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51. **CLASIFICACION INTERNACIONAL** A61K 9/20 //A61K31/505

71. **SOLICITANTE** *NOVARTIS AG.*

DOMICILIO *BASILEA, SUIZA*

74. **APODERADO** *JIMENA ESCOBAR URIBE*

22. **BOGOTA, D.C.,** *NOVIEMBRE 5 , 2004*

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PCT
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2 SOLICITANTE (71)	Nombre: NOVARTIS AG Dirección: Lichtstrasse 35, CH -4056 Basilea, Suiza Nacionalidad o Domicilio: Basilea, Suiza Lugar de Constitución : Suiza Teléfono: 41613241111 Fax: 416 13227532 E-mail:	IDENTIFICACIÓN C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Número
3 **REPRESENTANTE O APODERADO (74)**	Nombre: JIMENA ESCOBAR URIBE Dirección: Cra. 11A No. 94-76 (Of. 305) Teléfono: 6 162051/61 Fax: 6 161889 E-mail: tm-patent@escobaruribe.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] **Número 39.779.452T.P 68228**
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10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona Prot. 17.398
- [x] Poderes si fuere el caso **Protocolo No. 17.398**
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] 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 deposito 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

11 FIGURA CARACTERÍSTICA

12 Solicito la concesión de la patente

NOMBRE: JIMENA ESCOBAR URIBE

FIRMA:

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

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ANEXOS

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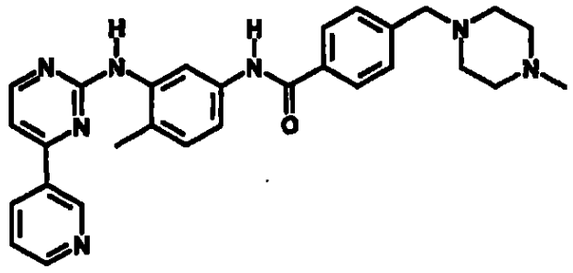
Solicito expresamente a nombre de la sociedad **NOVARTIS AG**, sociedad constituida de conformidad con las leyes de Suiza, domiciliada en Lichtstrasse 35, CH-4056 Basilea, Suiza, el otorgamiento de Patente para la invención titulada **"TABLETA CON ALTA CARGA DE FÁRMACO".**

Clase: A61K 9/16

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

RESUMEN

La presente invención pertenece a una tableta con alta carga de fármaco, la cual comprende, como ingrediente activo, el Compuesto I de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en una cantidad de aproximadamente el 30 por ciento al 80 por ciento en peso de la fracción activa, basándose en el peso total de la tableta.



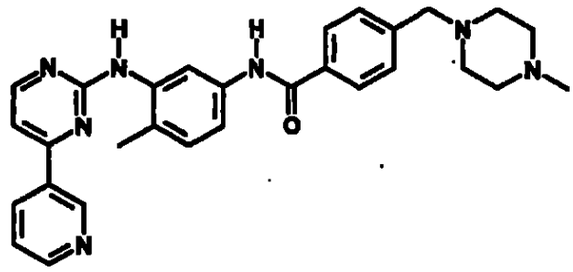
(1)

* * * * *

TABLETA CON ALTA CARGA DE FÁRMACO

La presente invención se refiere a tabletas farmacéuticas que comprenden 4-(4-metilpiperazin-1-ilmetil)-N-[4-metil-3-(4-piridin-3-il)pirimidin-2-ilamino)fenil]-benzamida o sales farmacéuticamente aceptables de la misma, y posteriormente es referida como el Compuesto I.

El Compuesto I tiene la fórmula (1):



(1)

La base libre del Compuesto I y sus sales aceptables, se dan a conocer en la Solicitud de Patente Europea Número 0564409. El mesilato del Compuesto I y las formas de cristal alfa y beta del mesilato del Compuesto I, se dan a conocer en la Solicitud de Patente Internacional Número WO 99/03854.

Normalmente, las dosificaciones diarias prescritas del mesilato del Compuesto I para el tratamiento de leucemia son altas, por ejemplo de 400 a 800 miligramos en adultos. Por consiguiente, existe una necesidad de una forma de dosificación oral que sea conveniente para administrarse, y pro-

porcione una cantidad de dosificación diaria del Compuesto I.

De acuerdo con lo anterior, la presente invención proporciona una tableta con una alta carga de fármaco, la cual comprende una cantidad farmacológicamente efectiva del Compuesto I o una sal farmacéuticamente aceptable del mismo, presente en una cantidad de aproximadamente el 30 por ciento al 80 por ciento, por ejemplo, de aproximadamente el 35, 40, 45, 50, ó 55 por ciento a aproximadamente el 60, 65, 70, 75, u 80 por ciento, de preferencia mayor al 55 por ciento. En particular, la cantidad del Compuesto I puede variar desde el 45 hasta el 80 por ciento, por ejemplo, del 50 al 70 por ciento en peso, basándose en el peso total de la tableta.

El Compuesto I puede estar en la forma de base libre o de sales farmacéuticamente aceptables del mismo, por ejemplo en la forma del monomesilato. La fracción activa corresponde al Compuesto I en la forma de base libre. Por ejemplo, 119.5 miligramos del mesilato del Compuesto I corresponden a 100 gramos de la fracción activa de base libre del Compuesto I.

La presente invención también proporciona una tableta que comprende:

(a) una cantidad farmacológicamente efectiva del Compuesto I, y

(b) cuando menos un excipiente farmacéuticamente aceptable adecuado para la preparación de tabletas, en donde

la cantidad del Compuesto I o de la sal farmacéuticamente aceptable del mismo, calculada como el porcentaje del contenido en peso de la fracción activa, basándose en el total de la tableta, es de aproximadamente el 30 por ciento al 80 por ciento, por ejemplo de cuando menos aproximadamente el 35, 40, 45, 50, ó 55 por ciento a aproximadamente, por ejemplo, el 60, 65, 70, 75, u 80 por ciento, de preferencia mayor al 55 por ciento. En particular, la cantidad del Compuesto I puede variar desde el 45 hasta el 80 por ciento, por ejemplo del 50 al 70 por ciento en peso de la fracción activa, basándose en el peso total de la tableta.

En otro aspecto, la presente invención proporciona una tableta en donde el Compuesto I está en una forma cristalina.

En un aspecto adicional de la invención, se utiliza la sal de monomesilato del Compuesto I.

En una modalidad preferida de la invención, la sal de monomesilato del Compuesto I está en una forma cristalina, por ejemplo en la forma del cristal alfa o beta, y de una manera muy preferible, la sal de monomesilato del Compuesto I está en la forma del cristal beta.

Puede haber uno o más excipientes farmacéuticamente aceptables presentes en las tabletas, por ejemplo aquéllos convencionalmente utilizados, por ejemplo, (1.1) cuando menos un aglutinante, por ejemplo celulosa microcristalina, hidro-

xipropilmetilcelulosa, (1.2) cuando menos un desintegrante, por ejemplo polivinilpirrolidinona reticulada, por ejemplo Crospovidone®, (1.3) cuando menos un derrapante, por ejemplo dióxido de silicio coloidal, (1.4) cuando menos un lubricante, por ejemplo estearato de magnesio, y/o (1.5) un recubrimiento básico. En la tableta de conformidad con la presente invención, se utiliza celulosa microcristalina como un aglutinante.

