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54. TITULO

COMPOSICIONES TOPICAS DE ASCOMICINA ANHIDRAS Y DESPROVISTAS DE
ETANOL.

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NOVARTIS AG

DOMICILIO

BAZILEA, SUIZA

74. APODERADO

JIMENA ESCOBAR URIBE

22. BOGOTA, D.C.,

(SS)

**FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
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SOLICITUD DE:

☒

Patente de Invención

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Patente de Modelo de Utilidad

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Capítulo I

☒

Capítulo II

2.

**SOLICITANTE
(71)**

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Dirección:

Nacionalidad o domicilio:

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6 **TÍTULO (54)** COMPOSICIONES TÓPICAS DE ASCOMICINA ANHIDRAS Y
DESPROVISTAS DE ETANOL.

7 **Clasificación Internacional (51)** A61K 47/10 A61K 31/445; A61P 31/00

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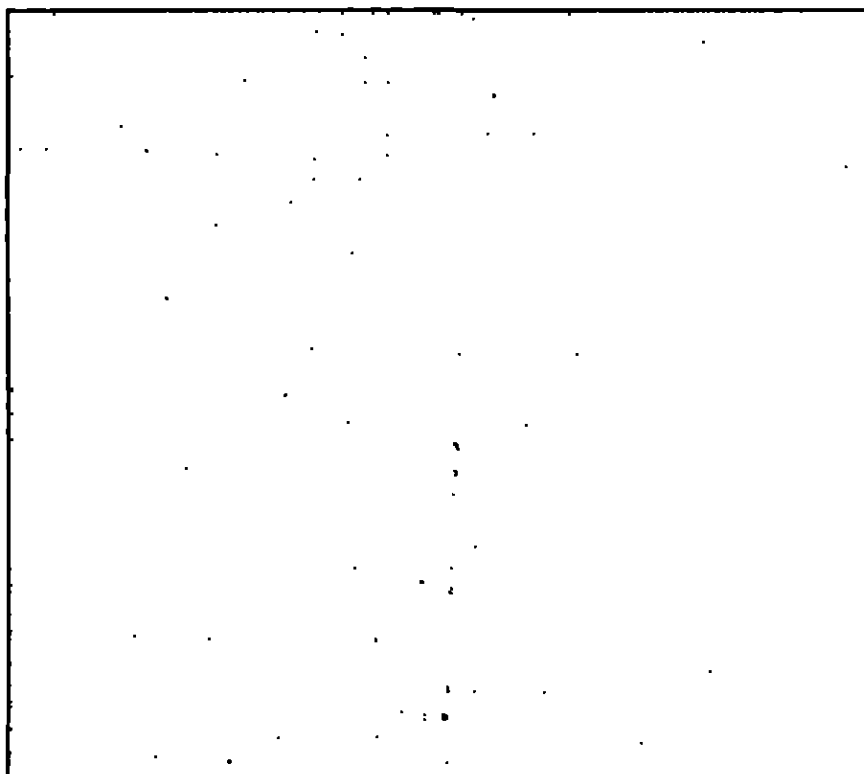
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- ☐ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Prot. 17.398
- ☐ Poderes si fuere el caso Protocolo No. 17.398
- ☐ Documento de cesión 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 de 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 " Opinión escrita "

11 FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente

NOMBRE: JIMENA ESCOBAR URIBE

FIRMA: *Jimena Escobar*

C.C. 39.779.452 DE Usaquén T.P. 68.228

As. 2795/PCT

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FECHA : FEBRERO 3 DE 2005

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***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50003-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
	TOTAL :	\$ 443,000.00

SOM: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

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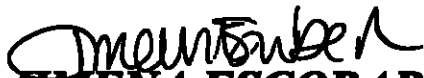
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Solicito expresamente a nombre de la sociedad
NOVARTIS AG, sociedad constituida de conformidad
con las leyes de Suiza, domiciliada en Lichtstrasse 35,
CH-4056 Basilea, Suiza, el otorgamiento de Patente
para la invención titulada "**COMPOSICIONES
TÓPICAS DE ASCOMICINA ANHIDRAS
Y DESPROVISTAS DE ETANOL**".

Clase: A61K 47/10


JIMENA ESCOBAR URIBE
C.C. 39.779.452 de Usaquen.
T.P. 68.228

RESUMEN

Composiciones farmacéuticas líquidas o semi-sólidas tópicas de una sola fase sustancialmente exentas de etanol y agua, y que comprenden una ascomicina, tal como pimecrolimus, en un vehículo portador que comprende una
5 mezcla de solventes de tres componentes que suman cuando menos el 40 por ciento en peso/peso del peso total de la composición, y que consiste en:

i) un alcohol de 3 a 8 átomos de carbono y/o
10 alcanodiol de 1 a 8 átomos de carbono;

ii) un alcohol graso; y

iii) un solvente adicional seleccionado a partir de:

a) un alquiléster de ácido alcancarboxílico
y/o alquiléster de ácido alcandicarboxílico, y/o

15 b) un co-componente hidrofílico, y/o

c) un triglicérido;

y opcionalmente, excipientes convencionales
adicionales.

* * * * *

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COMPOSICIONES TÓPICAS DE ASCOMICINA
ANHIDRAS Y DESPROVISTAS DE ETANOL

La invención se refiere a composiciones
5 farmacéuticas tópicas que comprenden una ascomicina para
el tratamiento de desórdenes de la piel, en la forma de una
composición líquida o semisólida de una sola fase
sustancialmente exenta de etanol y agua.

Las ascomicinas, tales como la ascomicina misma o
10 los derivados de las mismas, son ejemplos de los compuestos
de la clase FK506. FK506 (tacrolimus) es un antibiótico de
macrólido conocido que es producido por *Streptomyces*
tsukubaensis No. 9993. También es un potente
inmunosupresor. La estructura de FK506 se da en The Merck
15 Index 12^a Edición (1996) en la página 546 como la entrada
9200. Los métodos para preparar FK506 se describen, por
ejemplo, en la Patente Europea Número EP 184162.

Ahora se conocen un gran número de derivados,
antagonistas, agonistas, y análogos de FK506, que retienen
20 la estructura básica y cuando menos una de las propiedades
biológicas (por ejemplo, las propiedades inmunológicas de
FK506. Estos compuestos se describen en un gran número de
publicaciones, por ejemplo en las Patentes Números EP
184162, EP 315978, EP 323042, EP 423714, EP 427680, EP
25 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936,

EP 532088, EP 532089, EP 569337, EP 626385, y WO 93/5059. La ascomicina y sus derivados, incluyendo FK506, son referidos posteriormente en la presente como "ascomicinas".

5 Se sabe que las ascomicinas se indican para utilizarse, por ejemplo, en el tratamiento tópico de enfermedades inflamatorias e hiperproliferativas de la piel, y de manifestaciones cutáneas de enfermedades inmunológica-
10 ente mediadas. La condición de la piel que se vaya a tratar puede variar, por ejemplo, con la clase y grado de enfermedad; por ejemplo, la piel puede ser piel seca o grasosa. Además, la piel que se vaya a tratar puede tener pelo. Existe una necesidad de una composición farmacéutica que se pueda aplicar a la piel de una manera sustancialmente
15 independiente de la condición de la piel.

 Ahora se ha encontrado que se puede formular una ascomicina en una composición farmacéutica en la forma de una formulación tópica líquida o semisólida de una sola fase sustancialmente desprovista de etanol y agua. Estas
20 composiciones farmacéuticas son efectivas independiente-mente de la condición de la piel, de la uña, o de la mucosa, son bien toleradas, estables, y tienen propiedades de penetración particularmente interesantes.

 De una manera sorprendente, retienen y mejoran
25 las propiedades de penetración benéficas de formulaciones

más complejas o no homogéneas, tales como emulsiones o suspensiones basadas en agua o en hidrocarburos, mientras que son particularmente convenientes en términos de facilidad de administración y cumplimiento del paciente.

5 Por consiguiente, se ha encontrado que una gran parte del volumen de las composiciones, cuando menos el 40 por ciento en peso/peso, puede consistir en solventes simples, dando como resultado soluciones líquidas transparentes o soluciones semisólidas espesas, fácilmente
10 aplicables.

En particular, la invención se refiere a una composición farmacéutica líquida o semisólida tópica de una sola fase sustancialmente desprovista de etanol y agua, la cual comprende una ascomicina en un vehículo portador que
15 comprende una mezcla de solventes de tres componentes que suman cuando menos el 40 por ciento en peso/peso del peso total de la composición, y que consiste en:

- i) un alcanol de 3 a 8 átomos de carbono y/o alcanodiol de 1 a 8 átomos de carbono;
- 20 ii) un alcohol graso; y
- iii) un solvente adicional seleccionado a partir de:
 - a) un alquiléster de ácido alcancarboxílico y/o alquiléster de ácido alcandicarboxílico, y/o
 - b) un co-componente hidrofílico, y/o
 - 25 c) un triglicérido;

y opcionalmente, excipientes convencionales adicionales;

posteriormente en la presente se mencionan brevemente como "las composiciones de la invención".

