilado	0.05%p/p;
EDTA	0.011% P/P;
Ácido Cítrico	0.08% P/P;
Poloxámero 188	6% P/P;
Lactosa Anhidra	55% P/P;
Celulosa Microcristalina	28% P/P;
Croscarmelosa Sodio	4% P/P;
Deslizante	0.25% P/P; Y
Estearato de Magnesio	0.5% P/P.

Aún otro ejemplo de una unidad de dosificación adecuada, con porcentajes en peso basados en la composición no recubierta total, es:

CCI-779 (micronizada)	6% P/P;
Hidroxianizol Butilado (Micronizado)	0.022% P/P;
Hidroxitolueno Butilado (Micronizado)	0.05% P/P;
EDTA Calcio Disodio, Hidratada (Micronizada)	0.011% P/P;
Acido Cítrico Anhídrido (Micronizado)	1% P/P;
Lauril Sulfato de Sodio	6% P/P;

Povidona K-25	65% P/P;
Celulosa Microcristalina	23% P/P;
Lactosa Anhidra	50% P/P;
Croscarmelosa Sodio	6% P/P;
Dióxido de Silicio Coloidal	0.25% P/P; y
Estearato de Magnesio	0.50% P/P;

Opcionalmente, las tabletas son recubiertas con una película. Los recubrimientos de película adecuados son conocidos por aquellos expertos en la técnica. Por ejemplo, los recubrimientos de película se pueden seleccionar de entre polímeros adecuados tales como hidroxipropilmetilcelulosa, etil celulosa, polivinil alcohol, y combinaciones de éstos. Tales recubrimientos también pueden contener plastificadores y otros componentes deseables. En una modalidad, los recubrimientos son inertes. Otros recubrimientos de película adecuados pueden ser fácilmente seleccionados por un experto en la técnica. Donde se aplica, el porcentaje en peso del recubrimiento de película está generalmente en el rango de 1% p/p a 6% p/p, aproximadamente 2% p/p, aproximadamente 3% p/p, aproximadamente 4% p/p, o aproximadamente 5% p/p, y más deseablemente, aproximadamente 2% p/p, con base en el peso total de la composición recubierta.

La invención suministra además un método para suministrar CCI-779 a un paciente, dicho método comprende la etapa de administrar una unidad de dosificación CCI-779 micronizada de acuerdo con la invención.

Se contempla que cuando las formulaciones de esta invención son utilizadas como un agente inmunosupresor o anti inflamatorio, ellos se pueden administrar en conjunto con uno o más de otros agentes inmunoreguladores. Tales otros agentes quimioterapéuticos ante rechazo incluyen, pero no están limitados a azatioprina, corticosteroides, tales como prednisona y metilprednisolona, ciclofosfamida, ciclosporina A, FK-506, OKT-3, y ATG. Al combinar una o más formulaciones de la presente invención con otras de tales drogas o agentes para inducir la inmunosupresión o tratar las condiciones inflamatorias, se pueden requerir cantidades menores de cada uno de los agentes para lograr el efecto deseado. Ver, por ejemplo, *Transplantation Proc.* 23:507 (1991).

Los requisitos de dosis pueden variar la severidad de los síntomas presentados y el sujeto particular a ser tratado. Las dosis orales diarias de CCI-779 micronizado pueden ser 0.05 a 30 mg, aproximadamente 1 mg a 25 mg, aproximadamente 5 mg a aproximadamente 10 mg. En un ejemplo, cuando se utiliza CCI-779 micronizado en terapia de combinación a dosis diarias en el rango de 0.5 a 10 mg. En otro ejemplo, se utiliza CCI-779 micronizado en monoterapia a dosis diaria en el rango de 1 mg a 30 mg. En otras modalidades, las dosis diarias son 2 a 5 mg cuando se utiliza CCI-779 micronizado en terapia de combinación, y 5 a 15 mg cuando se utiliza CCI-779 micronizado como monoterapia.

El tratamiento se puede iniciar con dosis pequeñas menores de la dosis óptima del compuesto. Posteriormente la dosis se incrementa hasta que se alcanza el efecto óptimo de acuerdo con las circunstancias. Las dosis precisas se determinarán por el

médico administrante con base en la experiencia con el sujeto individual tratado. En general, las formulaciones de ésta invención son más deseablemente administradas a una concentración que logrará generalmente resultados efectivos sin producir ningún daño o efectos colaterales deletéreos inaceptables.

Los siguientes ejemplos de modalidades específicas ilustrativas de la invención no son una limitación e la presente invención. Lo siguiente suministra ejemplos representativos de las formulaciones de ésta invención. Estos ejemplos son ilustrativos solamente, y no limitan la invención.

EJEMPLO 1: Formulaciones de tableta directamente compresibles preparadas al emplear CCI-779 no micronizado.

Las composiciones incluidas en este ejemplo emplearon CCI-779 no micronizado y fueron preparadas con y sin tensoactivo. La formación de tabletas fue llevada a cabo mediante mezcla en seco y el método de compresión directa.

Tabla 1: Composición Cuantitativa de Tabletetas de CCI-779, 5 mg que Contienen CCI-779 no micronizado sin tensoactivo.