Se hace referencia a la extensa literatura sobre la materia para estos y otros excipientes y procedimientos mencionados en la presente; ver en particular, Handbook of Pharmaceutical Excipients, Tercera Edición, editado por Arthur H. Kibbe, American Pharmaceutical Association, Washington, E.U.A. y Pharmaceutical Press, Londres; y Lexikon der Hilfsstoffe für Pharmazie, Kosmetik and angrenzende Gebiete editado por H. P. Fiedler, 4ª Edición, Edito Cantor, Aulendrof, y las ediciones anteriores, que se incorporan a la presente como referencia.

Los aglutinantes (1.1) incluyen, pero no se restringen a, almidones, por ejemplo, almidón de papa, de trigo, o de maíz; celulosa microcristalina, por ejemplo productos tales como Avicel®, Filtrak®, Heweten®, ó Pharmacel®; hidroxipropilcelulosa; hidroxietilcelulosa; hidroxipropilmetilcelulosa, por ejemplo hidroxipropilmetilcelulosa-Tipo 2910 USP, hipromelosa, y polivinilpirrolidona, por ejemplo Povidone

K30 de BASF. De preferencia, se utiliza la hidroxipropilmetilcelulosa-Tipo 2910 USP.

Los desintegrantes (1.2) adecuados de acuerdo con la invención incluyen, pero no se restringen a, almidón de maíz; CMC-Ca; CMC-Na; celulosa microcristalina; PVP reticulada; por ejemplo como se conocen y están comercialmente disponibles bajo los nombres comerciales Crospovidone®, Polyplasdone®, disponibles comercialmente en la ISP Company, o Kollidon® XL; ácido algínico; alginato de sodio; y goma de guar. De preferencia, se utiliza PVP reticulada, por ejemplo Crospovidone®.

Como los derrapantes (1.3), se pueden utilizar uno o más de los siguientes: sílice; sílice coloidal, por ejemplo sílice coloidal anhidra, por ejemplo Aerosil® 200, trisilicato de magnesio, celulosa en polvo, almidón, y talco. De preferencia se utilizan sílice coloidal anhidra y/o dióxido de silicio coloidal.

Como los lubricantes (1.4), se pueden utilizar uno o más de los siguientes: estearato de Mg, de Al, ó de Ca, PEG 4000-8000, y/o talco. De preferencia se utiliza el estearato de magnesio.

Se pueden seleccionar y usar uno o más de estos excipientes, teniendo en consideración las propiedades deseadas particulares de la tableta, mediante una experimentación de rutina.

De acuerdo con la presente invención, la cantidad de aglutinante (1.1) puede variar dentro de un intervalo de aproximadamente el 1 al 40 por ciento, de preferencia del 1 al 30 por ciento, en particular del 1 al 25 por ciento en peso, basándose en el peso total de la tableta.

La cantidad de desintegrante (1.2) puede variar dentro de un intervalo del 5 al 40 por ciento, por ejemplo del 10 al 35 por ciento en peso, basándose en el peso total de la tableta.

La cantidad de derrapante (1.3) puede variar dentro de intervalos del 0.1 al 10 por ciento, en particular del 0.1 al 5 por ciento, por ejemplo del 0.5 al 3 por ciento en peso, basándose en el peso total de la tableta, o del 2 al 4 por ciento en peso, basándose en el peso total de la tableta.

La cantidad de lubricante (1.4) puede variar dentro de un intervalo del 0.1 al 5 por ciento, por ejemplo del 0.5 al 2 por ciento en peso, basándose en el peso total de la tableta.

La cantidad de recubrimiento básico (1.5) puede variar del 1 al 10 por ciento, de preferencia del 1.5 al 5 por ciento en peso, basándose en el peso total de la tableta.

Se apreciará que cualquier excipiente dado puede servir para más de una función, por ejemplo como desintegrante, aglutinante, derrapante, y/o lubricante.

En un aspecto preferido de la invención, la tableta

comprende los siguientes excipientes: uno o más aglutinantes en una cantidad total de aproximadamente el 1 por ciento al 25 por ciento en peso, basándose en el peso total de la tableta; uno o más desintegrantes en una cantidad total de aproximadamente el 10 por ciento al 35 por ciento en peso, basándose en el peso total de la tableta; uno o más derrapantes en una cantidad total de aproximadamente el 0.5 por ciento al 3 por ciento en peso, basándose en el peso total de la tableta; y/o uno o más lubricantes en una cantidad total de aproximadamente el 0.5 por ciento al 2 por ciento en peso, basándose en el peso total de la tableta.

Las cantidades absolutas de cada excipiente y las cantidades en relación con otros excipientes, dependen de una manera similar de las propiedades deseadas de la tableta, y también se pueden seleccionar mediante una experimentación de rutina. Por ejemplo, la tableta se puede seleccionar de tal forma que exhiba una liberación acelerada y/o demorada del Compuesto I con o sin el control cuantitativo de la liberación del agente activo. De preferencia, la tableta se selecciona de tal manera que exhiba una liberación inmediata del Compuesto I, por ejemplo la forma de cristal beta de la sal de monomesilato del Compuesto I.

La presente invención ha encontrado dificultades en la producción de tabletas del Compuesto I debido a los altos valores de fragilidad y a la mala resistencia a la abrasión.

Además, la flexibilidad en la cantidad de los excipientes, por ejemplo desintegrantes, está limitada debido a la alta carga de fármaco del producto. Por consiguiente, todavía existe una necesidad de formas de dosificación del Compuesto I comercialmente aceptables para administración oral con una buena conveniencia y aceptación de los pacientes.

De conformidad con la presente invención, ahora se ha encontrado de una manera inesperada, que se pueden obtener tabletas galénicas estables y convenientes que comprenden al Compuesto I. Los presentes Solicitantes han encontrado que se pueden obtener formas de dosificación sólida orales farmacéuticamente aceptables en la forma de tabletas, que son particularmente convenientes para administrarse y son estables, mediante la preparación de tabletas mediante métodos de compresión. De una manera más específica, las tabletas de la invención se pueden preparar mediante granulación, de preferencia granulación húmeda, seguida por los métodos de compresión. El Compuesto I, en especial la sal de mesilato, exhibe un alto tamaño de partículas, por ejemplo, teniendo el 60 por ciento del material de partida del Compuesto I un tamaño de partículas mayor o igual a 100 micras, por ejemplo, el 90 por ciento de las partículas son menores o iguales a 420 micras. El proceso de granulación húmeda usualmente se lleva a cabo con un material de partida de un tamaño de partículas menor a 100 micras.

Es una característica de la tableta de conformidad con la invención, que contiene un alto contenido del Compuesto I, dada la cantidad relativamente pequeña de los excipientes. Esto hace posible la producción de tabletas físicamente pequeñas. La cantidad total de excipientes en una dosificación unitaria dada, puede ser de aproximadamente el 70 por ciento o menos en peso, basándose en el peso total de la tableta, más particularmente del 50 por ciento o menos. De preferencia, el contenido del excipiente está en el intervalo de aproximadamente el 30 al 55 por ciento, más particularmente del 35 al 50 por ciento en peso, basándose en el peso total de la tableta.

