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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señor Superintendente
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

Trámite : 011
Evento : 378
Actuación : 412

Referencia : Expediente No. 07.090.237
Asunto : Solicitud de patente para: **COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE LA SAL DEL ÁCIDO P-TOLUENSULFÓNICO DE LA METILAMIDA DEL ÁCIDO 4{4-[3-(4-CLORO-3-TRIFLUOROMETILFENIL)-UREIDO]-FENOXI}-PIRIDIN-2-CARBOXÍLICO Y PROCESO PARA PREPARAR LA MISMA**
Solicitante : BAYER SCHERING PHARMA AG
Fecha solicitud : 03 de septiembre de 2007

I. RECURSO VÍA GUBERNATIVA

Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad **BAYER SCHERING PHARMA AG** solicitante de la patente de la referencia, por el presente escrito atentamente manifiesto a usted que debidamente notificada de la Resolución No. **49983** del 24 de agosto de 2012, interpongo en su contra el recurso de **REPOSICIÓN**, para que sea revocada y en consecuencia se conceda el privilegio de patente de invención para **"COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE LA SAL DEL ÁCIDO P-TOLUENSULFÓNICO DE LA METILAMIDA DEL ÁCIDO 4{4-[3-(4-CLORO-3-TRIFLUOROMETILFENIL)-UREIDO]-FENOXI}-PIRIDIN-2-CARBOXÍLICO Y PROCESO PARA PREPARAR LA MISMA"** a favor de **BAYER SCHERING PHARMA AG**.

II. OPORTUNIDAD DE LA IMPUGNACIÓN

La Resolución No. **49983** del 24 de agosto de 2012, fue publicada mediante listado único fijado el once (11) de septiembre de dos mil doce (2012) y con vencimiento del once (11) de octubre de 2012, por lo que el término para interponer el recurso de reposición vence el

diecinueve (19) de octubre de dos mil doce (2012). En consecuencia, me encuentro dentro de la oportunidad legal.

III. LA DECISIÓN RECURRIDA

3.1 Mediante la Resolución objeto de la presente impugnación, el Superintendente de Industria y Comercio decidió:

3.1.1 Denegar la patente de invención a la creación titulada: **“COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE LA SAL DEL ÁCIDO P-TOLUENSULFÓNICO DE LA METILAMIDA DEL ÁCIDO 4{4-[3-(4-CLORO-3-TRIFLUOROMETILFENIL)-UREIDO]-FENOXI}-PIRIDIN-2-CARBOXÍLICO Y PROCESO PARA PREPARAR LA MISMA”**

3.2 En la parte motiva de la providencia, se mencionaron los siguientes fundamentos:

3.2.1 “Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1, porque divulgan el compuesto metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico y su sal tosilato, y la forma como puede ser formulado en tabletas.

3.2.2 “El documento D1 enseña que la metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico puede formularse en composiciones farmacéuticas orales como tabletas con uno o más diluyentes usando el proceso de granulación y conteniendo otros excipientes. Como excipientes señala que se pueden utilizar como diluyentes preparaciones de celulosas, como desintegrante carboximetilcelulosa sádica, como aglutinante hidroxipropilmetil-celulosa, como lubricante estearato de magnesio, entre otros (párrafo [0033]). Adicionalmente enseña que el fármaco para composiciones en dosis unitaria puede estar en concentración de 20% a 90% (párrafo [0030]).

3.2.3 “La diferencia entre la invención, definida en la reivindicación 1 y la composición del documento D2 consiste en que el documento D2 no revela específicamente una composición que contenga el compuesto sal tosilato de la metilamida del ácido 4{4-[3-(4-cloro-3 trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico.