Ingredientes	Porcentaje Wt/Wt	Mg/tableta	Función
CCI-779 no micronizado	1.44	5.00	Activo
Hidroxianizol Butilado, NF	0.1	0.35	Antioxidante
AntioxidanteHidroxitolueno Butilado, NF	0.05	0.18	Antioxidante
EDTA, USP	0.01	0.04	Agente Quelante
Citrato de Sodio Anhidro	0.75	2.62	Modificador de

			pH
Acido Cítrico, Anhidro USP	0.25	0.87	Modificador de pH
Povidona, K17, USP	7.14	24.99	Llenador/Ligador
Lactosda Anhidra, NF	34.30	120.05	LLenador
Celulosa Microcristalina, NF	51.46	180.11	
(Avicel PH 112)			
Croscarmelosa Sodio, NF	4.00	14.0	Desintegrante
Estearato de Magnesio, NF	0.50	1.75	Lubricante
Total	0.05	350	

Tabla 2: Composición Cuantitativa de Tabletas de CCI-779, 25 mg que contienen CCI-779 no micronizado y Tensoactivo

Ingredientes	Porcentaje Wt/Wt	Mg/Tableta	Función
CCI-779 no micronizado	6.25	25.00	Activo
Lauril Sulfato de Sodio, NF	5.625	22.50	Tensoactivo
Povidona, K17, USP	31.25	125.00	Llenador/Ligador
Lactosa Anhidra, NF	33.75	135.00	Llenador
Celulosa Microcristalina, NF	16.375	65.50	Llenador/Ligador
(Avicel PH 112)			
Croscarmelosa Sodio, NF	6.0	24.00	Desintegrante
Dióxido de Silicio (Aerosol 200)	0.25	1.00	Deslizante
Estearato de Magnesio, NF	0.50	2.00	Lubricante
Total	100	400	

Las tabletas CCI-779 preparadas mediante compresión directa de CCI-779 micronizado con excipientes y llenadores estándar, en la presencia o ausencia de tensoactivos produjeron tabletas que no exhibieron liberación de droga rápida y completa, y dieron como resultado de esta manera una formulación no adecuada para CCI-779.

EJEMPLO 2: Formulación de tableta directamente compresible preparada al emplear CCI-779 micronizado, Lauril Sulfato de Sodio y Povidona.

Las formulaciones de tableta para este ejemplo son elaboradas utilizando el siguiente protocolo.

La celulosa microcristalina (Avicel PH 112) y povidona K-25 son pasadas a través de un tamiz y transferidas a un mezclador V de tamaño adecuado. El CCI-779 micronizado el premezclado con una porción de lactosa anhidra separadamente, luego pasada a través de un tamiz y agregada al mezclador V. Lauril sulfato de sodio, croscarmelosa sodio, dióxido de silicio y una porción de lactosa anhidra son pasadas a través de un tamiz y transferidas al mezclador V. La lactosa anhidra restante es pasada a través de un tamiz y transferida a un mezclador V y son cerradas las tapas. El material es mezclado sin activación de una barra intensificadora. Se pasa estearato de magnesio a través de un tamiz, se pre mezcla con una porción equivalente en peso de polvo, mezclada de un mezclador V, transferida a la pre mezcla lubricante al mezclador V y mezclada sin activación de la barra intensificadora. La

mezcla final es comprimida utilizando una prensa de tableta con herramienta adecuada.

Tabla 3: Composición Cuantitativa de Tabletas CCI-779, 25 mg que Contienen Bajo Nivel de Povidona.

Ingredientes	Porcentaje Wt/Wt	Mg/Tableta	Función
CCI-779 Micronizado	6.25	25.00	Activo
Lauril Sulfato de Sodio, NF	5.625	22.50	Tensoactivo
Povidona, USP K25	6.250	25.00	Llenador/Ligador
Lactosa Anhidra, NF	50.583	202.33	Llenador
Celulosa Microcristalina, NF	24.543	98.172	Llenador/Ligador
(Avicel PH 112)			
Croscarmelosa Sodio, NF	6.000	24.00	Desintegrante
Aerosil 200, NF	0.250	1.00	Deslizante
Estearato de Magnesio, NF	0.500	2.00	Lubricante
Total	100	400	

Tabla 4: Composición Cuantitativa de Tabletas CCI-779, 25 mg que Contienen Alto Nivel de Povidona.

Ingredientes	Porcentaje Wt/Wt	Mg/Tableta	Función
CCI-779 Micronizado	6.250	25.00	Activo
Lauril Sulfato	5.625	22.50	Tensoactivo

de Sodio, NF			
Povidona, USP K-25	31.250	125.00	Llenador/Ligador
Lactosa Anhidra, NF	33.850	135.00	Llenador
Celulosa Microcristalina, NF	16.375	65.50	Llenador/Ligador
(Avicel PH 112)			
Croscarmelosa Sodio, NF	6.000	24.00	Desintegrante
Dióxido de Silicio (Aerosil 200), NF	0.250	1.00	Deslizante
Estearato de Magnesio, NF	0.500	2.00	Lubricante
Total	100	400	

Ejemplo 3: Formulaciones de Tableta Directamente Compresibles Preparadas al Emplear CCI-779 Micronizado y Poloxámero como Tensoactivo.

Las formulaciones de tableta de éste ejemplo son elaboradas de acuerdo con e siguiente protocolo.

Pasar el poloxámero 188, la celulosa microcristalina (Avicel PH-112) y una porción de lactosa anhidra a través de un tamiz y mezclar. Moler la mezcla que contiene poloxámero con la ayuda de un molino Fitz y transferirlo a un mezclador V de un tamaño adecuado.

Pre mezclar una porción de lactosa anhidra con hidroxianizol butilado micronizado, hidroxitolueno butilado, EDTA calcio

disodio hidratado, y ácido cítrico anhidro. Cuando se agrega CCI-779 a esta pre mezcla, mezclar y agregar a mezclador V.

Tomar una porción de la lactosa anhidra, croscarmelosa de de sodio, y dióxido de silicio coloidal (Aerosil 200) y pasar a través de un tamiz, mezclar y transferirlo a un mezclador V. Pasar el resto de la lactosa anhidra a través de un tamiz y transferirlo al mezclador V. Cerrar las tapas y mezclar el material sin activación de la barra intensificadora. Pasar estearato de magnesio a través de un tamiz, pre mezclar con una porción equivalente en peso de mezcla de polvo y transferir la pre mezcla lubricante al mezclador V y mezclar sin la activación de la barra intensificadora. Comprimir la mezcla final utilizando una prensa de tableta equipada con una herramienta adecuada.

Tabla 5: Composición Cuantitativa de Tabletas CCI-779, 25 mg que Contienen Poloxámero.