Las tabletas de acuerdo con la invención sorprendentemente disponen la administración del Compuesto I en un tamaño más pequeño que el que era hasta ahora posible para una dosis unitaria dada del Compuesto I. Las tabletas de la invención son pequeñas, a pesar de la alta carga de fármaco, y por consiguiente, son convenientes de administrarse. Esto conduce a un mejor cumplimiento del paciente.

En otra modalidad, esta invención proporciona una tableta que comprende de 50 miligramos a 600 miligramos del Compuesto I, por ejemplo de 100 miligramos a aproximadamente 400 miligramos. De una manera más preferible, las tabletas de acuerdo con la invención son tabletas que contienen 100 miligramos y/o tabletas que contienen 400 miligramos del Com-

puesto I.

De conformidad con lo anterior, la presente invención proporciona tabletas que contienen una cantidad del mesilato del Compuesto I, por ejemplo la forma de cristal alfa del mesilato del Compuesto I y/o la forma de cristal beta del mesilato del Compuesto I, igual a 100 miligramos y/o 400 miligramos de la base libre del Compuesto I. De una manera más preferible, la forma de mesilato del Compuesto I utilizada para la tableta de acuerdo con la invención, es la forma del cristal beta.

De acuerdo con la invención, el proceso para la preparación de las tabletas consiste en formar una fase interna, mezclarla junto con una fase externa, comprimir la mezcla obtenida, y opcionalmente recubrir la tableta.

La fase interna comprende al Compuesto I. De preferencia, la fase interna comprende al Compuesto I y uno o más excipientes, más preferiblemente uno o más aglutinantes, y de una manera muy preferible, la cantidad de uno o más aglutinantes en la fase interna está en el intervalo de aproximadamente el 1 al 30 por ciento, de preferencia del 1 al 20 por ciento, y más preferiblemente del 1 al 15 por ciento. Los aglutinantes de la fase interna de conformidad con la invención, de preferencia son celulosa microcristalina e hidroxipropilmetilcelulosa. La cantidad de celulosa microcristalina en la fase interna puede variar desde aproximadamente el

10 hasta el 29 por ciento, en particular del 12 al 14 por ciento en peso, basándose en el peso total de la tableta. La cantidad de hidroxipropilmetilcelulosa en la fase interna puede variar del 1 al 5 por ciento, de preferencia del 1 al 2 por ciento en peso, basándose en el peso total de la tableta. El Compuesto I y los excipientes farmacéuticamente aceptables de la fase interna, se mezclan junto con agua, y la mezcla se procesa para la granulación, por ejemplo utilizando un granulador húmedo de alto esfuerzo cortante, para formar los granulados húmedos. Entonces los granulados húmedos se pueden secar, por ejemplo utilizando una secadora de lecho fluido.

La presente invención pertenece a un proceso para la preparación de tabletas que comprenden una fase externa. La fase externa consiste en una mezcla de la fase interna con uno o más excipientes. La fase interna y uno o más excipientes de la fase externa se mezclan entre sí utilizando, por ejemplo, una mezcladora de difusión. De preferencia, se agregan uno o más aglutinantes. De una manera más preferible, se agrega celulosa microcristalina. Todavía más preferiblemente, la celulosa microcristalina se agrega en el intervalo del 1 al 10 por ciento en peso, basándose en el peso total de la tableta. En una modalidad preferida de la invención, en la fase externa, la cantidad de celulosa microcristalina es de alrededor del 5 por ciento en peso, basándose en el peso total de la tableta. La fase externa de conformidad

con la invención también puede contener uno o más desintegrantes, más preferiblemente Crospovidone®. En una modalidad preferida, la cantidad de desintegrante en la fase externa está en el intervalo de aproximadamente el 10 al 30 por ciento, de preferencia del 12 al 25 por ciento, y muy preferiblemente es de aproximadamente el 15 por ciento.

En un aspecto particular de la invención, se incorporan uno o más derrapantes en la fase externa.

De acuerdo con la invención, se incorporan uno o más lubricantes en la fase externa.

En un aspecto adicional de la invención, las tabletas se preforman mediante compresión de la mezcla de las fases interna y externa utilizando, por ejemplo, una prensa formadora de tabletas.

De una manera opcional, las tabletas se pueden recubrir, de preferencia como se describe posteriormente en la presente.

En una modalidad de la invención, el proceso para la preparación de una tableta comprende:

(a) formar una fase interna, lo cual comprende:

(i) mezclar el Compuesto I junto con excipientes farmacéuticamente aceptables,

(ii) granular en húmedo;

(b) formar una fase externa, lo cual comprende:

(iii) agregar excipientes farmacéuticamente

aceptables adicionales a la fase interna, y mezclar;

(c) formar la tableta mediante:

(iv) comprimir la mezcla obtenida en el paso (iii), y opcionalmente,

(d) recubrir.

De una manera más específica, en un aspecto, la presente invención proporciona un proceso que comprende:

(i) mezclar el Compuesto I y excipientes farmacéuticamente aceptables, por ejemplo uno o más aglutinantes, por ejemplo celulosa microcristalina, en una mezcladora de alto esfuerzo cortante;

(ii) agregar agua; someter a la mezcla a humedecimiento/amasado, por ejemplo en una mezcladora de alto esfuerzo cortante; tamizar utilizando un molino de tamiz con una hélice giratoria, y secar, por ejemplo, en una secadora de lecho fluidizado;

(iii)agregar excipientes farmacéuticamente aceptables, por ejemplo excipientes tamizados, tales como uno o más desintegrantes, por ejemplo Crospovidone®; uno o más aglutinantes, por ejemplo celulosa microcristalina; uno o más derrapantes, por ejemplo dióxido de silicio coloidal; y mezclar, por ejemplo en una mezcladora de difusión;

(iv) agregar excipientes farmacéuticamente aceptables, tales como uno o más lubricantes, por ejemplo estearato

de magnesio; tamizar, por ejemplo tamizar manualmente, por ejemplo a 900 micras; y mezclar, por ejemplo en una mezcladora de difusión;

(v) formar tabletas con la mezcla obtenida en el paso (iv) mediante compresión, por ejemplo en una prensa formadora de tabletas convencional, por ejemplo en una máquina formadora de tabletas excéntrica EK-0 Korsch, o en una máquina formadora de tabletas giratoria, de preferencia en una máquina giratoria, y

(vi) recubrir, por ejemplo en un recubridor de bandeja, por ejemplo Glatt, Accela.

"Núcleo" significa la fase del granulado (pasos (i) y (ii)) que incluye al fármaco activo del Compuesto I, y la fase externa que consiste en los excipientes.

"Peso total de la tableta" significa el peso de una tableta formada por las fases interna y externa del recubrimiento (en su caso).