- 3.2.4 "No se evidencia un efecto técnico inesperado logrado por el hecho de formular una tableta de liberación inmediata que contenga la sal tosilato de la metilamida del ácido 4{4-[3-(4-cloro-3 trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico.
- 3.2.5 "Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: "Cómo formular una tableta de liberación inmediata que contenga la sal tosilato de la metilamida del ácido 4{4-[3-(4-cloro-3 trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico revelada en D2".
- 3.2.6 "Sin embargo, el documento D1 revela que el compuesto metilamida del ácido 4{4-[3-(4-cloro-3 trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico puede ser formulado en composiciones que lo contengan en concentración de 20% a 90%, y establece los excipientes que pueden ser usados para formularlo en una composición oral.
- 3.2.7 "[...] En consecuencia, la persona del oficio normalmente versada en la materia, se vería motivada por lo revelado en el documento D1 a formular una tableta que contenga el compuesto sal tosilato de la metilamida del ácido 4{4-[3-(4-cloro-3 trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico (revelada en el documento D2) en la proporciones establecidas, porque estas son las proporciones en las que se usan normalmente estas auxiliares de formulación⁸. reivindicación se considera obvia y sin altura inventiva.
- 3.2.8 "El documento D3 se considera el estado de la técnica cercano a la invención definida en la reivindicación 8, porque divulga que el proceso de granulación en húmedo es el método más general y más ampliamente utilizado de preparación de comprimidos (Pág. 2481 columna de la izquierda).
- 3.2.9 "La publicación enseña que inicialmente se deben mezclar el componente activo, el diluyente y el desintegrante (Pág. 2481, columna de la derecha) también enseña que la masa del polvo se humedece con la solución aglutinante hasta que adquiere la consistencia de nieve húmeda (Pág. 2482, columna de la izquierda). Adicionalmente enseña diferentes métodos para granular la mezcla (usando molinos trituradores o por medio de granulación en lecho fluido) (Pág. 2482-2485) y que después de la granulación se agrega el lubricante en forma de polvo fino (Pág. 2484 columna de la derecha y Pág. 2485 columna de la izquierda), para luego comprimir la mezcla.

También enseña que después de la compresión los comprimidos se recubren con una película de base acuosa (Pág. 2485 columna de la derecha).

- 3.2.10 “La diferencia entre la invención, definida en la reivindicación 8 y el procedimiento revelado en D3 consiste en que la presente solicitud reclama específicamente un procedimiento para fabricar una composición farmacéutica en la que el principio activo es la sal tosilato de la metilamida del ácido 4{4-[3-(4- cloro-3-trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico.
- 3.2.11 “Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: Cómo modificar el proceso revelado en D3 para obtener una composición que contenga la sal del ácido p-toluensulfónico de la metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-fenoxi}-piridin-2- carboxílico”.
- 3.2.12 “Sin embargo, el documento D2 revela la sal del ácido p-toluensulfónico de la metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico, composiciones que la contienen y establece que las composiciones orales pueden ser preparadas por métodos conocidos en el estado del arte (Pág. 18 líneas 3-15, ejemplo 42 y reivindicaciones 35-37).
- 3.2.13 “En consecuencia, la persona del oficio normalmente versada en la materia, incluiría la sal divulgada en D2 al proceso de D3 para llegar así al objeto de la reivindicación 8 de la solicitud, por lo cual se considera obvia, dado que corresponde a la aplicación de medios técnicos conocidos para preparar formulaciones de compuestos equivalentes terapéuticos sin que por ello se pueda concluir que hay un efecto inesperado.

IV. OBJETO DEL RECURSO

De acuerdo con los argumentos que expongo a continuación, solicito atentamente a su Despacho lo siguiente: .

1. Revocar la Resolución No. **49983** del 24 de agosto de 2012.
2. Conceder el privilegio de patente de invención para **“COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE LA SAL DEL ÁCIDO P-TOLUENSULFÓNICO DE LA METILAMIDA DEL ÁCIDO 4{4-[3-(4-CLORO-3-TRIFLUOROMETILFENIL)-UREIDO]-**

FENOXY-PIRIDIN-2-CARBOXÍLICO Y PROCESO PARA PREPARAR LA MISMA” a favor de BAYER SCHERING PHARMA AG.