Ingredientes	Porcentaje Wt/Wt	Mg/Tableta	Función
CCI-779 Micronizado	6.250	25.00	Activo
Hidroxianisol Butilado, NF	0.022	0.088	Antioxidante
Hidroxitolueno Butilado, NF	0.050	0.20	Antioxidante
EDTA, calcio disodio hidratado, USP	0.011	0.044	Agente Quelante
Acido cítrico, Anhidro USP	0.080	0.32	Modificador de PH
Ph	6.250	25.00	Tensoactivo
Lactosa Anhidra, NF	55.060	220.24	Llenador

Celulosa Microcristalina, NF	27.527	108.58	Llenador/ligador
(Avicel PH 112)			
Croscarmelosa Sodio, NF	4.000	16.00	Desintegrante
Aerosil 200, NF	0.250	1.00	Deslizante
Estearato de Magnesio, NF	0.500	2.00	Lubricante
Total	100	400	

EJEMPLO 4- disolución de Tableta CCI-779.

Todas las formulaciones de tableta de CCI-779 fueron evaluadas mediante ensayo de disolución.

El ensayo de disolución fue desarrollado utilizando un método USP II en 500 ml de lauril sulfato de sodio 0.4% con una velocidad de paleta de 75 RPM. La tabla 6 resume las características de disolución del CCI-779 API puro y varias formulaciones de tableta de CCI-779.

Tabla 6: Datos de Disolución de Formulaciones de Tableta CCI-779.

	Porcentaje De CCI-779 Disuelto					
Tiempo (min)	CCI-779 (API) L21296- 119*	Tanda Tabla 1	Tanda Tabla 2	Tanda Tabla 4	Tanda Tabla 3	Tanda Tabla 5
10	4	31	30	56	87	90
20	9	42	58	87	96	94
30	14	50	74	95	98	95
45	21	56	86	97	99	97
60	--	---	93	98	100	97

*El CCI-779 Puro se relleno en cápsulas de gelatina dura para ensayar su disolución.

Los resultados de disolución en la Tabla 6 muestran que las tabletas preparadas mediante método de compresión directa (Tabla 1) no exhibieron una liberación de droga rápida y completa. Aún la adición de un tensoactivo (Tabla 2) no mejora la disolución de CCI-779 de estas tabletas. Sin embargo, las composiciones directamente compresibles de la invención que contienen CCI-779 micronizado (Tablas 3, 4, 5) exhibieron liberación de droga rápida y completa.

EJEMPLO 5: Biodisponibilidad de CCI-779 en Humano -Evaluación de Formas de Dosis Oral.

Las tres formulaciones de tableta prototipo que contienen CCI-779 micronizado (Tablas 3, 4, y 5) fueron además evaluadas para absorción en voluntarios humanos. Una formulación química previamente utilizada preparada mediante un proceso de granulación en húmedo se utilizó como control. Los resultados de éste bioestudio son mostrados en la Tabla 7 de adelante.

La siguiente tabla se relaciona con los tratamientos del bio estudio de las composiciones en este documento y los números de tanda respectivos de las tandas clínicas:

Tratamiento	Composición en
Povidona Alta	Tabla 3
Povidona Baja	Tabla 4
Poloxamero	Tabla 5
Control	---

Tabla 7: Parámetros Farmacocinéticos (± S.D.) Luego de Administración Oral de Tableta de CCI-779, 25 mg a Voluntarios Humanos.

Tratamiento	T _{1/2} (hr)	C _{max} (ng/ml)	T _{max} (hr)	AUC _{0-∞} (ng.hr/ml)
Povidona Baja	79.5 (17.0)	17.06 (8.07)	2.16 (0.9)	554.6 (187.7)
Povidona Alta	81.8 (23.7)	18.7 (9.6)	2.86 (2.1)	575.4 (190)
Poloxamero	77.9 (18.7)	11.36 (7.0)	4.08 (2.12)	544.0 (150.4)
Control	81.8 (17.2)	27.458 (12.4)	1.39 (0.637)	664.1 (217.5)

EJEMPLO 6: CCI-779 10 MG Formulación de Tableta Recubierta con Película Preparada al Emplear CCI-779 micronizado.

Tabla 8: Composición Cuantitativa de Tabletetas de CCI-779, 10 mg.

Ingredientes	Porcentaje Wt/Wt	Mg/Tableta	Función
CCI-779 micronizado	6.25	10.0	Activo
Hidroxianisol Butilado, Micronizado	0.022	0.035	Antioxidante
Hidroxitolueno Butilado, Micronizado	0.050	0.080	Antioxidante
EDTA, Disodio Calcio, Hidratado,	0.011	0.044	Agente Quelante

Micronizado			
Acido Cítrico, Anhidro, Micronizado	1.038	1.661	Modificador de PH
Lauril Sulfato de Sodio	5.625	9.00	Tensoactivo
Povidona K-25	6.25	10.00	Llenador/Ligador
Celulosa Microcristalina	23.483	37.573	Llenador/Ligador
(Avicel PH 112)			
Lactosa Anhidra	50.521	80.833	Llenador
Croscarmelosa Sodio	6.00	9.00	Desintegrante
Dióxido de Silicio Coloidal (Aerosil 200)	0.25	0.40	Deslizante
Estearato de Magnesio	0.50	0.80	Lubricante
(Extracto Vegetal)			
Total (Peso de Tableta Núcleo)	100	160.0	
Opadri II® White 85F18422, HPMC y Otros Componentes Inertes	3.00	4.95	

EJEMPLO 7: CCI-779 30 mg Formulación de Tableta Recubierta con Película Preparada al Emplear CCI-779 Micronizado