5 Las composiciones de la invención tienen la ventaja de que consisten en pocos componentes, son directas de preparar, y son bien toleradas sobre la piel humana.

Las composiciones de la invención pueden estar, por ejemplo, en la forma de una solución tópica o de una
10 solución de rocío, un gel, una espuma o un ungüento, de preferencia están en la forma de un gel, una espuma, o un ungüento.

Se prefieren las composiciones semisólidas o espumosas.

15 "Una sola fase" significa en la presente que las composiciones de la invención son diferentes de los sistemas multifásicos, por ejemplo diferentes de los sistemas de dos fases, tales como cremas o emulsiones; pueden estar en cualquier forma de una sola fase, por ejemplo como una
20 solución o rocío, un gel, un ungüento, o, por ejemplo, el componente líquido de una espuma, en donde normalmente el ingrediente activo está en una forma disuelta.

"Líquidas o semilíquidas" significa que las composiciones de la invención son esencialmente soluciones
25 en una forma líquida, o líquida solidificada.

"Sustancialmente exentas de etanol y agua" significa que no se agrega etanol ni agua como una parte constituyente intencional de las composiciones de la invención. Sin embargo, por ejemplo, no obstante puede
5 haber presente una pequeña cantidad de humedad, por ejemplo hasta aproximadamente el 1 por ciento en peso/peso de agua, por ejemplo como una impureza intrínseca en algunos de los excipientes utilizados, o como parte del ingrediente activo cuando éste es, por ejemplo, un hidrato,
10 por ejemplo cuando se utiliza la forma del cristal A (ver la Publicación Internacional Número WO 99/01458) del compuesto A posteriormente en la presente.

Un aspecto particularmente benéfico de las composiciones de la invención es que, aunque los
15 componentes de la mezcla de solventes de tres componentes anterior son agentes solubilizantes, adicionalmente pueden poseer propiedades mejoradoras de penetración, contribuyendo de esta manera a mantener a las formulaciones tanto simples como efectivas. Además, se ha encontrado que
20 las soluciones se pueden espesar sin pérdida aparente alguna en la eficacia.

Las ascomicinas preferidas incluyen, por ejemplo:

- FK506 (tacrolimus);
- 32-[4-(3,5-dimetoxifenil)-imidazol-1-ilmetoxi]-
25 ascomicina (L-733725) (en el Ejemplo 1 y como el compuesto

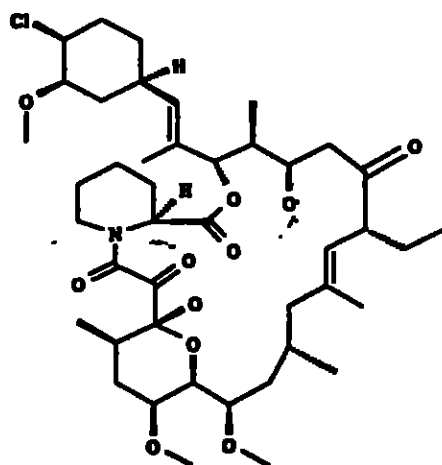
de la fórmula I en la Publicación Internacional Número WO 97/8182);

- 32-O-(1-hidroxetilindol-5-il)-ascomicina (L-732531) (Transplantation 65 [1998] 10-18, 18-26, Figura 1 en la página 11);

- (32-desoxi-32-epi-N1-tetrazolil)-ascomicina (ABT-281) (J. Invest. Dermatol. 12 [1999] 729-738, Figura 1 en la página 730);

- 33-epicloro-33-desoxi-ascomicina (pimecrolimus), es decir, {[1E-(1R,3R,4S)]-1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R}-12-[2-(4-cloro-3-metoxiciclohexil)-1-metilvinil]-17-etil-1,14-dihidroxi-23,25-dimetoxi-13,19,21,27-tetrametil-11,28-dioxa-4-azatriciclo-[22.3.1.0-(4,9)]-octacos-18-eno-2,3,10,16-tetraona, de la fórmula I:

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dada a conocer como el Ejemplo 66a en, por ejemplo, la Patente Europea Número EP 427680 (referida posteriormente en la presente como el Compuesto A);

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- {[1E-(1R,3R,4R)]1R,4S,5R,6S,9R,10E,13S,15S,16R,17S,19S,20S}-9-ethyl-6,16,20-trihydroxy-4-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-15,17-dimethoxy-5,11,13,19-tetramethyl-3-oxa-22-azatriciclo[18.6.1.0(1,22)]heptacos-10-eno-2,8,21,27-tetraona, dada a conocer como los Ejemplos 6d y 71 en, por ejemplo, la Patente Europea Número EP 589337 (referida posteriormente en la presente como el Compuesto b); y

- {1R,5Z,9S,12S-[1E-(1R,3R,4R)],13R,14S,17R,18E,21S,23S,24R,25S,27R}17-ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatriciclo-[22.3.1.0(4,9)]-octacos-5,18-dieno-2,3,10,16-tetraona, también conocida como 5,6-deshidro-ascomicina, dada a conocer como el Ejemplo 8 en, por ejemplo, la Patente Europea Número EP 626385 (referida posteriormente en la presente como el Compuesto C).

Aunque la mezcla de solventes de tres componentes, como se indica anteriormente, suma cuando menos el 40 por ciento en peso/peso del peso total de la composición, que por lo tanto puede contener opcionalmente ingredientes convencionales adicionales, de preferencia suma hasta más del 40 por ciento, por ejemplo de aproximadamente el 55 por ciento hasta casi aproximadamente el 100 por ciento, de preferencia de aproximadamente el 80 por ciento o

aproximadamente el 90 por ciento hasta aproximadamente el 99.95 por ciento, todavía más preferiblemente desde aproximadamente el 95 por ciento hasta aproximadamente el 99.50 por ciento del peso total.

5 Los componentes i) e ii) cada uno independiente-
mente de preferencia suman hasta aproximadamente el 50 por
ciento, más preferiblemente hasta aproximadamente el 20 por
ciento, en especial hasta aproximadamente el 15 por ciento
del peso total. En suma, de preferencia suman hasta
10 aproximadamente el 60 por ciento, de preferencia hasta
aproximadamente el 40 por ciento, en especial hasta
aproximadamente el 30 por ciento del peso total.

 El componente iii) de preferencia suma hasta
aproximadamente el 75 por ciento, más preferiblemente hasta
15 aproximadamente el 65 por ciento del peso total de la
composición, y de preferencia es de aproximadamente el 30
por ciento hasta aproximadamente el 75. por ciento del peso
total.

 El agente activo, por ejemplo, está presente en las
20 composiciones de la invención en una cantidad desde
aproximadamente el 0.05 por ciento hasta aproximadamente
el 10 por ciento en peso, por ejemplo desde el 0.1 por ciento
hasta el 6 por ciento en peso, de preferencia desde el 1 por
ciento hasta el 5 por ciento en peso, basándose en el peso
25 total de la composición.

El componente i) de alcohol de 3 a 8 átomos de carbono de preferencia es un alcohol saturado de cadena recta o ramificada, por ejemplo isopropanol. El componente i) de alcanodiol de 1 a 8 átomos de carbono de preferencia es propilenglicol (es decir, 1,2-propanodiol), butilenglicol, 2-etil-1,3-hexanodiol, y hexilenglicol (es decir, 2-metil-2,4-pentanodiol), en especial propilenglicol y hexilenglicol.

De preferencia, la ascomicina y el componente i) en las composiciones están presentes, cuando menos inicialmente, en una proporción en peso de aproximadamente 0.05 a 10:10 a 60, más preferiblemente en una proporción en peso de aproximadamente 0.5 a 10:50 a 60, todavía más preferiblemente en una proporción en peso de aproximadamente 1 a 3:50 a 60. Sin embargo, después de la administración a la piel, los componentes más volátiles, por ejemplo los alcoholes inferiores, se pueden evaporar para producir una solución supersaturada que puede contribuir a mejorar adicionalmente la penetración.

El componente ii) de preferencia es un alcohol graso mono- ó poli-insaturado, por ejemplo un alcohol graso mono- ó poli-insaturado de 12 a 24 átomos de carbono, por ejemplo de 16 a 18 átomos de carbono, de preferencia alcohol oleílico o alcohol elaídico; se prefiere en especial el alcohol oleílico.

De preferencia, la ascomicina y el componente ii)

en las composiciones, están presentes en una proporción en peso de aproximadamente 0.05 a 10:5 a 90, más preferiblemente en una proporción en peso de aproximadamente 0.5 a 10:5 a 50, todavía más preferiblemente en una proporción en peso de aproximadamente 1 a 5:10 a 20.

El componente iii)a) de preferencia es un alquiléster de ácido carboxílico de 12 a 24 átomos de carbono, de preferencia de 14 a 16 átomos de carbono, por ejemplo miristato de isopropilo, miristato de etilo, o palmitato de isopropilo, en especial miristato o palmitato de isopropilo, o un alquiléster de ácido alcandicarboxílico de 2 a 10 átomos de carbono, por ejemplo adipato de di-isopropilo ó adipato de dietilo, en especial adipato de di-isopropilo.