V. FUNDAMENTOS DEL RECURSO

Respetuosamente me permito disentir de lo expuesto por ese Despacho en la Resolución objeto del presente recurso, toda vez que la presente solicitud sí cumple con el requerimiento de nivel inventivo exigido en la Decisión 486, como se demostrará a continuación:

5.1 La presente solicitud sí tiene nivel inventivo

A pesar de lo anterior y con el fin de demostrar que la presente solicitud cumple no sólo con el requerimiento de novedad (como se demostró en respuesta al oficio No. 57) sino también con el requerimiento de nivel inventivo, se pone de presente lo siguiente:

El artículo 18 de la Decisión 486 señala lo siguiente:

Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.

Consecuentemente, una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo, para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

Respecto a lo anterior, el Tribunal de Justicia de la Comunidad Andina ha expuesto en la Interpretación Prejudicial del proceso 13-IP-2010:

"En este orden de ideas, se puede concluir que una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no es consecuencia clara y directa de dicho estado".

[señalado fuera del texto]

Por lo anterior, se entiende que para que una persona medianamente versada en la materia pudiera derivar de manera obvia una invención, requeriría simplemente aplicar sus conocimientos técnicos. En contraste, todo aquello que va más allá de la simple aplicación de los conocimientos técnicos y que no ha sido revelado en el estado de la técnica, debe ser considerado inventivo.

A este respecto, respetuosamente manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos atentamente la reconsideración de las razones por las cuales se decidió negar la patente, con base en la siguiente información:

En primer lugar, deseamos llamar la atención del Examinador en cuanto al error tipográfico presentado para la definición del documento D1, el cual se indicó en el numeral 8.2 de la Resolución acá impugnada como WO9615128, pero que según el título, los argumentos y definiciones, corresponde al documento D1 previamente citado, es decir **US 2003125359**. Por consiguiente los argumentos presentados en esta oportunidad harán referencia a este último documento y no al documento señalado por el Examinador como D1, el cual además no se relaciona con el campo técnico de la invención.

Ahora bien, las reivindicaciones de la presente invención definen una tableta de liberación inmediata que comprende la sal tosilato de la metil amida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico, es decir la sal tosilato de sorafenib (INN).

Por lo tanto, la diferencia de la presente solicitud respecto al documento D1 mencionado es que D1 no revela la sal tosilato de sorafenib sino solamente sorafenib como una base. Adicionalmente D1 no revela una tableta de liberación inmediata o sugiere si quiera una

tableta para dicha sustancia activa y mucho menos un proceso para su preparación. D1 solamente contiene una descripción general sobre los ingredientes empleados en una formulación farmacéutica. Así, no existe en D1 una motivación o guía respecto a la preparación de una tableta, en particular una tableta de liberación inmediata. Por otra parte, no hay indicaciones respecto a ningún tipo de sal a ser empleado ni en general ni en particular, tal como la sal tosilato de sorafenib.

Si la persona medianamente versada en la materia parte del documento D1 como el estado de la técnica más cercano, tendría primero que seleccionar la sal adecuada de sorafenib. A este respecto D2 no provee ninguna ayuda, toda vez que D2 no revela la sal tosilato de sorafenib específicamente, sino únicamente de manera general. La reivindicación 35 de D2 contiene una lista muy larga de posibles sales y depende de una reivindicación que comprende un alto número de compuestos. Esto significa que la persona medianamente versada en la materia tiene que realizar varias elecciones que son: seleccionar el compuesto adecuado y seleccionar la sal adecuada, a partir de las listas mencionadas. No existe además una enseñanza específica o sugerencia que lleve a la persona medianamente versada en la materia a seleccionar la sal tosilato en D2 o D1 y tampoco hay sugerencias en dichos documentos que indiquen que dicha sal es preferida.