De acuerdo con la invención, el proceso de recubrimiento se puede llevar a cabo a una baja temperatura, por ejemplo entre 30°C y 40°C, de preferencia entre 32°C y 39°C, más preferiblemente a una temperatura en el intervalo de alrededor de 35°C a alrededor de 38°C. El proceso de recubrimiento se puede llevar a cabo con una velocidad de rociado de preferencia en el intervalo de 30 a 105 gramos de dispersión

de recubrimiento por kilogramo de núcleos por hora, de preferencia de 35 a 105 gramos. De una manera sorprendente, se ha encontrado que si se hinchan los desintegrantes, por ejemplo la Crospovidone®, no se presenta adhesión de los núcleos durante el rociado de la mezcla de recubrimiento, como sería esperado por la persona experta en la materia, al procesar a bajas temperaturas.

Más aún, las tabletas exhiben una mejor resistencia a la abrasión. La estabilidad física y química se puede probar de una manera convencional, por ejemplo las tabletas se pueden probar como tales mediante la medición de la disolución, fragilidad, tiempo de desintegración, ensayo para determinar los productos de degradación del Compuesto I, apariencia y/o microscopio, por ejemplo después de su almacenamiento a temperatura ambiente, es decir, a 25°C, y/o su almacenamiento a 40°C.

La forma de los núcleos de tabletas puede variar, y pueden ser, por ejemplo, redondas, ovaladas, oblongas, cilíndricas, o con cualquier otra forma adecuada. Una característica de las tabletas de acuerdo con la invención es su tamaño pequeño, teniendo consideración de la cantidad del Compuesto I o de la sal del Compuesto I contenida en las mismas.

En una modalidad preferida de la invención, las tabletas obtenidas mediante el método de compresión descrito anteriormente, son redondas u ovaladas. Las orillas de las

tabletas se pueden biselar o redondear. De una manera más preferible, las tabletas son ovaladas y/o redondas. Las tabletas de conformidad con la invención se pueden marcar. La tableta ovalada puede ser de una dimensión pequeña, por ejemplo de 10 a 20 milímetros de longitud, de preferencia de 15 a 20 milímetros, más preferiblemente de 17 a 19 milímetros; de 5 a 10 milímetros de ancho, de preferencia de 6.5 a 8 milímetros. El grosor de la tableta es de 4 a 8 milímetros, de preferencia de 6 a 8 milímetros. Se emplean fuerzas de compresión de entre 10 y 20 kN para preparar la tableta comprimida; de preferencia de 12 a 18 kN. De una forma preferible, la tableta ovalada contiene 400 miligramos del Compuesto I. La tableta redonda puede ser de las siguientes dimensiones, por ejemplo, de 5 a 15 milímetros de diámetro, de preferencia de 7 a 10 milímetros, y de una manera más preferible, de aproximadamente 9 milímetros. El grosor de la tableta puede ser de 2 a 5 milímetros, de preferencia de 2.5 a 4 milímetros. Se emplean fuerzas de compresión de entre 6 y 18 kN para preparar la tableta comprimida, de preferencia de 8 a 14 kN. De una manera preferible, la tableta redonda contiene 100 miligramos del Compuesto I. De preferencia, la tableta de 100 miligramos es una tableta marcada, y más preferiblemente la tableta tiene una marca para romperse sobre un lado.

Las tabletas de la invención que comprenden aproximadamente 100 miligramos del Compuesto I pueden tener además

una dureza de aproximadamente 30 a 40 N, por ejemplo de 40 a 140 N, de 30 a 100 N, de 40 a 100 N, de preferencia de 50 a 80 N. Las tabletas de la invención que comprenden aproximadamente 400 miligramos del Compuesto I, pueden tener una dureza de 100 a 270 N, por ejemplo de 100 a 250 N, de 160 a 270 N, de 160 a 250 N, de preferencia de 195 a 235 N.

El tiempo de desintegración de la tableta puede ser de aproximadamente 20 minutos o menos. De preferencia, para la tableta de 100 miligramos del Compuesto I, el tiempo de desintegración está en el intervalo de aproximadamente 2 a 10 minutos, de preferencia de 4 a 10 minutos, por ejemplo de 4 a 8 minutos. Para la tableta de 400 miligramos del Compuesto I, el tiempo de desintegración de preferencia está en el intervalo de aproximadamente 7 a 15 minutos, de preferencia de 8 a 15 minutos, por ejemplo de 8 a 14 minutos.

La fragilidad de las tabletas se mide de acuerdo con la Farmacopea de Estados Unidos de Norteamérica. La fragilidad de las tabletas de acuerdo con la invención, monitoreada siguiendo la recomendación de la Farmacopea de Estados Unidos de Norteamérica, es del 0 por ciento.

Las tabletas de la invención pueden adicionalmente colorearse, y/o las tabletas o el recubrimiento se pueden marcar para impartir una apariencia individual y para hacerlas instantáneamente reconocibles. El uso de tintes puede servir para mejorar la apariencia así como para identificar

las tabletas. Los tintes adecuados para utilizarse en farmacia normalmente incluyen carotinoides, óxidos de hierro, o clorofila. Las tabletas de la invención se pueden marcar utilizando un código impreso.

Los procedimientos que se pueden emplear pueden ser los convencionales o conocidos en la materia, o se pueden basar en esos procedimientos, por ejemplo los descritos en L. Lachman y colaboradores, The Theory and Practice of Industrial Pharmacy, 3ª Edición, 1986, H. Sucker y colaboradores, Pharmazeutische Technologie, Thieme, 1991, Hagers Handbuch der pharmazeutischen Praxis, 4ª Edición (Springer Verlag, 1971), y Remington's Pharmaceutical Sciences, 13ª Edición (Mack Publ., Co.,1970) o las ediciones posteriores.

Las tabletas de la invención son útiles para la indicación humana del Compuesto I, por ejemplo para el tratamiento antitumoral, como se indica en las pruebas convencionales. La actividad y las características de las tabletas de la invención se pueden indicar en estudios clínicos convencionales y/o en estudios con animales.

Las tabletas de la invención son particularmente útiles para, por ejemplo, el tratamiento de desórdenes proliferativos no malignos y malignos, por ejemplo leucemias, gliomas, sarcomas, tumores de próstata, de mama, gastrointestinales, de pulmón, y de ovario.

Las tabletas de la invención que comprendan una

cantidad farmacológicamente efectiva del Compuesto I o de una sal del Compuesto I, se pueden administrar como el único fármaco activo, o con otro fármaco activo, por ejemplo junto con la administración simultánea o separada de otros fármacos.

Adicionalmente, las tabletas de la invención obtenidas son estables tanto en el proceso de producción como durante el almacenamiento, por ejemplo durante 2 años o incluso 3 años en el empaque convencional, por ejemplo en los paquetes de ampolla de aluminio sellados. Como se ha determinado en las pruebas convencionales, durante este tiempo se puede degradar menos de aproximadamente el 5 por ciento, por ejemplo el 2 ó 3 por ciento o menos del Compuesto I o de la sal del Compuesto I.

Las tabletas de la invención, por ejemplo, las tabletas de 100 y 400 miligramos, son bioequivalentes a las cápsulas de gelatina dura comerciadas (100 miligramos) del Compuesto I. La administración de 400 miligramos del Compuesto I en cápsulas de gelatina dura (4 x 100 miligramos) en la forma de una sola tableta recubierta con película, es bien tolerada.