El componente iii)b) de preferencia es un éter-diol farmacéuticamente aceptable, por ejemplo dipropilenglicol ó dietilenglicol; un diéter-alcohol, por ejemplo monoetiléter de dietilenglicol; un diéter o un éter parcial de un mono- ó polioxialcanodiol de bajo peso molecular, por ejemplo polietilenglicoléter de alcohol tetrahidrofurfurílico (Glycofurol); monoetiléter de dietilenglicol (Transcutol®); citrato de trietilo; N-metilpirrolidona; dimetilisosorbide (es decir, 1,4:3,6-dianhidro-2,5-di-O-metil-D-glucitol); o carbonato de propileno; en especial dimetilisosorbide.

El componente iii)c) de preferencia consiste en

triglicéridos de cadena mediana, tales como Miglyol 812 .

Las composiciones de la invención opcionalmente pueden comprender excipientes convencionales adicionales, por ejemplo para una aplicación más fácil, puede ser deseable una solución espesa, por ejemplo una solución semisólida, o un gel fluido o un gel transparente. Esto se puede lograr mediante la adición de agentes de consistencia convencionales (agentes mejoradores de viscosidad), con el fin de mejorar la viscosidad de las composiciones.

Los agentes de consistencia adecuados incluyen, por ejemplo:

- ácido poliacrílico, como se conoce bajo los nombres carboxipolimetileno, o polímero de carboxivinilo, o carbómero, o Carbopol®,
- derivados de celulosa, incluyendo, por ejemplo, etil-, propil-, metil-, hidroxipropil-, e hidroxipropil-metil-celulosas,
- dióxido de silicio coloidal, por ejemplo Aerosil®, por ejemplo Aerosil R972® ó Aerosil 200®,
- alcohol polivinílico,
- cera de abejas,
- aceite de ricino hidrogenado (Cutina HR®),
- polivinilpirrolidona,
- resinas de polimetilacrilato, por ejemplo Eudispert ó Eudragit , y

- alcoholes sólidos, que tengan, por ejemplo, una cadena de 12 a 24 átomos de carbono, por ejemplo alcohol cetílico y/o alcohol estearílico, comercialmente disponibles, por ejemplo, bajo las marcas comerciales registradas Lorol® C16 y Lorol® C18, respectivamente, de Henkel, Alemania;

de preferencia hidroxipropilcelulosa, dióxido de silicio coloidal, cera de abejas, aceite de ricino hidrogenado, polivinilpirrolidona, o Eudragit®.

10 Otros excipientes convencionales son, por ejemplo, una base de ungüento, tal como hidrocarburos minerales, por ejemplo parafina líquida, petrolato, y cera microcristalina. La base de ungüento, donde su presencia sea apropiada, está en una cantidad, por ejemplo, de aproximadamente el 0.1 por ciento a aproximadamente el 40 por ciento, por ejemplo de 15 aproximadamente el 30 por ciento a aproximadamente el 40 por ciento del peso total de la composición.

Las composiciones también pueden incluir antioxidantes, tales como butil-hidroxitolueno, palmitato de 20 ascorbilo, piro-sulfito de sodio, butil-hidroxianisol, p-hidroxibenzoato de propilo, p-hidroxibenzoato de metilo, y tocoferol, según sea apropiado. Adicionalmente, la adición de conservadores, tales como alcohol bencilico, parabenos, ácido sórbico, y alcohol fenílico, sirve para prevenir el 25 crecimiento bacteriano. Cuando es apropiada la presencia de

antioxidantes y/o conservadores, de preferencia están presentes en una cantidad de aproximadamente el 0.01 por ciento a aproximadamente el 2.5 por ciento en peso/peso de cada uno.

5 Las composiciones de la invención de preferencia no tienen tensoactivo, excepto como sea requerido durante el procesamiento para, por ejemplo, una formulación de espuma, y están sustancialmente desprovistas de etanol y agua, como se define anteriormente.

10 Para el tratamiento de piel grasa o con pelo, se prefieren las formulaciones no grasosas, tales como se proporcionan, por ejemplo, en los Ejemplos 1 a 17, 22 y 23 posteriormente en la presente. La ausencia de grasa y los residuos bajos después de la aplicación, pueden conducir a
15 una mayor conveniencia, en especial en la piel con pelo.

Los componentes de las composiciones de la invención se describen, entre otros, en H.P. Fiedler, "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, Cuarta
20 edición revisada y expandida (1996), cuyo contenido se incorpora a la presente como referencia.

Se prefieren en particular las composiciones de la invención en donde la ascomicina es, por ejemplo, pimecrolimus, y

25 - el componente i) es isopropanol y/o

hexilenglicol;

- el componente ii) es alcohol oleílico; y
- el componente iii) es:

a) adipato de di-isopropilo y/o miristato de
5 isopropilo, y/o

b) dimetilisosorbide, y/o

c) triglicéridos de cadena mediana;

y opcionalmente excipientes convencionales
adicionales;

10 en especial las composiciones de los Ejemplos 17 a
20 y 23, en particular del Ejemplo 17 posteriormente en la
presente.

Las composiciones de la invención se indican para
utilizarse en el tratamiento de enfermedades inflamatorias e
15 hiperproliferativas de la piel, y de manifestaciones cutáneas
de enfermedades inmunológicamente mediadas. Los términos
"piel" y "cutáneas" deben entenderse ampliamente para
comprender también las enfermedades, por ejemplo, de las
uñas o de la mucosa. Los ejemplos de las enfermedades
20 inmunológicamente mediadas incluyen alopecia areata,
psoriasis, dermatitis atópica, dermatitis por contacto, y otras
dermatitis eczematosas, dermatitis seborreica, líquen planus,
pemfigo, pemfigoide buloso, epidermólisis bulosa, urticaria,
angioedemas, vasculitidas, eritemas, eosinofiliias cutáneas, y
25 lupus eritematoso. Los ejemplos de las enfermedades de la

piel incluyen dermatomiositis, leucoderma vulgaris, ictiosis vulgaris, sensibilidad fotoalérgica, linfoma de células T cutáneo, acné, enfermedades autoinmunes tales como artritis reumatoide crónica, escleroderma, y similares.

5 La invención proporciona además una composición como se define anteriormente, para utilizarse en el tratamiento de enfermedades inflamatorias e hiperproliferativas de la piel, y de manifestaciones cutáneas de enfermedades inmunológicamente mediadas.

10 Además proporciona un método para el tratamiento de enfermedades inflamatorias e hiperproliferativas de la piel, o de manifestaciones cutáneas de enfermedades inmunológicamente mediadas, el cual comprende administrar una composición de la invención a la piel de un paciente que
15 lo necesite.

 Todavía además, proporciona el uso de una composición de la invención en la preparación de un medicamento para el tratamiento de enfermedades inflamatorias e hiperproliferativas de la piel, y de
20 manifestaciones cutáneas de enfermedades inmunológicamente mediadas.

 Además proporciona el uso de un vehículo portador como se define anteriormente para mejorar la penetración de una ascomicina en la piel humana, en las uñas, o en la
25 mucosa.

Las composiciones de la invención se pueden preparar de una manera convencional mediante el procesamiento de los componentes en una composición farmacéutica. Por ejemplo, las composiciones de la invención
5 se pueden obtener mediante la disolución de una ascomicina en un alcohol farmacéuticamente aceptable, por ejemplo un alcohol de 3 a 8 átomos de carbono, un alcanodiol de 1 a 8 átomos de carbono, y/o un alcohol graso. Se pueden agregar otros componentes, por ejemplo alquilésteres alcan-
10 carboxílicos y/o ésteres alcandicarboxílicos, y/o co-componentes hidrofílicos, triglicéridos, y excipientes convencionales opcionales adicionales, en el momento apropiado como es convencional.

Los siguientes ejemplos ilustran la invención. No
15 son limitantes.

Todos los porcentajes referidos en la presente son en peso/peso (porcentaje en peso/peso), excepto donde se indique de otra manera. Se debe entender que el término "estable" significa que no se observa separación alguna de
20 los componentes de la composición respectiva cuando se almacena a temperatura ambiente durante un período de cuando menos 3 meses o más, y no hay descomposición del agente activo. Sin embargo, ocasionalmente puede tener lugar alguna cristalización no intencional, por ejemplo, sobre
25 su almacenamiento, y se debe entender, por lo tanto, que la

presencia de una pequeña cantidad de ingrediente activo en forma cristalizada en las composiciones de la invención todavía cae dentro del ámbito de la invención.

El análisis químico del agente activo se emprende
5 utilizando HPLC de fase inversa con detección ultravioleta; λ = 210 nanómetros. El límite de cuantificación es el 0.1 por ciento en peso.

En los Ejemplos 1 a 25, el Compuesto A (pimecrolimus) puede ser reemplazado con el compuesto B; el
10 compuesto C; tacrolimus; L-733725; L-732531; y ABT-281.