Aún si la persona medianamente versada en la materia hubiese seleccionado tosilato de sorafenib como sustancia activa, tendría además que seleccionar la formulación adecuada que es aplicable para una liberación efectiva del ingrediente activo. Existe una gran cantidad de posibilidades tales como líquido, tabletas, polvos, gránulos, formulación retardada, cápsulas, etc. No obstante, no existen sugerencias en D1 o D2 sobre una tableta de liberación inmediata como la forma preferida. Existe por lo tanto una gran cantidad de trabajo a ser realizado, es decir, la elección de la sal adecuada para el medicamento y posteriormente la elección de la formulación adecuada.

En el caso menos probable que la persona medianamente versada en la materia hubiese seleccionado una tableta de liberación inmediata para el ingrediente activo, no existen indicaciones en D1 y D2 sobre el contenido de dicho ingrediente activo y en qué forma. D1 solamente enseña la base de sorafenib pero no indica nada sobre la sal tosilato. La persona medianamente versada en la materia debe entonces encontrar el rango correcto de dosis y forma del medicamento que permite una liberación inmediata de la tableta.

De manera sorprendente, la tableta de la presente invención muestra una liberación inmediata del ingrediente activo, tal como se demuestra en los resultados experimentales anteriormente presentados. Los cuales, consideramos son una prueba relevante del efecto técnico sorpresivo e inesperado de la presente solicitud.

Por otra parte, respecto a los comentarios del Examinador se puede establecer lo siguiente:

- El Examinador considera que el párrafo [0030] de D1 revela una tableta que contiene sorafenib en una proporción de 20 a 90%. Esto no es correcto. El párrafo [0030] solamente menciona una composición farmacéutica y no indica el tipo de composición farmacéutica y mucho menos el ingrediente activo que deberá ser contenido. Este párrafo solamente hace referencia al "inhibidor apropiado". Esto sin embargo, podría indicar todos los inhibidores RAF-MEK-ERK como se enseña en el párrafo [0028] de D1. Por lo tanto, no existe una enseñanza como la que afirma el Examinador.
- Lo mismo aplica para D2, segundo cuadro de la tabla 1 bajo el encabezado "D2". Como se explicó anteriormente, las reivindicaciones 35 a 37 de D2 solamente contienen listas muy largas de compuestos y sales posibles pero no revelan específicamente la sal tosilato de sorafenib y mucho menos una tableta que contiene sorafenib. En consecuencia, las afirmaciones en este sentido no son correctas.
- El Examinador no está en lo correcto cuando establece que se esperaría que las tableras que contienen la sal tosilato se desintegren más rápido que la tableta que contiene la base de sorafenib. Ninguno de los documentos citados revela la solubilidad de sorafenib o de la sal tosilato de sorafenib. Así, la persona medianamente versada en la materia no tendría ninguna indicación sobre qué podría esperarse. Esto es un indicio de análisis en retrospectiva por parte del Examinador. Adicionalmente, la solubilidad y la desintegración de una tableta son parámetros diferentes y no pueden compararse directamente. La persona medianamente versada en la materia esperaría lo contrario, por cuanto la celulosa microcristalina es conocida como un muy buen desintegrante, independientemente de su solubilidad. La persona medianamente versada en la materia esperaría que la tableta con una mayor cantidad de desintegrante se desintegraría más rápido. No existe ninguna indicación en el estado de la técnica sobre las propiedades de desintegración de sorafenib o de la sal tosilato de sorafenib. De manera sorprendente se

ha encontrado que la tableta que contiene la sal tosilato se desintegra más rápido. Esto no podía ser esperado y demuestra el nivel inventivo de la presente solicitud.

- No resulta revelante cuál era la materia inicialmente contenida en el pliego reivindicatorio sino el alcance del pliego reivindicatorio actual el que debe ser discutido. En consecuencia, los comentarios en relación con la materia inicial resultan irrelevantes.

5.2 Conclusión

El documento D1, el documento D2 o su combinación, no resultan anterioridades válidas capaces de afectar el nivel inventivo de la tableta de liberación inmediata de la presente solicitud.