Dependiendo de la edad, de la condición individual, del modo de administración, y del cuadro clínico en cuestión, se administran dosis efectivas, por ejemplo una dosificación diaria de las tabletas de la invención que comprenda, por ejemplo, de 100 a 1000 miligramos, por ejemplo de 100 a 800

miligramos, de preferencia de 100 a 600 miligramos, en especial 400 miligramos del Compuesto I, a pacientes de un peso corporal de aproximadamente 70 kilogramos.

La invención también se refiere a un método para administrar, a un sujeto humano que necesite dicho tratamiento, el Compuesto I o una sal farmacéuticamente aceptable del mismo en la forma de una tableta, una vez al día durante un período mayor a 3 meses. La invención se refiere en especial a este método en donde se administra una dosis diaria de 100 a 1000 miligramos, de preferencia de 100 a 800 miligramos, en especial de 200 a 600 miligramos, de preferencia 400 miligramos del Compuesto I a un adulto. Se entenderá que el nivel de dosificación específico para cualquier paciente particular dependerá de una variedad de factores, incluyendo la edad, el peso corporal, la salud general, la combinación del fármaco con uno o más fármacos activos, el tipo y severidad de la enfermedad.

De conformidad con lo anterior, en un aspecto adicional, la presente invención proporciona un método para el tratamiento de un sujeto, el cual comprende administrar una tableta de acuerdo con la invención, que comprenda una cantidad farmacológicamente efectiva de una sal del Compuesto I, a un sujeto que necesite dicho tratamiento, opcionalmente con la administración simultánea, en secuencia, o separada de otro fármaco, por ejemplo una ciclosporina, una rapamicina,

metilcelulosa[1]	(1.1)	2.500		3.500	
Celulosa microcristalina [3]	(1.1)	9.850		13.790	
Crospovidona	(1.2)	28.000		39.200	
Sílice coloidal anhidra/ dióxido de silicio coloidal	(1.3)	1.250		1.750	
Estearato de magnesio	(1.4)	1.400		1.960	
Recubrimiento básico de premezcla amarilla	(1.5)	7.125	8.550[4]	9.975	14.364[4]
Recubrimiento básico de premezcla roja	(1.5)	0.375	0.450[4]	0.525	0.756[4]
Peso total		**195.000**	**196.500**	**273.000**	**≈275.000**
Unidades/lote				**1,400,000**	

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[1] Componentes del granulado, [2] 119.5 miligramos del mesilato del Compuesto I son iguales a 100 miligramos de la base libre del Compuesto I, [3] Se agrega celulosa microcristalina en la fase externa como un aglutinante seco, [4] Se incluye un excedente de manufactura del 20 por ciento de la dispersión de recubrimiento, para cubrir cualesquiera pérdidas por rociado durante el paso del proceso de recubrimiento.

Se prepararon tabletas de 100 miligramos de la base libre del Compuesto I de acuerdo con la invención y de la tableta anterior, mediante la granulación húmeda de una mezcla

de la sal del Compuesto I con (1.1), mezcla con ^{3}(1.1), (1.2), (1.3), y (1.4), compresión y recubrimiento de las tabletas resultantes con una dispersión acuosa de la mezcla de recubrimiento (1.5).

El proceso de recubrimiento se puede llevar a cabo a una baja temperatura, por ejemplo en el intervalo de alrededor de 35°C a alrededor de 38°C. El proceso de recubrimiento se puede llevar a cabo con una velocidad de rociado de preferencia en el intervalo de 30 a 105 gramos de dispersión de recubrimiento por kilogramo de núcleos (el "núcleo" corresponde a las fases interna y externa comprimidas) por hora, por ejemplo, de 35 a 105 gramos por kilogramo de núcleos por hora.

Ejemplo 2: Formulación de Tableta (tableta de 400 miligramos.

Se prepararon tabletas de 400 miligramos del Compuesto I de acuerdo con la invención, y de la siguiente tableta, mediante la granulación húmeda de una mezcla de una sal del Compuesto I con (1.1),. mezcla con ^{3}(1.1), (1.2), (1.3), y (1.4), compresión y recubrimiento de las tabletas resultantes con una dispersión acuosa de la mezcla de recubrimiento (1.5).

Composición por forma de dosificación unitaria y cantidad por

lote.

Componente		Composición por unidad (mg)		Cantidad por lote (kg)	
Mesilato del Compuesto I[1]		[2]478.000		167.300	
Celulosa microcristalina[1]	(1.1)	100.000		35.000	
Hipromelosa/Hidroxipropil-metilcelulosa[1]	(1.1)	10.000		3.500	
Celulosa microcristalina [3]	(1.1)	39.400		13.790	
Crospovidona	(1.2)	112.000		39.200	
Sílice coloidal anhidra/ dióxido de silicio coloidal	(1.3)	5.000		1.750	
Estearato de magnesio	(1.4)	5.600		1.960	
Recubrimiento básico de premezcla amarilla	(1.5)	17.100	20.425[4]	5.985	8.588[4]
Recubrimiento básico de premezcla roja	(1.5)	0.900	1.075[4]	0.315	0.452[4]
Peso total		**768.000**	**771.500**	**268.800**	**≈270.000**
Unidades/lote					**350,000**

[1] Componentes del granulado, [2] 478 miligramos del mesilato del Compuesto I son iguales a 400 miligramos de la base libre del Compuesto I, [3] Se agrega celulosa microcristalina en la fase

externa como un aglutinante seco, [4] Se incluye un excedente de manufactura del 20 por ciento de la dispersión de recubrimiento, para cubrir cualesquiera pérdidas por rociado durante el paso del proceso de recubrimiento.

El proceso de recubrimiento se puede llevar a cabo a una baja temperatura, por ejemplo en el intervalo de alrededor de 35°C a alrededor de 38°C. El proceso de recubrimiento se puede realizar con una velocidad de rociado de preferencia en el intervalo de 30 a 105 gramos de dispersión de recubrimiento por kilogramo de núcleos (el "núcleo" corresponde a las fases interna y externa comprimidas) por hora, por ejemplo de 35 a 105 gramos por kilogramo de núcleos por hora.

Ejemplo 3: Dimensiones de las tabletas.

Base libre del Comp.I/tableta	**Forma y Dimensiones**
100 mg	Redonda, diámetro de 9.1 a 9.3 milímetros, curva, orillas biseladas, grosor: 2.8-3.4 milímetros, marca para romper sobre un lado.
400 mg	Ovalada, 18.1-18.3 x 7.2-7.4 milímetros, curva, orillas biseladas, grosor: 6.6-7.2 milíme-

tros.

Base libre del Comp.I/tableta	Forma y Dimensiones
100 mg	Redonda, diámetro de 9.1 a 9.4 milímetros, curva, orillas biseladas, grosor: 2.8-3.4 milímetros, marca para romper sobre un lado.
400 mg	Ovalada, 18.1-18.4 x 7.2-7.5 milímetros, curva, orillas biseladas, grosor: 6.6-7.2 milímetros.

REIVINDICACIONES

1. Una tableta que comprende una cantidad farmacológicamente efectiva del Compuesto I o una sal farmacéuticamente aceptable del mismo, en una cantidad de aproximadamente el 30 por ciento al 80 por ciento en peso de la fracción activa, basándose en el peso total de la tableta.