Ejemplos 1 y 2 (soluciones) y 3 (gel en una sola fase)

Se preparan las siguientes composiciones:

15	Ingredientes	Ejemplo 1	Ejemplo 2	Ejemplo 3
	Compuesto A	1.0	8.0	1.0
	i) isopropanol	49.0	42.0	47.0
	propilenglicol	-	-	-
	ii) alcohol oleílico	10.0	10.0	10.0
20	iii) miristato de isopropilo	40.0	-	40.0
	iii)b) dimetilisosorbide	-	40.0	-
	<u>Ingredientes Adicionales:</u>	-	-	2.0
	hidroxipropilcelulosa			
	(agente de consistencia)			

Las composiciones de los Ejemplos 1 a 3 son estables.

Ejemplos 4 a 9 (soluciones)

5 Se preparan las siguientes composiciones:

	Ingredientes	Ej.4	Ej.5	Ej.6	Ej.7	Ej.8	Ej.9
	Compuesto A	1.0	1.0	1.0	1.0	1.0	1.0
10	i) isopropanol	39.0	39.0	39.0	39.0	39.0	39.0
	hexilenglicol	-	-	10.0	10.0	10.0	10.0
	ii) alcohol oleílico	10.0	10.0	10.0	10.0	10.0	10.0
	iii)a) miristato de isopropilo	-	-	40.0	-	-	-
15	palmitato de isopropilo	-	-	-	40.0	-	-
	adipato de di-isopropilo	-	50.0	-	-	-	40.0
	iii)b) dimetilisosorbide	50.0	-	-	-	40.0	-

20 Las composiciones de los Ejemplos 4 a 9 son estables.

Ejemplos 10 a 16 (soluciones)

Se preparan las siguientes composiciones:

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	Ingredientes	Ej.10	Ej.11	Ej.12	Ej.13	Ej.14	Ej.15
	Compuesto A	2.0	2.0	0.5	0.5	5.0	2.0
	i) propilenglicol	38.0	38.0	-	-	-	-
	hexilenglicol	-	-	39.5	39.5	35.0	38.0
5	ii) alcohol oleílico	10.0	10.0	10.0	10.0	10.0	10.0
	iii)a) miristato de isopropilo	-	-	50.0	-	-	-
	palmitato de isopropilo	-	-	-	50.0	-	-
	adipato de di-isopropilo	-	50.0	-	-	-	50.0
10	iii)b) dimetilisosorbide	50.0	-	-	-	50.0	-

Las composiciones de los Ejemplos 10 a 15 son estables.

15 **Ejemplos 16 y 17 (soluciones)**

Se preparan las siguientes composiciones:

	Ingredientes	Ejemplo 16	Ejemplo 17
	Compuesto A	1.0	1.0
20	i) isopropanol	-	10.0
	hexilenglicol	5.0	5.0
	ii) alcohol oleílico	10.0	10.0
	iii)a) adipato de di-isopropilo	84.0	74.0

Las composiciones de los Ejemplos 16 y 17 son estables.

Ejemplos 18 a 21 (ungüentos semisólidos)

Se preparan las siguientes composiciones:

	Ingredientes	Ej.18	Ej.19	Ej.20	Ej.21*
5	Compuesto A	1.0	1.0	1.0	0.3
	i) isopropanol	10.0	10.0	10.0	-
	hexilenglicol	5.0	5.0	5.0	10.0
	ii) alcohol oleílico	10.0	10.0	10.0	10.0
10	iii)a) adipato de di-isopropilo	32.0	54.0	64.0	-
	iii) c) triglicéridos de cadena mediana (Miglyol 812)	-	-	-	44.0
15	<u>Ingredientes adicionales:</u> parafina líquida (base de ungüento)	32.0	-	-	29.7
	dióxido de silicio (Aerosil R972) (agente de consistencia)	10.0	-	-	6.0
20	cera de abejas (agente de consistencia)	-	20.0	-	-
	aceite de ricino hidrogenado (Cutina HR) (agente de consistencia)	-	-	10.0	-

25 * oleogel.

Las composiciones de los Ejemplos 18 a 21 son estables.

Ejemplos 22 a 25 (soluciones)

Se preparan las siguientes composiciones:

5		Ingredientes	Ej.22	Ej.23	Ej.24	Ej.25
		Compuesto A	0.8	4.0	0.6	0.2
		i) isopropanol	10.0	10.0	10.0	-
		hexilenglicol	5.0	5.0	10.0	10.0
10		ii) alcohol oleílico	10.0	10.0	10.0	10.0
		iii)a) miristato de isopropilo	-	-	-	49.8
		adipato de di-isopropilo	-	71.0	-	-
15		iii) c) triglicéridos de cadena mediana (Miglyol 812)	74.2	-	39.4	-
		<u>Ingredientes adicionales:</u> parafina líquida (base de ungüento)	-	-	30.0	30.0

20 Las composiciones de los Ejemplos 22 a 25 son estables.

La utilidad de las composiciones de la invención se puede observar en estudios clínicos convencionales, tales como la prueba estipulada más adelante, utilizando una
25 concentración del 0.005 por ciento al 10 por ciento en

peso/peso (de preferencia del 0.1 por ciento al 3 por ciento en peso/peso) del agente activo.

Un estudio clínico representativo se lleva a cabo como sigue:

5 Se realiza un estudio de pacientes internos controlado con vehículo, doble-ciego, de selección aleatoria, que compara la composición de la invención en una dosis del 0.1 por ciento al 3 por ciento en peso (basándose en el peso total de la composición) del agente activo, sobre el área de
10 la piel enferma, por ejemplo 200 centímetros cuadrados, correspondiente a de aproximadamente 0.5 a 50 miligramos/centímetro cuadrado, de preferencia de 1 a 10 miligramos/centímetro cuadrado de la composición, y placebo sobre el área de la piel enferma como un control positivo, en
15 pacientes que sufren de enfermedades inflamatorias e hiperproliferativas de la piel, o de manifestaciones cutáneas de enfermedades inmunológicamente mediadas.

Los pacientes se tratan con la composición dos veces al día durante 6 meses. Se evalúa el efecto
20 terapéutico, y se utiliza el tiempo hasta la liberación parcial para determinar la eficacia. Se registran la tolerabilidad local de los medicamentos en estudio y los parámetros de seguridad de rutina, incluyendo hematología y química clínica.

25 La utilidad también se puede observar utilizando el

ensayo establecido de dermatitis por contacto alérgica experimentalmente inducida en cerdos domésticos jóvenes (J. Investig. Dermatol. 98 [1992] 851-855). Se probaron varias formulaciones para determinar la inhibición de los cambios inflamatorios (intensidad y extensión de enrojecimiento e infiltración) mediante examen clínico. La eficacia se evaluó mediante una comparación de los cambios inflamatorios en los sitios de prueba contralaterales tratados y no tratados en los mismos animales.

10 Los resultados obtenidos son como sigue:

	Formulación del Ejemplo No.	Eficacia contra los sitios no tratados (% medio; n = 12**)
	16	79
15	17	73
	18	78
	20	70
	Pimecrolimus, crema al 1%	68

20 **Cada formulación se probó en dos sitios de prueba en 6 animales.

 La cantidad exacta de composición de la invención que se vaya a administrar depende de diferentes factores, por ejemplo de la duración deseada del tratamiento y de la velocidad de liberación del agente activo. Se obtienen resultados satisfactorios en mamíferos superiores, por

25

ejemplo en seres humanos, con la aplicación local sobre el área que se vaya a tratar de un 0.05 por ciento a un 10 por ciento en peso/peso, de preferencia del 0.1 por ciento al 3 por ciento de concentración del agente activo una vez o
5 varias veces al día (por ejemplo, de 2 a 5 veces al día). En general, la composición se puede aplicar a áreas de la piel tan pequeñas como de 1 centímetro cuadrado, hasta tan grandes como de 0.5 metros cuadrados, y de preferencia la composición se aplicará al área de la cabeza en el
10 tratamiento de enfermedades inflamatorias e hiperproliferativas de la piel, o de manifestaciones cutáneas de enfermedades inmunológicamente mediadas. Las cargas de piel adecuadas del agente activo caen dentro del rango de 0.005 miligramos/centímetro cuadrado a 1 miligramo/
15 centímetro cuadrado.

Se encuentra que las composiciones de la invención son efectivas independientemente de la condición de la piel, y son bien toleradas en la piel. Se pueden aplicar fácilmente a grandes áreas de la piel utilizando un aplicador
20 convencional, por ejemplo brocha, cotonete de algodón, filamento, rociador tópico, o aplicador de bola giratoria, y por lo tanto, son muy convenientes en el uso.

REIVINDICACIONES

1. Una composición farmacéutica líquida o semisólida tópica de una sola fase sustancialmente desprovista de etanol y agua, la cual comprende una ascomicina en un vehículo portador que comprende una mezcla de solventes de tres componentes que suman cuando menos el 40 por ciento en peso/peso del peso total de la composición, y que consiste en:

10 i) un alcohol de 3 a 8 átomos de carbono y/o alcanodiol de 1 a 8 átomos de carbono;

ii) un alcohol graso; y

iii) un solvente adicional seleccionado a partir de:

15 a) un alquiléster de ácido alcancarboxílico y/o alquiléster de ácido alcandicarboxílico, y/o

b) un co-componente hidrofílico, y/o

c) un triglicérido;

y opcionalmente, excipientes convencionales adicionales.