Por lo tanto, consideramos que el Examinador está pasando por alto el hecho de que el inventor en el momento de solucionar el problema técnico de la solicitud tuvo que emplear habilidad inventiva, pues la presente invención no resulta de la mera extrapolación de las enseñanzas del arte previo, como se afirma. Se está desconociendo el mérito investigativo empleado y que está aportando una ventaja al arte previo.

Dicho mérito investigativo ha sido reconocido por distintas oficinas internacionales de patentes, quienes han otorgado el privilegio de patente para una invención equivalente. Tal es el caso de las oficinas de patentes de Europa, patente No. EP 1 868 579 B1 (de la cual se adjunta copia para mejor referencia), Taiwán, patente No. TWI324928 (B), Marruecos, patente No. MA29378 (B1), Rusia, patente No. 283 (C2) y Australia, patente No. AU2006222365 (B2).

Por todo lo anterior, consideramos que la presente solicitud cumple a cabalidad con los requerimientos de patentabilidad exigidos por la legislación actual, por lo que atentamente solicitamos en consideración lo siguiente:

VI. PETICIÓN

Por todo lo anterior, solicito a ese Despacho lo siguiente:

6.1 Que al considerar las razones precedentes se revoque la decisión contenida en la Resolución No. **49983** del 24 de agosto de 2012, en cuanto resuelve negar el privilegio de patente de invención.

6.2 Que se otorgue el privilegio de patente de invención para: que sea revocada y en consecuencia se conceda el privilegio de patente de invención para **"COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE LA SAL DEL ÁCIDO P-TOLUENSULFÓNICO DE LA METILAMIDA DEL ÁCIDO 4{4-[3-(4-CLORO-3-TRIFLUOROMETILFENIL)-UREIDO]-FENOXI}-PIRIDIN-2-CARBOXÍLICO Y PROCESO PARA PREPARAR LA MISMA"** a favor de **BAYER SCHERING PHARMA AG.**

VII. NOMBRE Y DIRECCIÓN

El nombre y la dirección de la solicitante recurrente son los siguientes:

BAYER SCHERING PHARMA AG

Muellerstrasse 178,
13353 Berlín,
Alemania

VIII. NOTIFICACIONES

Atentamente manifiesto a usted que recibiré notificaciones en la Secretaría de su Despacho o en mi oficina de abogada situada en la Carrera 4ª. No. 72-35, piso 4º, de esta ciudad de Bogotá, D.C.

IX. ANEXOS

Copia de la patente Europea EP 1 868 579 B1.

Señor Superintendente,


LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555

COLO-15846-0845-023-0
COLO-14033-841-050-3
JMS\JMS\ID-228190\WPC15846
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(11) **EP 1 868 579 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

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of the grant of the patent:
29.09.2010 Bulletin 2010/39

(51) Int Cl.:
A61K 9/20 (2006.01) **A61K 9/22** (2006.01)
A61K 9/36 (2006.01) **A61K 31/4412** (2006.01)
A61P 35/00 (2006.01)

(21) Application number: **06707141.5**

(86) International application number:
PCT/EP2006/001574

(22) Date of filing: **22.02.2006**

(87) International publication number:
WO 2006/094626 (14.09.2006 Gazette 2006/37)

(54) **PHARMACEUTICAL COMPOSITION COMPRISING AN OMEGA-CARBOXYARYL SUBSTITUTED
DIPHENYL UREA FOR THE TREATMENT OF CANCER**

PHARMAZEUTISCHE ZUSAMMENSETZUNG MIT EINEM OMEGA-CARBOXYARYL-
SUBSTITUIERTEN DIPHENYLHARNSTOFF ZUR BEHANDLUNG VON KREBS

COMPOSITION PHARMACEUTIQUE COMPRENANT UNE DIPHÉNYLURÉE SUBSTITUÉE PAR UN
OMÉGA-CARBOXYARYLE POUR LE TRAITEMENT DU CANCER

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI
SK TR**
Designated Extension States:
AL BA HR MK