2. Una tableta, la cual comprende:

(a) una cantidad farmacológicamente efectiva del Compuesto I, y

(b) uno o más excipientes farmacéuticamente aceptables, adecuados para la preparación de las tabletas,

en donde el Compuesto I o la sal farmacéuticamente aceptable del mismo, está presente en una cantidad de aproximadamente el 30 por ciento al 80 por ciento en peso de la fracción activa, basándose en el peso total de la tableta.

3. Una tableta de acuerdo con la reivindicación 1 ó 2, en donde el Compuesto I o una sal farmacéuticamente aceptable del mismo, está presente en una cantidad de aproximadamente el 50 por ciento al 80 por ciento en peso de la fracción activa, basándose en el peso total de la tableta.

4. Una tableta de acuerdo con cualquiera de las reivindicaciones 1 a 3, en donde el Compuesto I está en la forma de la sal de monomesilato.

5. Una tableta de acuerdo con la reivindicación 4, en donde el monomesilato del Compuesto I está en la forma

del cristal beta del mismo.

6. Una tableta de acuerdo con cualquiera de las reivindicaciones 1 a 5, en donde el excipiente comprende cuando menos un aglutinante.

7. Una tableta de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde los excipientes comprenden:

cuando menos un aglutinante en una cantidad total de aproximadamente el 1 por ciento al 25 por ciento en peso, basándose en el peso total de la tableta,

cuando menos un desintegrante en una cantidad total de aproximadamente el 10 por ciento al 35 por ciento en peso, basándose en el peso total de la tableta,

cuando menos un derrapante en una cantidad total de aproximadamente el 0.5 por ciento al 3 por ciento en peso, basándose en el peso total de la tableta, y/o

cuando menos un lubricante en una cantidad total de aproximadamente el 0.5 por ciento al 2 por ciento en peso, basándose en el peso total de la tableta.

8. Una tableta de acuerdo con la reivindicación 6 ó 7, en donde el aglutinante comprende celulosa microcristalina o hidroxipropilmetilcelulosa, o una mezcla de las mismas.

9. Una tableta de acuerdo con la reivindicación 7 u 8, en donde el desintegrante comprende polivinilpirrolidinona reticulada.

10. Una tableta de acuerdo con cualquiera de las reivindicaciones 7 a 9, en donde el derrapante comprende dióxido de silicio coloidal y/o sílice coloidal anhidra.

11. Una tableta de acuerdo con cualquiera de las reivindicaciones 7 a 10, en donde el lubricante comprende estearato de magnesio.

12. Un proceso para la preparación de una tableta de acuerdo con cualquiera de las reivindicaciones anteriores, cuyo proceso comprende:

(i) mezclar el Compuesto I o las sales farmacéuticamente aceptables del mismo y los excipientes farmacéuticamente aceptables;

(ii) granular en húmedo;

(iii)mezclar con los excipientes farmacéuticamente aceptables para formar una mezcla; y

(iv) comprimir la mezcla obtenida en el paso (iii) para formar una tableta.

13. El proceso de acuerdo con la reivindicación 12, en donde la tableta se recubre.

14. Una tableta de acuerdo con cualquiera de las reivindicaciones 1 a 11, preparada mediante un proceso de granulación húmeda.

15. Un método para el tratamiento de un sujeto, el cual comprende administrar una tableta de acuerdo con cualquiera de las reivindicaciones 1 a 11 ó 14, la cual comprende

una cantidad farmacológicamente efectiva del Compuesto I, a un sujeto que necesite dicho tratamiento.

RESUMEN

PCT

REQUEST

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

For receiving Office use only

PCT/EP 03 / 04 151
International Application No.

22 APR 2003 (22.04.03)
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 -32460A

Box No. I TITLE OF INVENTION

High drug load tablet

Box No. II APPLICANT ☐ This person is also inventor

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

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This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

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

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

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

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

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Sheet No. ...2...

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

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

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

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

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State *(that is, country)* of nationality: FR

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This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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

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

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State *(that is, country)* of nationality: DE

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This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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

Applicant's registration No. with the Office

State *(that is, country)* of nationality: DE

State *(that is, country)* of residence: DE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☐ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

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☐ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

RO/EP

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

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

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

☒ NI Nicaragua	☐	☐
☐	☐	☐

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

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

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

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

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

(v) If, in Box No. 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.

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) 23 April 2002 (23.04.02)	0209265.8 /	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	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) in paper form, the following number of sheets:

request (including declaration sheets)	:	6
description (excluding sequence listings and/or tables related thereto)	:	13
claims	:	2
abstract	:	1
drawings	:	0
Sub-total number of sheets	:	22
sequence listings	:	
tables related thereto	:	
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)		
Total number of sheets	:	22

(b) ☐ only in computer readable form (Section 801(a)(i))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

(c) ☐ also in computer readable form (Section 801(a)(ii))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

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)

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
1. ☒ fee calculation sheet	:	1
2. ☒ original separate power of attorney	:	1
3. ☐ original general power of attorney	:	
4. ☒ copy of general power of attorney; reference number, if any: AV 38671 + 46171	:	2
5. ☐ statement explaining lack of signature	:	
6. ☒ priority document(s) identified in Box No. VI as item(s): (1)	:	1
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listings in computer readable form *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column	:	
10. ☐ tables in computer readable form related to sequence listings *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:	
11. ☐ other *(specify)*:	:	

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

11.04.2003

GRUBB, Philip AV 38671 + 46171

For receiving Office use only

1. Date of actual receipt of the purported international application: (22.04.03) 22 APR 2003
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 November 2003 (06.11.2003)

PCT

(10) International Publication Number
WO 03/090720 A1

(51) International Patent Classification[7]: A61K 9/16, 9/26, 9/28, 47/32, 47/38, 31/505

(21) International Application Number: PCT/EP03/04151

(22) International Filing Date: 22 April 2003 (22.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0209265.8 23 April 2002 (23.04.2002) GB

(71) Applicant *(for all designated States except AT, US)*: NOVARTIS AG [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LUFTENSTEINER, Christian-Peter [AT/DE]; Am Rheinpark 2, 79576 Weil am Rhein (DE). BIANCHI, Jean-Claude [FR/FR]; Rue Kellergruben, 68730 Blotzheim (FR). OGORKA, Jörg [DE/DE]; Im Steinbrunnen 19/3, 79585 Steinen (DE). KALB, Oskar [DE/DE]; Belchenstrasse 9, 79539 Lörrach (DE).

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

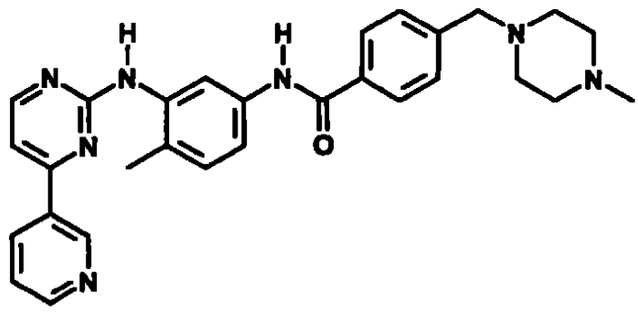
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG,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

Published:
— *with international search report*

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

(54) Title: HIGH DRUG LOAD TABLET



(I)

(57) Abstract: The present invention pertains to a high drug load tablet comprising as active ingredient Compound I of Formula (I) or a pharmaceutically acceptable salt thereof in an amount from about 30% to 80% in weight of the active moiety based on the total weight of the tablet.