20 2. Una composición de acuerdo con la reivindicación 1, en donde la ascomicina es pimecrolimus.

3. Una composición de acuerdo con la reivindicación 1 ó 2, en donde:

25 - el componente i) es isopropanol y/o hexilenglicol;

- el componente ii) es alcohol oleílico; y

- el componente iii) es:

a) adipato de di-isopropilo y/o miristato de isopropilo, y/o

5 b) dimetilisosorbide, y/o

c) triglicéridos de cadena mediana;

y opcionalmente excipientes convencionales adicionales.

4. Una composición de acuerdo con la
10 reivindicación 1 ó 2, la cual comprende excipientes convencionales adicionales seleccionados a partir de hidroxipropilcelulosa, parafina líquida, dióxido de silicio coloidal, cera de abejas, y aceite de ricino hidrogenado.

5. Una composición de acuerdo con la
15 reivindicación 1 ó 2, en donde la ascomicina está presente en una cantidad del 1 por ciento al 5 por ciento en peso de la composición.

6. Una composición de acuerdo con la
reivindicación 1 ó 2, la cual está en la forma de un gel, una
20 espuma, o un ungüento.

7. Una composición de acuerdo con la
reivindicación 1 ó 2, para utilizarse en el tratamiento de
enfermedades inflamatorias e hiperproliferativas de la piel, y
de manifestaciones cutáneas de enfermedades inmunológica-
25 mente mediadas.

8. Un método para el tratamiento de enfermedades inflamatorias e hiperproliferativas de la piel, o de manifestaciones cutáneas de enfermedades inmunológicamente mediadas, el cual comprende administrar una
5 composición de acuerdo con la reivindicación 1 ó 2 a la piel de un paciente que lo necesite.

9. El uso de una composición de acuerdo con la reivindicación 1 ó 2, en la preparación de un medicamento para el tratamiento de enfermedades inflamatorias e
10 hiperproliferativas de la piel, y de manifestaciones cutáneas de enfermedades inmunológicamente mediadas.

10. El uso de un vehículo portador como se define en la reivindicación 1, para mejorar la penetración de una ascomicina en la piel humana, en las uñas, o en la mucosa.

15

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PCT

REQUEST

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

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PCT/EP 03 / 08999

International Application No.

(13.08.2003)

13 AUG 2003

International Filing Date

EUROPEAN PATENT OFFICE

PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 4 -32616A

Box No. I TITLE OF INVENTION

Pharmaceutical compositions

Box No. II APPLICANT

☐ This person is also inventor

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☐ all designated States

☐ all designated States except the United States of America

☐ the United States of America only

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

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

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| ☒ CU Cuba | ☒ LU Luxembourg | ☐ TZ United Republic of Tanzania |
| ☒ CZ Czech Republic | ☒ LV Latvia | ☒ UA Ukraine |
| ☒ DE Germany | ☒ MA Morocco | ☐ UG Uganda |
| ☒ DK Denmark | ☒ MD Republic of Moldova | ☒ US United States of America |
| ☒ DM Dominica | ☐ MG Madagascar | ☒ UZ Uzbekistan |
| ☒ DZ Algeria | ☒ MK The former Yugoslav Republic of Macedonia | ☒ VC Saint Vincent and the Grenadines |
| ☒ EC Ecuador | ☒ MN Mongolia | ☒ VN Viet Nam |
| ☒ EE Estonia | ☐ MW Malawi | ☒ YU Yugoslavia |
| ☒ ES Spain | ☒ MX Mexico | ☒ ZA South Africa |
| ☒ FI Finland | ☐ MZ Mozambique | ☐ ZM Zambia |
| ☒ GB United Kingdom | ☒ NO Norway | ☒ ZW Zimbabwe |
| ☒ GD Grenada | | |
| ☒ GE Georgia | | |
| ☒ GH Ghana | | |

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

- ☒ NI Nicaragua
- ☒ PG Papua New Guinea
- ☒ SY Syrian Arab Republic
- ☐
- ☐

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

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(1) 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. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
 - (vi) If, in Box No. VI, there are more than five 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, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

Continuation of Box No. II

Novartis AG is applicant for all designated States with the exception of: AT (Austria) and US (USA)

Continuation of Box No. III

Novartis Pharma GmbH is applicant for AT (Austria) only.

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37**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) 14 August 2002 (14.08.02) /	0218996.7 /	GB /		
item (2)				
item (3)				
item (4)				
item (5)				

☐ 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) ☐ item (4) ☐ item (5) ☐ 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 /

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 | : |

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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) : 6	2. ☐ original separate power of attorney	:
description (excluding sequence listings and/or tables related thereto) : 13	3. ☐ original general power of attorney	:
claims : 2	4. ☒ copy of general power of attorney, reference number, if any: AV 36671 + 46171	2
abstract : 1	5. ☐ statement explaining lack of signature	:
drawings : 0	6. ☐ priority document(s) identified in Box No. VI as item(s): (1) (will follow)	:
Sub-total number of sheets : 22	7. ☐ translation of international application into (language):	:
sequence listings :	8. ☐ separate indications concerning deposited microorganism or other biological material	:
tables related thereto :	9. ☐ sequence listings 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 : 22	(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter	:
(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 listings mentioned in left column	:
(i) ☐ sequence listings	10. ☐ tables in computer readable form related to sequence listings (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)(i) or (c)(i) 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 listings	(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): Power of Attorney will follow	:
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the		
☐ sequence listings:		
☐ 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).

In the name of the applicants
The representative

10.07.2003

GRUBB, Philip AV 36671 + 46171

For receiving Office use only		2. Drawings: ☐ received: ☐ not received:
1. Date of actual receipt of the purported international application:	(13.08.03) 13 AUG 2003	
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:

(12) SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE COOPERACION
EN MATERIA DE PATENTES (TCP)
OMPI

(19) Organización Mundial de la Propiedad Intelectual Oficina Internacional	TCP	(10) Número de la Publicación Internacional: WO 2004/016289 A1
(43) Fecha de la Publicación Internacional: 26 de febrero de 2004 (26.02.2004)		
(51) Clasificación de Patente Internacional ² : A61K 47/10, 47/14, 47/26, 31/445	(74) Agentes: GRUBB, Philip; Novartis AG, Corporación de Propiedad Intelectual, CH-4002 Basel (CH).	
(21) Número de Solicitud Internacional: PCT/EP2003/008999	(81) Estados Designados (nacionales): AE, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.	
(22) Fecha de Presentación Internacional: 13 de agosto de 2003 (13.08.2003)	(84) Estados Designados (regionales): Patente Eursiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, BG, CH, CY, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).	
(25) Idioma de Presentación: Inglés	Publicado: -con reporte de búsqueda internacional -antes del término del límite de tiempo para enmendar las reivindicaciones y para ser publicado en el evento de recepción de enmiendas.	
(26) Idioma de Publicación: Inglés	Para dos códigos de cartas y otras abreviaturas, referir al "Guidance Notes on Codes and Abbreviations" que aparece al principio de cada derecho regular de la Gaceta TCP.	
(30) Información de Prioridad: 0218996.7 14 de agosto de 2002 (14.08.2002) GB		
(71) Solicitante: (para todos los Estados designados excepto AT, US): NOVARTIS AG [CH/CH]; Lichstrasse 35, CH- 4056 Basel (CH).		
(71) Solicitante: (solo para AT): NOVARTIS PHARMA GMBH. [AT/AT]: Brunner Strasse 59, A-1230 Viena (AT).		
(72) Inventores; y		
(75) Inventores/Solicitantes (solo para US): LENDERGERBER, Dorothea [DE/DE]; Richenstrasse 125, 79594 Indlingen (DE). SONNTAG, Jean-Claude [FR/FR]; Rue de Dahlia 9, F-68260 Kingersheim (FR). KRIWET, Katrin [DE/DE]; Allmendweg 9, 79639 Grenzach-Wyhlen (DE). SEKKAT, Nabila [MA/CH]; Davidsbodenstrasse 34, CH-4056 Basel (CH).		
(54) Título: COMPOSICIONES TÓPICAS DE ASCOMICINA ANHIDRAS Y DESPROVISTAS DE ETANOL.		
(57) Resumen: Composiciones farmacéuticas líquidas o semi-sólidas tópicas de una sola fase sustancialmente exentas de etanol y agua, y que comprenden una ascomicina, tal como pimecrolimus, en un vehículo portador que comprende una mezcla de solventes de tres componentes que suman cuando menos el 40 por ciento en peso/peso del peso total de la composición, y que consiste en:) un alcohol de 3 a 8 átomos de carbono y/o alcanodiol de 1 a 8 átomos de carbono; ii) un alcohol graso; y iii) un solvente adicional seleccionado a partir de: a) un alquiléster de ácido alcancarboxílico y/o alquiléster de ácido alcandicarboxílico, y/o b) un co-componente hidrofílico, y/o c) un triglicérido; y opcionalmente, excipientes convencionales adicionales.		