Tabla 9: Composición Cuantitativa de Tabletas de CCI-779, 30 mg

Ingredientes	Porcentaje Wt/Wt	Mg/tableta	Función
CCI-779	6.25	30.000	Activo
Micronizado			
Hidroxianisol	0.022	0.105	Antioxidante
Butilado,			
Micronizado			
Hidroxitolueno	0.050	0.240	Antioxidante
Butilado,			
Micronizado			
EDTA, Calcio	0.011	0.054	Agente Quelante
Disodio,			
Hidratado,			
Micronizado			
Ácido Cítrico,	1.038	4.983	Modificador de
Anhidro,			pH
Micronizado			
Lauril Sulfato	5.625	27.00	Tensoactivo
de Sodio			
Povidona K-25	6.25	30.000	Llenador/Ligador
Celulosa	23.483	112.718	Llenador/Ligador
Microcristalina			
(Avicel PH 112)			
Lactosa Anhidra	50.521	242.501	Llenador
Croscarmelosa	6.00	28.800	Desintegrante
Sodio			
Dióxido de	0.25	1.200	Deslizante
Silicio			
Coloidal			
(Aerosil 200)			
Estearato de	0.50	2.400	Lubricante
Magnesio			
(Extracto			
Vegetal)			
Total (Peso de	100	480.00	
Tableta Núcleo)			
Opadry II®	2.00	9.796	
White 85F18422.			
HPMC y otros			
componentes			
inertes			

Los documentos citados a través de esta especificación se incorporan aquí como referencia. Las variaciones y modificaciones menores a los métodos y materiales establecidos en la descripción detallada anterior y los ejemplos ilustrativos serán fácilmente evidentes para aquellos expertos en la técnica y están comprendidos dentro del alcance de la invención.

REIVINDICACIONES

1. Una composición farmacéutica que comprende CCI-779 micronizado.
2. Una composición farmacéutica de acuerdo a la reivindicación 1, donde el CCI-779 micronizado tiene un rango de tamaño de partícula de 10% son menores o iguales a aproximadamente 3 μ , 50% son aproximadamente 10 μ , y 90% son menores o iguales a aproximadamente 20 μ determinadas por el método Malvern.
3. Una composición farmacéutica de acuerdo a la reivindicación 1, en donde el CCI micronizado tiene un rango de tamaño de partícula de 10% son menores o iguales a aproximadamente 2 μ , 50% son aproximadamente 5 μ , y 90% son menores o iguales a aproximadamente 16 μ determinadas por el método Malvern.
4. Una composición farmacéutica de acuerdo a una cualquiera de las reivindicaciones 1 a 3 que es una forma de dosis sólida de liberación inmediata.
5. Una composición farmacéutica de acuerdo a una cualquiera de las reivindicaciones 1 a 3 seleccionada del grupo que consiste de una tableta directamente compresible, una capsula, un polvo y una suspensión.

6. Una composición farmacéutica de acuerdo a una cualquiera de las reivindicaciones 1 a 5 en donde el CCI-779 micronizado está presente en una cantidad desde 5% p/p a 10% p/p de la composición.

7. Una composición farmacéutica de acuerdo a una cualquiera de las reivindicaciones que comprende además:

Aproximadamente 5% p/p a aproximadamente 6.5% p/p de tensoactivo;

Aproximadamente 75% p/p a aproximadamente 85% p/p de llenador/ligador;

Aproximadamente 4% p/p a aproximadamente 6% p/p de desintegrante.

8. Una composición farmacéutica de acuerdo a la reivindicación 7, en donde el tensoactivo es lauril sulfato de sodio.

9. Una composición farmacéutica de acuerdo a la reivindicación 7 u 8, en donde el llenador/ligador es seleccionado del grupo que consiste de povidona, lactosa, y celulosa microcristalina y mezclas de estos.

10. Una composición farmacéutica de acuerdo a una cualquiera de las reivindicaciones 7 a 9, en donde el desintegrante es croscarmelosa sodio.

11. Una composición farmacéutica de acuerdo a una cualquiera de las reivindicaciones 1 a 11 que comprende además uno o más antioxidantes, un agente quelante, y/o un modificador de pH.
12. Una composición farmacéutica de acuerdo a la reivindicación 11, en donde una cualquiera del uno o más antioxidantes, un agente quelante y/o el modificador de pH se microniza.
13. Una unidad de dosificación de CCI-779 que comprende CCI-779 micronizado, un tensoactivo, un llenador/ligador, un desintegrante, un deslizante y un lubricante.
14. Una unidad de dosificación de CCI-779 oral de acuerdo con la reivindicación 13, en donde el CCI-779 micronizado tiene un rango de tamaño de partícula de 10% son menores o iguales a aproximadamente 2 μ , 50% son aproximadamente 5 μ , y 90% son menores o iguales a aproximadamente 16 μ determinadas por el método Malvern.
15. Una unidad de dosificación de CCI-779 oral de acuerdo con la reivindicación 13 o reivindicación 14, en donde el CCI-779 micronizado está presente en una cantidad desde 0.1% p/p a 10% p/p de la unidad de dosificación, con base en el peso total no recubierto.
16. Una unidad de dosificación de CCI-779 oral de acuerdo a una cualquiera de las reivindicaciones 13 a 15 en donde el

tensoactivo se selecciona del grupo que consiste de lauril sulfato de sodio y el tensoactivo poloxámero.

17. Una unidad de dosificación de CCI-779 oral de acuerdo a una cualquiera de las reivindicaciones 13 a 16, en donde el llenador se selecciona del grupo que consiste de celulosa microcristalina, lactosa anhidra, povidona y mezclas de estos.
18. Una unidad de dosificación de CCI-779 oral de acuerdo a una cualquiera de las reivindicaciones 13 a 17, en donde el desintegrante es croscarmelosa sodio.
19. Una unidad de dosificación de CCI-779 oral de acuerdo a una cualquiera de las reivindicaciones 13 a 18, en donde el lubricante es estearato de magnesio.
20. Una unidad de dosificación de CCI-779 oral de acuerdo a la reivindicación 15 que comprende:
 - 6 a 7% p/p de CCI-779 micronizado;
 - 5 a 7% p/p de tensoactivo;
 - 50 a 90% p/p de llenador;
 - 3 a 8% p/p de desintegrante;
 - Menos de 1% p/p de deslizante; y
 - Menos de 1% p/p de lubricante.
21. Una unidad de dosificación de CCI-779 oral de acuerdo a la reivindicación 20 que comprende:

CCI-779 micronizado 6.25% p/p;
Lauril Sulfato de Sodio 5.6% p/p;
Povidona 6.25% p/p;
Lactosa Anhidra 50% p/p;
Celulosa Microcristalina 25% p/p;
Croscarmelosa Sodio 6% p/p;
Deslizante 0.25% p/p; y
Estearato de Magnesio 0.25% p/p.