WO 03/090720 A1

(4)
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23.09.2003
4-32460A
Vinca Lardans

VT
PCT
EP03/04151

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
NOVARTIS AG
Corporate Intellectual Property
Attn. Grubb, Philip
CH-4002 Basel
SWITZERLAND

Corporate Intellectual Property
23. Juli 2003
APPL. | M/D | F/L | PS | Copy:

	Date of mailing *(day/month/year)* 23/07/2003
Applicant's or agent's file reference 4-32460A	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP 03/04151	International filing date *(day/month/year)* 22/04/2003
Applicant NOVARTIS AG	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Panayota Georgakopoulou

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 48.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

(4)
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
4-32460A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 03/ 04151	22/04/2003	23/04/2002
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 6 sheets.

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

1. **Basis of the report**

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

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

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

   [ ] contained in the international application in written form.

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

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

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

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

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

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

4. With regard to the title,

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

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

5. With regard to the abstract,

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

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

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

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/04151

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/26 A61K9/28 A61K47/32 A61K47/38 A61K31/505

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, MEDLINE, BIOSIS, 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.
Y	WO 99 03854 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); BUERGER HANS MICHA) 28 January 1999 (1999-01-28) cited in the application page 17, paragraph 2 page 18, paragraph 1 example 4 — 4-30096	1-15
Y	WO 01 47507 A (NOVARTIS ERFINDUNGEN ;NOVARTIS AG (CH); LECOUTRE PHILIPP (DE); GAM) 5 July 2001 (2001-07-05) See formula III page 18, paragraph 2 page 34, paragraphs 2,3 page 35, paragraph 1 example 8 — 4-31244	1-15

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 July 2003	23/07/2003

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

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

INTERNATIONAL SEARCH REP RT

International Application No
PCT/EP 03/04151

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 564 409 A (CIBA GEIGY AG) 6 October 1993 (1993-10-06) cited in the application page 13, line 45 - line 52 page 14, line 1 - line 4 examples 32,33	1-15

4-19046

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

International Application No. PCT/EP 03 04151

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 15 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.

Continuation of Box I.1

Claims Nos.: 15

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/04151

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. [X] Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/04151

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9903854 A	28-01-1999	AU 740713 B2	15-11-2001
		AU 8975998 A	10-02-1999
		BR 9810920 A	15-08-2000
		CN 1264375 T	23-08-2000
		WO 9903854 A1	28-01-1999
		EP 0998473 A1	10-05-2000
		HU 0003230 A2	28-06-2001
		JP 3276359 B2	22-04-2002
		JP 2001510192 T	31-07-2001
		NO 20000227 A	17-01-2000
		NZ 502295 A	21-12-2001
		PL 338129 A1	25-09-2000
		SK 432000 A3	12-06-2000
		TR 200000060 T2	21-09-2000
		TW 491845 B	21-06-2002
		US 2002115858 A1	22-08-2002
		ZA 9806362 A	22-01-1999
WO 0147507 A	05-07-2001	IT MI992711 A1	27-06-2001
		AU 2171901 A	09-07-2001
		BR 0016817 A	01-10-2002
		CA 2394944 A1	05-07-2001
		CN 1414858 T	30-04-2003
		WO 0147507 A2	05-07-2001
		EP 1250140 A2	23-10-2002
EP 0564409 A	06-10-1993	AT 188964 T	15-02-2000
		AU 3569493 A	07-10-1993
		BR 1100739 A3	06-06-2000
		CA 2093203 A1	04-10-1993
		CN 1077713 A ,B	27-10-1993
		CZ 9300560 A3	16-02-1994
		DE 59309931 D1	24-02-2000
		DK 564409 T3	19-06-2000
		EP 0564409 A1	06-10-1993
		ES 2142857 T3	01-05-2000
		FI 931458 A	04-10-1993
		GR 3032927 T3	31-07-2000
		HU 64050 A2	29-11-1993
		IL 105264 A	11-04-1999
		JP 2706682 B2	28-01-1998
		JP 6087834 A	29-03-1994
		KR 261366 B1	01-08-2000
		LU 90908 A9	30-04-2003
		MX 9301929 A1	29-07-1994
		NO 931283 A	04-10-1993
		NZ 247299 A	26-07-1995
		PT 564409 T	30-06-2000
		RU 2125992 C1	10-02-1999
		SG 43859 A1	14-11-1997
		SK 28093 A3	06-04-1994
		US 5521184 A	28-05-1996
		ZA 9302397 A	04-10-1993

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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/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

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

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference: 4 -32460A
International application No.: PCT/EP 03/04151	International filing date *(day/month/year)*: 22 April 2003 (22.04.03)	(Earliest) Priority date *(day/month/year)*: 23 April 2002 (23.04.02)
Title of invention: High drug load tablet		

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No. / Facsimile No. / Teleprinter No. / Applicant's registration No. with the Office
Novartis AG Lichtstrasse 35 4056 Basel CH	+4161 324 11 11 +4161 322 75 32

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CH	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:	State *(that is, country)* of residence:
AT	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.)*

LUFTENSTEINER, Christian-Peter
Am Rheinpark 2
79576 Weil am Rhein
DE

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

☒ Further applicants are indicated on a continuation sheet.

Sheet No. 2.

International application No.
PCT/EP 03/04151

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.)*

BIANCHI, Jean-Claude
Rue Kellergraben
68730 Blotzheim
FR

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

OGORKA, Jörg
Im Steinbrunnen 19/3
79585 Steinen
DE

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

KALB, Oskar
Belchenstrasse 9
79539 Lörrach
DE

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

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

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/EP 03/04151

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

The following person is [X] agent [ ] common representative

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

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

[X] 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:

   [X] the international application as originally filed

   the description
   [X] as originally filed
   [ ] as amended under Article 34

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

   the drawings
   [ ] as originally filed
   [ ] as amended under Article 34

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

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

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

Language for the purposes of international preliminary examination: English

[X] 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.

[X] which is the language of publication of the international application.

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

Box No. V ELECTION OF STATES

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

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

Sheet No. .4.

International application No.
PCT/EP 03/04151

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:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

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

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

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

25.07.2003

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.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

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CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/EP 03/04151	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 4 -32460A	Date stamp of the IPEA

Applicant
Novartis AG et al.