WO 2004/016289 A1

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
26 February 2004 (26.02.2004)

PCT

(10) International Publication Number
WO 2004/016289 A1

(51) International Patent Classification⁷: A61K 47/10,
47/14, 47/26, 31/445

SEKKAT, Nabila [MA/CH]; Davidsbodenstrasse 34,
CH-4056 Basel (CH).

(21) International Application Number:
PCT/EP2003/008999

(74) Agent: GRUBB, Philip; Novartis AG, Corporate Intellectual
Property, CH-4002 Basel (CH).

(22) International Filing Date: 13 August 2003 (13.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0218996.7 14 August 2002 (14.08.2002) GB

(71) Applicant (for all designated States except AT, US): NO-
VARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel
(CH).

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

(84) Designated States (regional): Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU,
IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

(71) Applicant (for AT only): NOVARTIS PHARMA GMBH
[AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LEDERGERBER,
Dorothea [DE/DE]; Riehenstrasse 125, 79594 Inzlin-
gen (DE). SONNTAG, Jean-Claude [FR/FR]; Rue de
Dahlia 9, F-68260 Kingersheim (FR). KRIWET, Katrin
[DE/DE]; Allmendweg 9, 79639 Grenzach-Wyhlen (DE).

Published:

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

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

(54) Title: TOPICAL ANHYDROUS AND ETHANOL-FREE ASCOMYCIN COMPOSITIONS

(57) Abstract: Single-phase topical liquid or semi-solid pharmaceutical compositions substantially free of ethanol and water and comprising an ascomycin, such as pimelicrolimus, in a carrier vehicle comprising a 3-component solvent mixture amounting to at least 40 w/w of the total weight of the composition and consisting of: i) a C₃₋₈ alkanol and/or C₁₋₈ alkanediol; ii) a fatty alcohol; and iii) a further solvent selected from: a) an alkane carboxylic acid alkyl ester and/or alkane dicarboxylic acid alkyl ester and/or b) a hydrophilic co-component and/or c) a triglyceride; and optionally further conventional excipients.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4-32616A	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/EP 03/08999	International filing date (day/month/year) 13/08/2003	(Earliest) Priority Date (day/month/year) 14/08/2002
Applicant NOVARTIS AG		

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 5 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, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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

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

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

TOPICAL ANHYDROUS AND ETHANOL-FREE ASCOMYCIN COMPOSITIONS

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 III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

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

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08999

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

ALL
PCT ✓

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08999

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y3

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/10 A61K47/14 A61K47/26 A61K31/445

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, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 074 255 A (FUJISAWA PHARMACEUTICAL CO) 7 February 2001 (2001-02-07) paragraphs '0028!', '0033!', '0037!', '0038!' examples <i>= ③ Figure p. 24.4.98</i>	1, 2, 4-10
A	WO 96 13249 A (SANDOZ AG ; SCHMOCK FRITZ (AT); POPP XUE PING (CH); JACKMAN MARTIN) 9 May 1996 (1996-05-09) examples <i>= ③ 109-8185</i>	1-10
A	EP 1 147 766 A (NOVARTIS ERFIND VERWALT GMBH ; NOVARTIS AG (CH)) 24 October 2001 (2001-10-24) examples <i>= ③ 109-8185/A1/D1</i>	1-10

☐

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

10 December 2003

Date of mailing of the international search report

18/12/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Villa Riva, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08999

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44

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1074255 (7)	A	07-02-2001	AU 749475 B2	27-06-2002
			AU 3537299 A	16-11-1999
			BR 9910336 A	25-09-2001
			CA 2326222 A1	04-11-1999
			EP 1074255 A1	07-02-2001
			HU 0104452 A2	28-03-2002
			NO 20005399 A	26-10-2000
			NZ 507345 A	20-12-2002
			CN 1307475 T	08-08-2001
			WO 9955332 A1	04-11-1999
			PL 343627 A1	27-08-2001
			RU 2203058 C2	27-04-2003
			TR 200003108 T2	21-02-2001
			US 2002061907 A1	23-05-2002
			ZA 200005378 A	23-08-2002
WO 9613249 (5)	A	09-05-1996	AT 214593 T	15-04-2002
			AU 714254 B2	23-12-1999
			AU 3845195 A	23-05-1996
			AU 5833699 A	06-01-2000
			BR 9509530 A	14-10-1997
			CA 2200966 A1	09-05-1996
			CN 1401325 A	12-03-2003
			CN 1162259 A ,B	15-10-1997
			CY 2211 A	08-11-2002
			CZ 9701232 A3	13-08-1997
			CZ 290219 B6	12-06-2002
			DE 19581804 T0	22-01-1998
			DE 69525957 D1	25-04-2002
			DE 69525957 T2	14-11-2002
			DK 786986 T3	29-04-2002
			WO 9613249 A1	09-05-1996
			EP 1147766 A2	24-10-2001
			EP 0786986 A1	06-08-1997
			ES 2173978 T3	01-11-2002
			FI 971018 A	18-04-1997
			GB 2308546 A ,B	02-07-1997
			HU 77140 A2	02-03-1998
			JP 10508588 T	25-08-1998
			NO 971951 A	25-04-1997
			NZ 295170 A	25-02-1999
			NZ 331824 A	28-01-2000
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			PT 786986 T	31-07-2002
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			SK 52097 A3	10-09-1997
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			CY 2212 A	08-11-2002
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			PL 184908 B1	31-01-2003
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			AU 714254 B2	23-12-1999
			AU 3845195 A	23-05-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08999

46
45

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1147766	A	AU 5833699 A	06-01-2000
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		DK 786986 T3	29-04-2002
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		ES 2173978 T3	01-11-2002
		FI 971018 A	18-04-1997
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		HU 77140 A2	02-03-1998
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		PL 319599 A1	18-08-1997
		PL 185320 B1	30-04-2003
		PT 786986 T	31-07-2002
		SK 52097 A3	10-09-1997
		US 2001031769 A1	18-10-2001
		CY 2212 A	08-11-2002
		GB 2327610 A ,B	03-02-1999
		PL 184908 B1	31-01-2003
		RU 2181592 C2	27-04-2002

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

IPEA/ _____

Aktenexerplar

1 A | ~~DE~~ | DIV

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only		
Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 4-32616A
International application No. PCT/EP 03/08999	International filing date (day/month/year) 13.August 2003 (13.08.03)	(Earliest) Priority date (day/month/year) 14. August 2002 (14.08.02)
Title of invention TOPICAL ANHYDROUS AND ETHANOL-FREE ASCOMYCIN COMPOSITIONS		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Novartis AG Lichtstrasse 35 4056 Basel CH		Telephone No. +4161 324 11 11
		Facsimile No. +4161 322 75 32
		Teleprinter No.
		Applicant's registration No. with the Office
State (that is, country) of nationality: CH		State (that is, country) of residence: CH
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.) Novartis Pharma GmbH Brunner Strasse 59 1230 Vienna AT		
State (that is, country) of nationality: AT		State (that is, country) of residence: AT
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.) LEDERGERBER, Dorothea Riehenstrasse 125 79594 Inzlingen DE		
State (that is, country) of nationality: DE		State (that is, country) of residence: DE
☒ Further applicants are indicated on a continuation sheet.		

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Continuation of Box No. II APPLICANT(S)

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

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

SONNTAG, Jean-Claude
Rue de Dahlia 9
68260 Kingersheim
FR

State (that is, country) of nationality:
FR

State (that is, country) of residence:
FR

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.)

KRIWET, Katrin
Allmendweg 9
79639 Grenzach-Wylen
DE

State (that is, country) of nationality:
DE

State (that is, country) of residence:
DE

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.)

SEKKAT, Nabila
Davidsbodenstrasse 34
4056 Basel
CH

State (that is, country) of nationality:
MA

State (that is, country) of residence:
CH

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

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 3

International application No.
PCT/EP 03/08999

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

The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)GRUBB, Philip
Novartis AG
Corporate Intellectual Property
4002 Basel
CH

Telephone No.

+4161 324 11 11

Facsimile No.

+4161 322 75 32

Teleprinter No.

Agent's registration No. with the Office

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

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

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

☒ the international application as originally filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

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

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☒ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received not received

☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

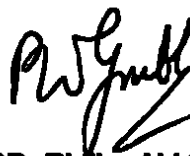
The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to a sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

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

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

In the name of the applicants, the representative



16.02.2004

GRUBB, Philip AV 36671 + 46171

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

- | | |
|--|--|
| 3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
☐ The applicant has been informed accordingly. | 6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply. |
| 4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5. | 7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5. |
| 5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | 8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82. |

For International Bureau use only

Demand received from IPBA on:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)51
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Applicant's or agent's file reference 4-32616A	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA/16)	
International application No. PCT/EP 03/08999	International filing date (day/month/year) 13.08.2003	Priority date (day/month/year) 14.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K47/10		
Applicant NOVARTIS AG et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 68.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 19.02.2004	Date of completion of this report 18.01.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2369 - 0 Tlx 523656 epmu d Fax: +49 89 2369 - 4465	Authorized Officer Villa Riva, A Telephone No. +49 89 2369-8404 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/08999**

1. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*)

Description, Pages

1-13 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1. and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/08999**

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

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 8 (ia)

because:

- ☒ the said international application, or the said claims Nos. 8 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the Standard.
- ☐ the computer readable form has not been furnished or does not comply with the Standard.