22. Una unidad de dosificación de CCI-779 oral de acuerdo a la reivindicación 20 que comprende

CCI-779 micronizado 6 % p/p;
Lauril Sulfato de Sodio 6% p/p;
Povidona 31% p/p;
Lactosa Anhidra 34% p/p;
Celulosa Microcristalina 16% p/p;
Croscarmelosa Sodio 6% p/p;
Deslizante 0.25% p/p; y
Estearato de Magnesio 0.5% p/p.

23. Una unidad de dosificación de CCI-779 oral de acuerdo a la reivindicación 20 que comprende:

CCI-779 micronizado 6 % p/p;
Hidroxianisol Butilado 0.022% p/p;
Hidroxitolueno Butilado 0.05% p/p;
EDTA 0.011% p/p;

Ácido Cítrico	0.08% p/p;
Poloxámero 188	6% p/p;
Lactosa Anhidra	55% p/p;
Celulosa Microcristalina	28% p/p;
Croscarmelosa Sodio	4% p/p;
Deslizante	0.25% p/p; y
Estearato de Magnesio	0.5% p/p.

24. Una unidad de dosificación de CCI-779 oral de acuerdo a la reivindicación 20 que comprende:

CCI-779 micronizado (Micronizado)	6 % p/p;
Hidroxianisol Butilado (Micronizado)	0.022% p/p;
Hidroxitolueno Butilado (Micronizado)	0.05% p/p;
EDTA Calcio Disodio, Hidratado (Micronizado)	0.011% p/p;
Ácido Cítrico Anhidro (Micronizado)	1% p/p;
Lauril Sulfato de Sodio	6% p/p;
Povidona	6% p/p;
Celulosa Microcristalina	24% p/p;
Lactosa Anhidra	51% p/p;
Croscarmelosa Sodio	6% p/p;
Dióxido de Silico Coloidal	0.25% p/p; y
Estearato de Magnesio	0.5% p/p.

25. Una unidad de dosificación de CCI-779 oral de acuerdo a cualquiera de las reivindicaciones 13 a 24, en donde dicha unidad de dosificación comprende un recubrimiento de sello.

26. Una unidad de dosificación de CCI-779 oral de acuerdo a la reivindicación 25, en donde dicho sello comprende aproximadamente 2% p/p de hidroxipropilmetilcelulosa de la composición recubierta.
27. Una unidad de dosificación de CCI-779 oral de acuerdo a cualquiera de las reivindicaciones 13 a 26, en donde dicha unidad de dosificación se selecciona del grupo que consiste de una tableta y una cápsula.
28. Un método para suministrar CCI-77 a un paciente, dicho método comprende la etapa de administrar una unidad de dosificación de CCI-779 oral de acuerdo a cualquiera de las reivindicaciones 13 a 27.
29. Uso de CCI-779 micronizado para preparar un medicamento.
30. Uso de acuerdo a la reivindicación 29 en donde dicho CCI-779 micronizado es directamente comprimido para formar el medicamento.
31. Uso del CCI-779 micronizado para preparar una unidad de dosificación oral de acuerdo a cualquiera de las reivindicaciones 13 a 27.

From the INTERNATIONAL BUREAU

000060

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To

KODROFF, Cathy, A
Howson and Howson
321 Nantstown Road, Suite 200
Spring House Corporate Center
P O Box 457
Spring House, PA 19477
ETATS-UNIS D'AMERIQUEDate of mailing (day/month/year)
07 March 2005 (07 03 2005)Applicant's or agent's file reference
AM-101453PCT

IMPORTANT NOTIFICATION

International application No
PCT/US04/042178International filing date (day/month/year)
14 December 2004 (14 12 2004)

International publication date (day/month/year)

Priority date (day/month/year)
08 January 2004 (08 01 2004)

Applicant

WYETH et al

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 OfficeDate of receipt
of priority document

08 January 2004 (08 01 2004)

60/534,951

US

31 January 2005 (31 01 2005)

MAR 14 2005

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

Authorized officer

Sontag Frederic

Facsimile No +41 22 740 14 35

Facsimile No +41 22 338 89 70

Telephone No +41 22 338 8391

From the INTERNATIONAL BUREAU

000061

PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47 1(c))

Date of mailing (day/month/year)
11 August 2005 (11 08 2005)

Applicant's or agent's file reference
AM-101453PCT

To

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

IMPORTANT NOTICE

International application No
PCT/US2004/042178

International filing date (day/month/year)
14 December 2004 (14 12 2004)

Priority date (day/month/year)
08 January 2004 (08 01 2004)

Applicant

WYETH et al

1 **ATTENTION** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does apply, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date)

2 Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis 1. The International Bureau has effected that communication on the date indicated below
04 August 2005 (04 08 2005)

CH

In accordance with Rule 47 1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s)

3 The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis 1

LU, SE, TZ, UG, ZM

In accordance with Rule 47 1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application

4. TIME LIMITS for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 20 MONTHS from the priority date

In practice time limits other than the 20-month time limit will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For regular updates on the applicable time limits (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>

It is the applicant's sole responsibility to monitor all these time limits

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

Facsimile No +41 22 740 14 35

Authorized officer

Agnes Wittmann-Regis

Facsimile No +41 22 338 89 70

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47 1(c))

To

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

Date of mailing (day/month/year)
11 May 2006 (11 05 2006)

Applicant's or agent's file reference
AM-101453PCT

IMPORTANT NOTICE

International application No
PCT/US2004/042178

International filing date (day/month/year)
14 December 2004 (14 12 2004)

Priority date (day/month/year)
08 January 2004 (08 01 2004)

Applicant

WYETH et al

1 **ATTENTION** For any designated Office(s) for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308(First Notice) issued previously