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	EUR 1530.–	P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	EUR 159.–	H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1689.– TOTAL		

MODE OF PAYMENT

- [X] authorization to charge deposit account with the IPEA (see below)
- [ ] cash
- [ ] cheque
- [ ] revenue stamps
- [ ] postal money order
- [ ] coupons
- [ ] bank draft
- [ ] other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT
(This mode of payment may not be available at all IPEAs)

IPEA/ EP

- [X] Authorization to charge the total fees indicated above.
- [X] *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 2811 0031

Date: 25.07.2003

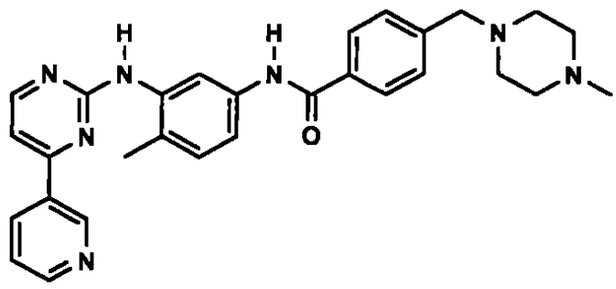
Name: Novartis AG

Signature: S. Gaus

Form PCT/IPEA/401 (Annex) (March 2001; reprint January 2003) *See Notes to the fee calculation sheet*

CLAIMS:

1. A tablet comprising a pharmacologically effective amount of Compound I of formula (1)



or a pharmaceutically acceptable salt thereof in an amount from about 30% to 80% in weight of the active moiety based on the total weight of the tablet.

2. A tablet according to claim 1 wherein Compound I of formula (1) or a pharmaceutically acceptable salt thereof is present in an amount from about 50% to 80% in weight of the active moiety based on the total weight of the tablet.

3. A tablet according to claim 2 wherein Compound I of formula (1) is in the monomesylate salt form.

4. A tablet according to claim 3 wherein Compound I of formula (1) monomesylate is in the beta crystal form thereof.

5. A tablet according to any one of claims 1 to 4 wherein the tablet comprises one or more pharmaceutically acceptable excipients suitable for the preparation of tablets.

6. A tablet according to claim 5 wherein the excipient comprises at least one binder.

7. A tablet according to claims 5 wherein the excipients comprise:

at least one binder in a total amount of about 1% to 25% in weight based on the total weight of the tablet,

at least one disintegrant in a total amount of about 10% to 35% in weight based on the total weight of the tablet

at least one glidant in a total amount of about 0.5% to 3% in weight based on the total weight of the tablet, and/or

at least one lubricant in a total amount of about 0.5% to 2% in weight based on the total weight of the tablet.

8. A tablet according to claim 6 or 7 wherein the binder comprises microcrystalline cellulose or hydroxypropylmethyl cellulose or a mixture thereof.

9. A tablet according to claim 7 wherein the disintegrant comprises cross-linked polyvinylpyrrolidinone.

10. A tablet according to claim 7 wherein the glidant comprises colloidal silicon dioxide and/or colloidal anhydrous silica.

11. A tablet according to claim 7 wherein the lubricant comprises magnesium stearate.

12. A process for the preparation of a tablet according to any one of the preceding claims, which process comprises

(i) mixing the Compound I of formula (1) or pharmaceutically acceptable salts thereof and pharmaceutically acceptable excipients;

(ii) wet-granulating;

(iii) mixing with pharmaceutically acceptable excipients to form a mixture; and

(iv) compressing the mixture obtained in step (iii) to form a tablet.

13. The process according to claim 12 wherein the tablet is coated.

14. A tablet according to any one of claims 1 to 11 prepared by a wet-granulation process.

15. A method of treating a subject which comprises administering a tablet according to any one of claims 1 to 11 or 14 comprising a pharmacologically effective amount of Compound I of formula (1) to a subject in need of such a treatment.

PATENT COOPERATION TREATY

VL

Corporate Intellectual Property
29. Aug. 2003 1C59
APPL. | M/D | F/L. | PS | Copy:

PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	27.08.2003
Applicant's or agent's file reference 4-32460A	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP03/04151	22.04.2003	23.04.2002

Applicant
NOVARTIS AG

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

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

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

4. **REMINDER**

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

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

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

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Longo, E Tel. +49 89 2399-8141

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32460A	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP03/04151	International filing date *(day/month/year)* 22.04.2003	Priority date *(day/month/year)* 23.04.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/16		
Applicant NOVARTIS AG		

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 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

Date of submission of the demand	Date of completion of this report
28.07.2003	27.08.2003
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 Giménez Miralles, J Telephone No. +49 89 2399-8655

Form PCT/IPEA/409 (Cover Sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATI N REPORT

International application No. PCT/EP03/04151

I. 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

1-15 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/EP03/04151

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. 15 as to IA

   because:

   ☒ the said international application, or the said claims Nos. 15 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	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-15
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Present claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT, namely a method for the therapeutic treatment of the human or animal body. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT). (See Item V-3 below).

Re Item V

1) Reference is made to the following documents:

D1: WO-A-99 03854 (NOVARTIS AG)

D2: WO-A-01 47507 (NOVARTIS AG)

2) The present application appears to comply with the requirements of Article 33(2) and (3) PCT.

The closest prior art (D1 or D2) discloses directly compressed 100 mg tablets of imatinib mesylate ("Gleevec™) containing ca. 22% w/w of the active agent based on the total weight of the tablet. 100 mg capsules containing ca. 31% w/w of the active agent are also disclosed.

The technical problem is to provide tablets having higher doses of the active agent (e.g. 400 mg which is the usual daily dose), i.e. tablets comprising ca. 50% w/w of active agent. Stable tablets overcoming problems of high friability and poor abrasion resistance are obtained by first granulating the active agent with microcrystalline cellulose and/or HPMC (wet granulation), and then compressing the granulate together with further excipients into tablets (dragée cores). The solution is not obvious in the light of the prior art, which does not address the

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 04111533 00000000 Folios: 64
Fecha (AMD): 2004-11-05 16:16 22
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: PROM DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ **MODELO DE UTILIDAD**	( )	(✓)
Indicación de que se solicita la concesión de una patente	( )	(✓)
Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(✓)
Descripción de la invención.	( )	(✓)
Dibujos de ser estos pertinentes<	( )	(✓)
Comprobante de pago de las tasas establecidas		
COMPLETA ( ) **INCOMPLETA**	( )	( )
DISEÑO INDUSTRIAL ( )		
Indicación de que se solicita el registro de Diseño Industrial	( )	( )
Datos de identificación del solicitante o de la persona que 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 Claudia M Nieto

Fecha

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO

MANTENIMIENTO DE PROTOCOLOS

Número : 17398
Fecha : 16/04/1997
Conferido: NOVARTIS AG (NOVARTIS SA) (NOVARTIS INC.)

Pais : CH SUIZA
Ciudad : 3 BASILEA
Represent: S Sustituir : S Desistir : S
No. Radicación : 97 19953 Clase: 0 Seev: 0 Seac: 0

scncia	Codigo Ctr	Nombre
1	5376	ESCOBAR URIBE JIMENA
2	267	ESCOBAR URIBE IGNACIO

Encontrados (1/1) registro(s)

670

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá D C

Doctor(a)
JIMENA ESCOBAR URIBE
Apoderado(a)
NOVARTIS AG.

Oficio N°
10589

ASUNTO:

Radicación N°	04-111533
Solicitud internacional	PCT/EP03/04151
Fecha inicio fase nacional	23/11/2004
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 traducción de las reivindicaciones, tal como fueron modificadas . (Numeral 5.2.5 capítulo quinto del título décimo de la Circular Unica de la SIC)
- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).
- El solicitante debe presentar un nuevo título, que permita identificar la materia de la cual trata la solicitud, ya que el relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente (Regla 4.3 PCT, Art. 27, 27 Decisión 486, Circular Única 5.2.9).

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,
19 NOV. 2004

202044

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