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

1. Statement

Novelty (N)	Yes: Claims	1-10
	No: Claims	
Inventive step (IS)	Yes: Claims	1-10
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-7,9,10
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/08999

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

Claim 8 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1 (EP-A- 1 074 255), disclosing anhydrous and ethanol-free ascomycin (fk506, pimecrolimus) compositions for dermatological use; D2 (WO 96 13 249 A) and D3 (EP-A- 1 147 766), disclosing dermatologic ascomycin compositions (emulsions) containing also oleyl alcohol, miglyol, hexylene glycol and water.

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

D1 is considered the closest prior art. In fact, the examples contain diethylene glycol monoethyl ether (DGME) instead of an alcohol (component ii) in claim 1; however, fatty alcohols are indicated as an alternative to the ethers in paragraph [0038].

The problem is the same as in the present application, namely to provide ascomycin formulation excipients with good dissolution and absorption/permeation promoting properties.

Nevertheless, the overall teaching of D1 is to use the ethers, and in particular DGME, as a preferred embodiment.

Therefore, also in view of the additional technical data which show the good effects of an oleyl alcohol containing composition, the subject-matter of claims 1-10 is considered novel and inventive (Art. 33 PCT).

As for the documents D2 and D3, they disclose examples of a number of known ascomycin dermatological preparations which contain all of the components i) - iii), but

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/08999

also a substantial amount of water. Therefore, they are not considered detrimental to novelty or inventive step for the present set of claims.

For the assessment of the present claim 8 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

Corporate Intellectual Property

- 4. Okt. 2004

F/F M/D F/L PS Copy

From the
INTERNATIONAL P.

To:

GRUBB, Philip
NOVARTIS AG
Corporate Intellectual Property
CH-4002 Basel
SUISSE

PCT

WRITTEN OPINION
(PCT Rule 66)Date of mailing
(day/month/year)

01.10.2004

Applicant's or agent's file reference

4-32616A

REPLY DUE

within 3 month(s)
from the above date of mailing

International application No.

PCT/EP 03/08999

International filing date (day/month/year)

13.08.2003

Priority date (day/month/year)

14.08.2002

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

A61K47/10

Applicant

NOVARTIS AG et al.

1st Exam of 14.5.04: not used
written = done at ISR, agedocument X and for Y (in ③, cited under
+)

1. This written opinion is the second drawn up by this International Preliminary Examining Authority.

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

- I ☒ Basis of the opinion
II ☐ Priority
III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV ☐ Lack of unity of invention
V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI ☐ Certain documents cited
VII ☐ Certain defects in the international application
VIII ☐ Certain observations on the international application

(⑤ - den A)

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.**Also:** For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 14.12.2004

Name and mailing address of the international
preliminary examining authority:European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax +49 89 2399 - 4465

Authorized Officer

Villa Riva, A

Formalities officer (incl. extension of time limits)

Longo, E

Telephone No. +49 89 2399-8141



WRITTEN OPINION

International application No. PCT/EP 03/08999

I. Basis of the opinion

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, Pages

1-13 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

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

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

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WRITTEN OPINION

International application No. **PCT/EP 03/08999**

☐ the entire international application,

☒ claims Nos. 8 (ia) *method of t.*

because:

☒ the said international application, or the said claims Nos. 8 relate to the following subject matter which does not require an international preliminary examination (specify):

~~see separate sheet~~

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1,2,4-10
Inventive step (IS)	Claims	1,2,4-10
Industrial applicability (IA)	Claims	

2. Citations and explanations

~~see separate sheet~~

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/EP 03/08999

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

well
-f
to
Claim 8 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V**Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D2 = D3 ! 2

D1 (EP-A-1 074 255), disclosing anhydrous and ethanol-free ascomycin (fk506, pimecrolimus) compositions for dermatological use; D2 (WO 96/13 249 A) and D3 (EP-A-1 147 766), disclosing dermatologic ascomycin compositions (emulsions) containing also oleyl alcohol, miglyol, hexylene glycol and water.

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

D1 is considered novelty destroying for the subject-matter of present claims 1,2,4-10 under Art. 33(1) and (2) EPC. In fact, the examples contain diethylene glycol monoethyl ether instead of an alcohol (component ii) in claim 1; however, fatty alcohols are indicated as an alternative to the ethers in paragraph [0038].

The specific combination in claim 3 is not disclosed nor suggested, and provided it has a surprising effect, it could be considered novel and inventive.

As for the D2 and D3, they are examples of a number of known ascomycin dermatological preparations which contain all of the components i) - iii), but they also contain a substantial amount of water. Therefore, they are not considered detrimental to novelty or inventive step for the present set of claims.

For the assessment of the present claim 8 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/EP 03/08999

compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

} =
cannot
claim
already



ALL / Ent ✓
PCT ✓

Dr. Lucien Vallet
Patent Attorney, Group Head

Novartis AG
Corporate Intellectual Property
CH-4002 Basel
Switzerland
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Fax: +41 61 322 75 32
lucien.vallet@group.novartis.com

61
60

International Preliminary Examining Authority
European Patent Office

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Germany

From: +41 61 322 7532
To: 0049-89-2399-4465

Total pages: 4

December 29, 2004

Your Ref:
PCT/EP03/08999

Our Ref:
NI CIP / VA

URGENT

Case 4-32616 – International application No. PCT/EP03/08999

Dear Sirs,

We refer to the second Written Opinion, dated October 1, 2004.

Our comments are as follows:

1. As to Item III (claim 8):

We shall delete or amend this claim directed to a method of treatment during the National phase as appropriate.

2. As to Item V (novelty and inventive step):

2.1. As regards D2/D3:

Of the documents cited in the ISR, namely D1 (Fujisawa EP-A-1'074'255) and

⑤ D2/D3 (Sandoz WO 96/13249 and Novartis EP 1'147'766A), the IPEA has acknowledged that D2/D3 are not considered detrimental to novelty or inventive step for present claims 1-10, essentially in view of the presence of a substantial amount of water in the compositions disclosed therein.

2.2. As regards D1:

We respectfully disagree with the Examining Division's view that that disclosure should be novelty-destroying for the subject matter of claims 1, 2 and 4 to 10:

2.2.1. Indeed, as pointed out by the Examining Division, in all the Examples of D1 (except Composition 6 on pages 9-10), diethylene glycol monoethyl ether is included as an excipient, and in paragraph 0038 thereof it is indicated that fatty alcohols may be used in place of ethers.

However, such ethers and alcohols are disclosed as "compatibilizing agents for optional use" (page 7, line 11), and not as dissolution/absorption promoters (which are disclosed on page 6, line 39 to page 7, line 3): they function as compatibilizing agents (page 7, lines 11-25). This clearly shows at least that such compounds are not at the core of the invention disclosed. They are there "to improve the compatibility of the dissolution/absorption promoter with the pharmaceutical base" (page 7, lines 11-12), and thus of rather ancillary utility.

Further, the alcohols are not preferred in that function, but rather the ethers (page 7, line 20), and when the ethers are used, "good cutaneous retention of the macrolide compound can be expected" (page 7, line 21-22): the disclosure is silent on any particularly positive result when alcohols are used for formulation in place of ethers.

2.2.2. Further, the disclosure of D1 overall focusses on dissolution/absorption, while also mentioning cutaneous retention in passing. Dissolution concerns technology involved in the preparation of galenical formulations. Absorption is specified as being "cutaneous absorption" (on page 2, line 34 of D1) and thus suggests penetration through the skin, a property which is not particularly desirable with the compositions of the present invention, which should penetrate/permeate through the outer layers of skin, but exert their pharmacological activity in the skin itself, with no or only insignificant systemic activity. As to the third aspect, cutaneous retention, as pointed out above this is limited to the situation where diethylene glycol monoethyl ether is used.

2.2.3. Further, the pharmaceutical bases for the compositions of D1 preferably are hydrophilic (page 7, line 6), and the thickeners preferably water-soluble (page 7, line 28), thereby implying, it seems, the presence of some water in the compositions of D1, whereas the compositions of the present invention are substantially free of water (specification on page 2, line 9).

2.2.4. Further, in D1 the pharmaceutical base, e.g. propylene glycol, is present in large amounts (see the Examples), about 70-90 %, whereas component i) of the present invention (an alkanol or alkanediol) preferably amounts to just up to about 50 % of the total weight (specification on page 4, line 16).

2.2.5. Still further, there is no concrete disclosure of any specific formulation in D1 comprising any fatty alcohol, i.e. any component ii) of the present invention.

2.3. Comparative test data: The surprising effect achieved with the compositions of the present invention is evidenced i.a. by the attached experimental data (Enclosure) comparing the in vitro skin penetration/permeation of the pimecrolimus composition of Example 18 of the present application, with a pimecrolimus cream essentially corresponding to Example 14 of D2/D3, but wherein the amount of Compound B, i.e. pimecrolimus, i.e. 33-epichloro-33-desoxyascomycin, is 1 % in place of 0.3 %, and the preserving agent benzyl alcohol 1 % replaces Methyl/Propyl Paraben.