2 Notice is hereby given that the following designated Office(s) for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, has/have requested that the communication of the international application as provided for in Article 20 be effected under Rule 93bis 1. The International Bureau has effected that communication on the date indicated below
04 August 2005 (04 08 2005)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, PG, RU, SY, TM, US

In accordance with Rule 47 1(c-bis)(i) those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s)

3 The following designated Offices for which the time limit under Article 22(1) as in force from 1 April 2002 does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis 1

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SG, SK, SL, SM, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZW

In accordance with Rule 47 1(c-bis)(ii) those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing under Article 22 by the applicant of a copy of the international application

4. **TIME LIMITS** for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date

In practice, time limits other than the 30-month time limit will continue to apply for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>

It is the applicant's sole responsibility to monitor all these time limits

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

Authorized officer

Agnes Wittmann-Regis

Facsimile No +41 22 740 14 35

Facsimile No +41 22 338 89 70

000063



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1150
 Alexandria, Virginia 22313-1450
 www.uspto.gov

APPL NO	FILING OR 371 (c) DATE	ART UNIT	FIL FEE REC'D	ATTY DOCKET NO	DRAWINGS	TOT CLMS	IND CLMS
60/534,951	01/08/2004		160	AM-101453L1			

CONFIRMATION NO 7861

38199

HOWSON AND HOWSON

CATHY A KODROFF

ONE SPRING HOUSE CORPORATE CENTER

BOX 457

SPRING HOUSE, PA 19477

FILING RECEIPT



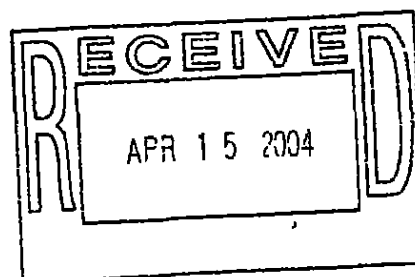
OC000000012300945

Date Mailed 04/07/2004

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U S APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Muhammad Ashraf, Elmwood Park, NJ,
 Eric J Benjamin, Jamestown, NC,



If Required, Foreign Filing License Granted: 04/07/2004

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Directly compressible pharmaceutical composition for oral administration of CCI-779

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

AM-101453L1USA

ASSIGNMENT

WHEREAS, Muhammad Ashraf and Eric J. Benjamin, hereinafter referred to as ASSIGNORS, have invented and are the owners of an invention entitled DIRECTLY COMPRESSIBLE PHARMACEUTICAL COMPOSITION FOR ORAL ADMINISTRATION OF CCI-779, said invention being fully set forth and described in the application for Letters Patent of the United States which has been prepared in connection with said invention, and filed on January 8, 2004.

WHEREAS, Wyeth, a corporation organized and existing under and by virtue of the laws of the state of Delaware and engaged in business at Five Giralda Farms, Madison, New Jersey 07940, hereinafter referred to as ASSIGNEE, is desirous of acquiring the said invention and any and all applications for Letters Patent and any and all Letters Patent of the United States and foreign countries which may be issued therefore,

NOW, THEREFORE, THIS IS TO WITNESS that in consideration of the sum of One Dollar (\$1.00) paid to ASSIGNORS by ASSIGNEE, the receipt of which is hereby acknowledged, and for other good and valuable consideration, ASSIGNORS have sold, assigned and set over, and hereby do sell, assign and set over, unto ASSIGNEE, its successors and assigns, the entire right, title and interest for, to and within the United States and all foreign countries, in and to the aforesaid invention and in and to any application for Letters Patent which ASSIGNEE at its expense may cause to be filed in the United States, under an international treaty, or in any foreign country, and in any United States or foreign patent which may be granted on said invention, including any extensions, divisions, reissues, continuations, or continuations-in-part.

And ASSIGNORS hereby authorize and request the Director of the USPTO to issue any and all Letters Patent of the United States to ASSIGNEE, its successors and assigns, as owner of all right, title and interest therein,

And for said consideration, it is hereby covenanted and agreed that at the request and expense of ASSIGNEE, its successors and assigns, ASSIGNORS will execute any further papers and do such other acts and things as may be necessary and proper to procure Letters Patent of said invention in the United States and in such foreign countries as ASSIGNEE, its successors and assigns may elect, and vest the full title thereto in ASSIGNEE, its successors and assigns,

And ASSIGNORS hereby authorize and direct its attorneys to insert, in the space provided below, the serial number and filing date of the aforesaid application for Letters Patent of the United States when the same shall have been made known to them by the United States Patent and Trademark Office.

IN WITNESS WHEREOF, this assignment has been executed on the dates indicated below.

Date 15 Jan 2004

Muhammad Ashraf (SEAL)
Muhammad Ashraf

NOTARIAL CERTIFICATE

State of New York

County of Rockland

: ss.

Before me, the undersigned, a notary public, in and for the county aforesaid, on this 15th day of January, 2004, personally appeared Muhammad Ashraf to me known to be the person described in and who executed the foregoing instrument and who acknowledged the execution of the same as a free act and deed and desired the same to be recorded as such.

ROSEANN D. JASTROW
NO. 01JA005816
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 01-06-2007

Rose Ann D. Jastrow
Notary Public

Date Jan 16, 2004

Eric J Benjamin
 (SEAL)
 Eric J. Benjamin

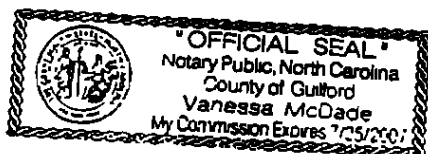
NOTARIAL CERTIFICATE

State of North Carolina

: SS

County of Guilford

Before me, the undersigned, a notary public, in and for the county aforesaid, on this 16th day of January, 2004, personally appeared Eric J. Benjamin to me known to be the person described in and who executed the foregoing instrument and who acknowledged the execution of the same as a free act and deed and desired the same to be recorded as such.