It appears therefrom that skin concentration is 2.7 times and skin permeation is 1.7 times higher with e.g. the composition of Example 18 of the present application, than with the pimecrolimus cream.

This result is in line with further studies effected on the in vivo anti-inflammatory activity found in acute allergic contact dermatitis in domestic pigs using a procedure similar to that described in

(2a) J. Invest. Dermatol. (1992) 851-855; the efficacy obtained thereby with e.g. the formulation of Example 18 is 1.74, as compared with 1.0 for the pimecrolimus cream.

2.4. Conclusion: It appears in our view from the above that, surprisingly, beneficial pharmaceutical compositions could be prepared that are very different from the formulations of D1 and are not comprising water, but nevertheless are superior in terms of efficacy to related water-containing compositions.

We thus do not feel that amendment of the claims is appropriate at this stage and trust that both novelty and inventive step can now be acknowledged for all claims, and look forward to receipt of the International preliminary examination report.

Yours very truly,
Novartis AG



Lucien Vallet
Professional Representative GA No. 36671

Enclosure: Comparative test results

h:\data\4-32616\fm-pe-dec04.doc

Enclosure

Comparative test data

Skin penetration/permeation in vitro

1. Summary

The skin penetration/permeation of the gel formulation of Example 18 was compared with the penetration/permeation of pimecrolimus (33-epichloro-33-desoxyascomycin) 1 % cream, i.e. with Example 14 of D1/D2, WO 96/13249 and EP 1'147'766 A, but wherein the amount of pimecrolimus (Compound B) is 1 % in place of 0.3 %, and the preserving agent is benzyl alcohol 1 % in place of Methyl/Propyl Paraben. Split-thickness human cadaver skin was used and formulations containing 1 % radiolabeled pimecrolimus were applied.

2. Method

The formulations contained [^3H]-labeled pimecrolimus. Drug concentration was 1 % in all cases. Target radioactivity per 10 g of formulation was 18.5 MBq in case of the gel and 185 MBq for cream. The actual radioactivity is measured by suspending aliquots (about 20 mg) of formulation in 1 ml of ethanol, followed by addition of 5 ml scintillation cocktail (UltimaGold MV, Packard) and scintillation counting using a TriCarb 2000CA instrument (Packard) which is calibrated with ^3H -standards prior to use.

Full-thickness skin is obtained from human cadaver. The skin is dermatomed to 0.4 mm; so-called split-thickness skin is prepared, consisting of epidermis and the upper part of the dermis with no subcutaneous fatty tissue attached.

Percutaneous penetration is studied in vitro using static Franz-type diffusion cells as described in Skin Pharmacol. 6 (1993) 116-124. With the cells used the exposed skin area was 2.54 cm², and the volume of the receptor chamber varied between 4.7 and 6.05 ml. Phosphate-buffered saline / fetal calf serum 2:1 containing penicillin/streptomycin to prevent the growth of microorganisms is used as receptor phase. All experiments are performed at 32°C in quadruplicates for 48 hours. To the epicutaneous side of the skin 300 mg of test formulations are applied. Chambers are stirred at 500 rpm during the experiments.

Samples of 100 µl are withdrawn from the receptor phase at various time points during the 48 hour experiment and replaced by fresh receptor fluid. To the samples, 5 ml of scintillation cocktail are added. Samples are subjected to liquid scintillation counting (5 min).

At the end of the experiment the skin is taken from the diffusion cells and the stratum corneum is removed with transparent adhesive tape. Specimens from the stripped skin are taken with a biopsy punch, weighed and then added to 1 ml of Soluene 350 (Packard). Samples are heated to 65°C for 3 hours. After cooling, 5 ml of scintillation cocktail are added, followed by counting.

The dpm-values obtained from the skin punch biopsies are converted to µg active compound per g of skin using the experimental activity of the formulations and the known contents of cold and radiolabeled drug substance. Likewise, the dpm-values obtained from the receptor samples are converted to ng active compound per ml of receptor. From the linear ng/ml versus time plots, the permeation rates are calculated in ng/ml/hour.

3. Results

The results on skin penetration/permeation of pimecrolimus are as follows:

Formulation	Skin concentration ^a [µg-eq/g]	Permeation rate ^a	
		[ng-eq/ml/hr]	[ng-eq/cm ² /hr]
gel (Example 18)	12.0	4.0	9.1
pimecrolimus cream	4.5	2.3	5.2
^a mean (n=4)			

Permeation of pimecrolimus through the skin was thus higher for the formulation of Example 18 than for the cream by a factor of 1.7. The formulation also yielded enhanced levels of the drug in the skin, showing 2.7-fold increased skin concentration as compared to pimecrolimus cream.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

GRUBB, Philip
NOVARTIS AG
Corporate Intellectual Property
CH-4002 Basel
SUISSE

WRITTEN OPINION

(PCT Rule 66)

Date of mailing
(day/month/year) 14/05/2004

Applicant's or agent's file reference
4-32616A

REPLY DUE
within 1 / 00 months/days
from the above date of mailing

International application No.

PCT/EP03/08999

International filing date (day/month/year)

13/08/2003

Priority date (day/month/year)

14/08/2002

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

A61K47/10

Applicant

NOVARTIS AG et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

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

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

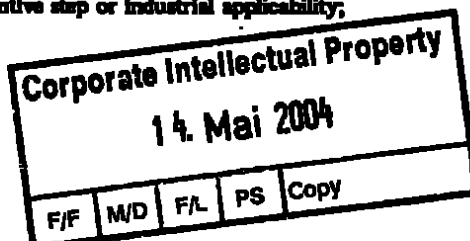
When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3.
For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.5.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 14/12/2004



Name and mailing address of the IPEA/



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Authorized officer
Examiner

Formalities officer
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WRITTEN OPINION

International application No.

PCT/EP03/08999

I. Basis of the opinion

The basis of this written opinion is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, Inventive step and Industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:
2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).
3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

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International Preliminary Examining Authority
European Patent Office

D-80298 Munich
Germany

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From: +41 61 322 7532
To: 0049-89-2399-4465

Total pages: 1

June 10, 2004

Your Ref:
PCT/EP03/08999

Our Ref:
NI CIP / VA

URGENT

Case 4-32616 – International application No. PCT/EP03/08999

Dear Sirs,

We refer to the Written Opinion under PCT Rule 66, dated May 14, 2004, and herewith request detailed substantive examination, whereby we would much appreciate being provided a second, detailed written opinion.

Please consider that the compositions of the present invention comprise a narrowly defined 3-component solvent mixture amounting to at least 40 % of the total weight.

We look forward to hearing from you further and remain,

Yours very truly,
Novartis AG

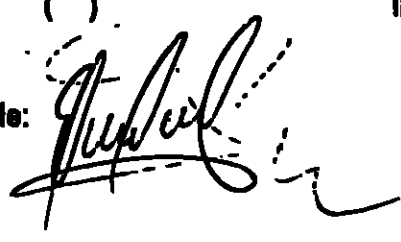
Lucien Vallet
Professional Representative GA No. 36671

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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
- 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 serenos pertinentes.	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o 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 solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable:



Fecha:

SUPERINDUSTRIA Y COMERCIO
Radicación : 000000/6 00000000 Folios: 69
Fecha UNB: 2005-05-07 16:12:01
Tramite : 011 PCI-PATENT 379 PAGE NNCI 411 PRESENTAL
dependencia: 2000 DIVISION DE MARCAS Y DISEÑOS



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Industria y Comercio
SUPERINTENDENCIA

INFORME DE PROTOCOLO

Expediente 05 - 20876

Fecha: 18 de abril de 2005

Se certifica que:

Desde fecha 16 de abril de 1997,
del folio 90.643 al folio 90.650 del
libro de Protocolo N° 311, obra el poder
N° 17.398 conferido por NOVARTIS AG
(NOVARTISSA) (NOVARTIS INC.)
domiciliado(a) en Basilea - Suiza
al doctor JIMENA ESCOBAR URIBE y/o IGNACIO
ESCOBAR URIBE.
Representante en Santafé de Bogotá D.C. Los
mismos.

Facultad para desistir y sustituir SI.

Revisado 202027.

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69

Industria y Comercio
SUPERINTENDENCIA

Folio 72

2020
Bogotá, D.C.,Doctor(a)
JIMENA ESCOBAR URIBE
Apoderado
NOVARTIS AGOficio N°
" 12671

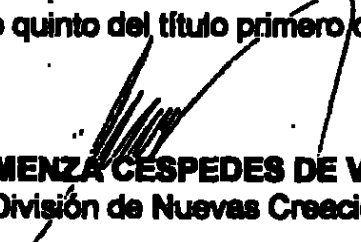
ASUNTO:	Radicación N°	05-20876
	Solicitud internacional	PCT/EP2003/008999
	Fecha inicio fase nacional	14/03/2005
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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:

- 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).

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 Única N° 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, 29 ABR. 2005

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Bogotá, D.C., Colombia

ARMENIA LEYES DE LA
la División de Nuevas Creaciones
500/10/1005