Vanessa McDade
 Notary Public

Application for United States Letters Patent Serial Number 60/534,951, filed
January 8, 2004

Howson and Howson
 Howson and Howson

000007



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D C 20231

67



JANUARY 30, 2004

PTAS

7000630104

HOWSON AND HOWSON
CATHY A. KODROFF
SPRING HOUSE CORPORATE CENTER, BOX 457
SPRING HOUSE, PA 19477

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 01/28/2004

REEL/FRAME: 014288/0038
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ASHRAF, MUHAMMAD

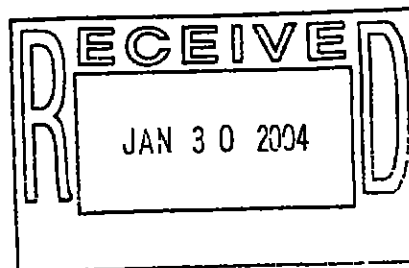
DOC DATE: 01/15/2004

ASSIGNEE:
WYETH
FIVE GIRALDA FARMS
MADISON, NEW JERSEY 07940

SERIAL NUMBER: 60534951
PATENT NUMBER:

FILING DATE:
ISSUE DATE:

STEVEN POST, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS





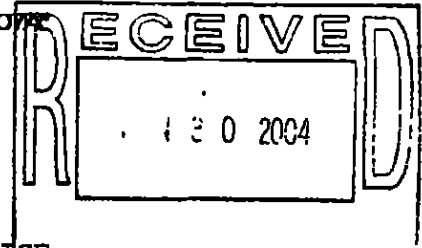
000068
UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JANUARY 30, 2004

PTAS

*70006300772

HOWSON AND HOWSON
CATHY A. KODROFF
SPRING HOUSE CORPORATE CENTER, BOX 457
SPRING HOUSE, PA 19477



UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 01/28/2004

REEL/FRAME: 014288/0001
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

BENJAMIN, ERIC J.

DOC DATE: 01/16/2004

ASSIGNEE:

WYETH
FIVE GIRALDA FARMS
MADISON, NEW JERSEY 07940

SERIAL NUMBER: 60534951
PATENT NUMBER:

FILING DATE:
ISSUE DATE:

SHARON LATIMER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM-101453 PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as where applicable, item 5 below	
International application No PCT/US2004/042178	International filing date (day/month/year) 14/12/2004	(Earliest) Priority Date (day/month/year) 08/01/2004
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 3 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, unless otherwise indicated under this item.

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

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

2 ☐ Certain claims were found unsearchable (See Box II)**3** ☐ Unity of invention is lacking (see Box 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

DIRECTLY COMPRESSIBLE PHARMACEUTICAL COMPOSITION OF THE RAPAMYCIN ESTER CCI-779

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

A CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/4745 A61K9/20 A61K9/48		
According to International Patent Classification (IPC) or to both national classification and IPC		
B FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, PAJ, WPI Data, EMBASE, BIOSIS, MEDLINE		
C DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 2002/091137 A1 (DUKART GARY ET AL) 11 July 2002 (2002-07-11) paragraph '0038! claim 1	1-31
A	US 5 362 718 A (SKOTNICKI ET AL) 8 November 1994 (1994-11-08) cited in the application column 7, line 23 - line 38	1-31
☐ Further documents are listed in the continuation of box C ☒ Patent family members are listed in annex		
* Special categories of cited documents "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 3 March 2005		Date of mailing of the international search report 15/03/2005
Name and mailing address of the ISA European Patent Office, P B 5818 Patentplan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl Fax (+31-70) 340-3016		Authorized officer Sindel, U

INTERNATIONAL SEARCH REPORT
Information on patent family members

national Application No
PCT/US2004/042178

000071

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2002091137	A1	11-07-2002	US 2003153593 A1	14-08-2003
			AU 2731302 A	27-05-2002
			BR 0115323 A	17-02-2004
			CA 2429020 A1	23-05-2002
			EP 1335725 A2	20-08-2003
			HU 0400521 A2	28-06-2004
			JP 2004517065 T	10-06-2004
			NO 20032181 A	14-05-2003
			WO 0240000 A2	23-05-2002
			ZA 200304603 A	13-09-2004
US 5362718	A	08-11-1994	AT 234307 T	15-03-2003
			AU 679854 B2	10-07-1997
			AU 2247495 A	10-11-1995
			BR 9507323 A	30-09-1997
			CA 2187024 A1	26-10-1995
			CN 1149296 A ,C	07-05-1997
			CY 2378 A	04-06-2004
			CZ 9603052 A3	13-08-1997
			DE 69529897 D1	17-04-2003
			DE 69529897 T2	06-11-2003
			DK 763039 T3	05-05-2003
			EP 1266899 A2	18-12-2002
			EP 0763039 A1	19-03-1997
			ES 2191704 T3	16-09-2003
			HK 1011352 A1	13-06-2003
			HU 77410 A2	28-04-1998
			IL 113179 A	15-06-1998
			JP 9512018 T	02-12-1997
			NZ 283988 A	28-07-1998
			PL 316948 A1	17-02-1997
			PT 763039 T	30-06-2003
			RU 2134267 C1	10-08-1999
			SI 763039 T1	31-08-2003
			SK 133096 A3	09-04-1997
			WO 9528406 A1	26-10-1995
			ZA 9503090 A	14-10-1996

From the
INTERNATIONAL SEARCHING AUTHORITY

To
see form PCT/ISA/220

PCT

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

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/US2004/042178

International filing date (day/month/year)
14.12.2004

Priority date (day/month/year)
08.01.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/4745, A61K9/20, A61K9/48

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

Sindel, U

Telephone No +49 89 2399-7064



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No
PCT/US2004/042178

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

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No
PCT/US2004/042178

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	1-31
	No	Claims	
Inventive step (IS)	Yes	Claims	1-31
	No	Claims	
Industrial applicability (IA)	Yes	Claims	1-31
	No	Claims	

2 Citations and explanations**see separate sheet**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No

PCT/US2004/042178

Reference is made to the following documents

D1. US 2002/091137

D2. US 5 362 718

Item V

1 Novelty and Inventive Step

The subject matter of claims 1-31 seems to be new in the sense of Article 33(2) PCT and to involve an inventive step in the sense of Article 33(3) PCT

The problem to be solved in the present application is the provision an oral solid formulation of the rapamycin ester CCI-779 showing high bioavailability of the active compound

The solution provided is a pharmaceutical composition comprising CCI-779 in micronized form.

Closest prior art is D2 mentioning powder and tablet formulations comprising a carrier and a rapamycin ester like e.g. CCI-779 in admixture (see column 7, lines 23-38)

There is no hint given that an improved bioavailability of CCI-779 could be reached by using the active in micronized form

2 Industrial applicability

The subject matter of claims 1-19 is industrially applicable in the sense of Article 33(4) PCT

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-101453PCT

Box No. I TITLE OF INVENTION

DIRECTLY COMPRESSIBLE PHARMACEUTICAL COMPOSITION FOR THE ORAL ADMINISTRATION OF CCI-779

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
973-683-2112

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)

Ashraf, Muhammad
67 Boulevard
Elmwood Park, New Jersey 07407 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
Pakistan

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

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request</i>	
Name and address <i>(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.)</i> Benjamin, Eric J. 3211 Morris Farm Drive Jamestown, North Carolina 27282 US	This person is ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality US	State <i>(that is, country)</i> 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	
Name and address <i>(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.)</i>	This person is ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality	State <i>(that is, country)</i> of residence
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	
Name and address <i>(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.)</i>	This person is ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality	State <i>(that is, country)</i> of residence
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	
Name and address <i>(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.)</i>	This person is ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality	State <i>(that is, country)</i> of residence
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 another continuation sheet	

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 patent 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 I I(a)(iii) and 49bis I(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 I I(a)(iv) and 49bis I(d))*

"Continuation of Box No IV"

Kita, Stanley B , Reg No 24,561
 Smith, Jr , George A , Reg No 24,442
 Bak, Mary E , Reg No 31,215
 Bak, William, Reg. No 37,277
 Duminiak, Robert J , Reg No 51,636
 Palovich, Tracy, Reg No 47,840 (patent agent)

All above attorneys are members of the firm of
 Howson and Howson

Address of all is indicated in Box No IV

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) 08 January 2004 (08/01/04)	60/534,951	United States		
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

Box No. IX CHECK LIST, LANGUAGE OF FILING

This international application contains	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)	Number of items
(a) in paper form, the following number of sheets	1 ☒ fee calculation sheet	1
request (including declaration sheets) 5	2 ☐ original separate power of attorney	
description (excluding sequence listing and/or tables related thereto) 18	3 ☐ original general power of attorney	
claims 5	4 ☒ copy of general power of attorney, reference number, if any	1
abstract 1	5 ☐ statement explaining lack of signature	
drawings	6 ☐ priority document(s) identified in Box No VI as item(s)	
Sub-total number of sheets 29	7 ☐ translation of international application into (language)	
sequence listing	8 ☐ separate indications concerning deposited microorganism or other biological material	
tables related thereto	9 ☐ sequence listing in computer readable form (indicate type and number of carriers)	
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form, see (c) below)	(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)	
Total number of sheets 29	(ii) ☐ (only where check-box (b)(i) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter	
(b) ☐ only in computer readable form (Section 801(a)(i))	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column	
(i) ☐ sequence listing	10 ☐ tables in computer readable form related to sequence listing (indicate type and number of carriers)	
(ii) ☐ tables related thereto	(i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application)	
(c) ☐ also in computer readable form (Section 801(a)(ii))	(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)	
(i) ☐ sequence listing	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	
(ii) ☐ tables related thereto	11 ☒ other (specify) Transmittal letter to the USRO	1
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)		
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

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)

By Cathy A Kodroff
Cathy A Kodroff
Attorney for the Applicant(s)

For receiving Office use only		2 Drawings ☐ received ☐ not received
1 Date of actual receipt of the purported international application	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



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCION PCT

000081

(21) N° de solicitud		(51) Int Cl	A61K 9/00
22) Fecha de solicitud		(71) Solicitante(s)	WYETH
01/08/06			
(30) Prioridad	(31) No.	32) Fecha	(33) País
	80/534,951	08/01/04	US
		(72) Inventor(es)	ASHRAF, Muhammad BENJAMIN, Eric, J.
		(74) Apoderado.	ALVARO CORREA ORDOÑEZ
(85)	Fecha límite inicio fase nacional		08/08/06
(86)	Datos relativos a la presentación de la solicitud PCT		
	Fecha de presentación de la solicitud		14/12/04
	No de solicitud PCT/US2004/042178		
(87)	Publicación internacional		
	Fecha.		04/08/05
	N° publicación		WO2005/070393
(54) Título			
COMPOSICIÓN FARMACÉUTICA DIRECTAMENTE COMPRESIBLE PARA LA ADMINISTRACIÓN ORAL DE CCI-779			

Reivindicación(es)

1. Una composición farmacéutica que comprende CCI-779 micronizado.
23. Una unidad de dosificación de CCI-779 que comprende CCI-779 micronizado, un tensoactivo, un llenador/ligador, un desintegrante, un deslizante y un lubricante.
29. Uso de CCI-779 micronizado para preparar un medicamento.

**Delegatura de Propiedad Industrial
División de Nuevas Creaciones**

**REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL
TRAMITE**

PATENTE DE INVENCION (✓)	MODELO DE UTILIDAD ()	USUARIO ()	RADICADOR ()
-Indicación de que se solicita la concesión de una patente.		(✓)	()
-Datos de identificación del solicitante o de la persona que se 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 se 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 Diseño Industrial.		()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	()
-Representación gráfica del Esquema Trazado.		()	()
-Comprobante de Pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA ()	()	()

Firma Responsable:

Fdo B

Fecha:

Agosto 1, 2006

88

83

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO

REFERENCIA	Radicación No.	6 75262
	Solicitud internacional	US2004/042178
	Fecha inicio fase nacional	08/08/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	10488

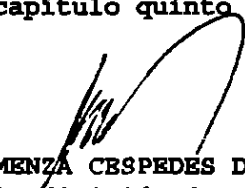
Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se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

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

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 15 SET. 2006
adpal