(56) References cited:
WO-A-2005/009367 US-A1- 2003 125 359
US-A1- 2003 207 872

(30) Priority: **07.03.2005 US 658827 P**

(43) Date of publication of application:
26.12.2007 Bulletin 2007/52

(73) Proprietor: **Bayer Schering Pharma
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(72) Inventors:
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• **WOLLENSCHLÄGER, Axel**
51467 Bergisch Gladbach (DE)

(74) Representative: **Heiner, Thomas et al**
Bayer Schering Pharma AG
Patents and Licensing
Müllerstrasse 178
13353 Berlin (DE)

- **WILHELMSCOTT METAL: "BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis" CANCER RESEARCH, vol. 64, no. 19, 1 October 2004 (2004-10-01), pages 7099-7109, XP002384320 ISSN: 0008-5472**
- **AHMAD T ET AL: "Kinase inhibition with BAY 43-9006 in renal cell carcinoma" CLINICAL CANCER RESEARCH, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 10, no. 18 Pt 2, 19 March 2004 (2004-03-19), pages 6388S-6392S, XP002362669 ISSN: 1078-0432**
- **KRAMER BORIS W ET AL: "Use of mitogenic cascade blockers for treatment of C-Raf induced lung adenoma in vivo: CI-1040 strongly reduces growth and improves lung structure." BMC CANCER [ELECTRONIC RESOURCE]. 1 JUN 2004, vol. 4, 1 June 2004 (2004-06-01), page 24, XP002384321 ISSN: 1471-2407**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 868 579 B1

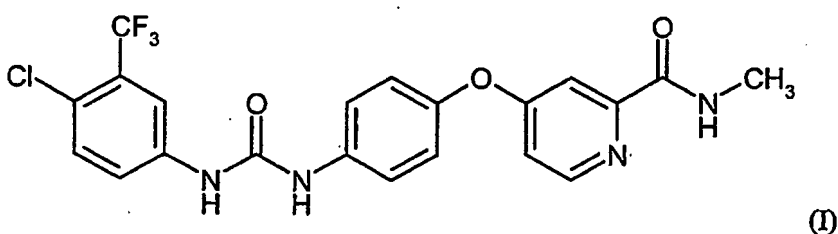
Description

Field of the Invention

5 [0001] This invention relates to novel pharmaceutical compositions and their use for treating hyper-proliferative disorders such as cancer, either as a sole agent or in combination with other anti-cancer therapies and their process for preparing.

Background of the Invention

10 [0002] Diarylureas are a class of serine-threonine kinase inhibitors as well as tyrosine kinase inhibitors known in the art (Smith et al., Bioorg. Med. Chem. Lett. 2001, 11, 2775-2778, Lowinger et al., Clin. Cancer Res. 2000, 6(suppl.), 335, Lyons et al., Endocr.-Relat. Cancer 2001, 8, 219-225, Lowinger et al., Curr. Pharm. Design 2002, 8, 99-110). Omega-Carboxyaryl diphenyl ureas are disclosed in WO00/42012 and WO00/41698. In particular, it has been discovered that
15 the diphenyl urea of formula (I),



also referred as "BAY 43-9006" or 4-{4-[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]-amino]phenoxy}-N-methylpyridine-2-carboxamide, and its pharmaceutically acceptable salts are potent inhibitors of raf, VEGFR-2, p38, and
30 PDGFR kinases. These enzymes are all molecular targets of interest for the treatment of hyper-proliferative diseases, including cancer. Therefore, the compound of formula (I) will be used as medicine for the treatment of the above mentioned diseases.

[0003] US 2003/0125359 describes the use of RAF-MEK-ERK pathway inhibitors like BAY 43-9006 for the treatment of chronic myelogenous leukemia. Several possible pharmaceutical compositions are described comprising tablets,
35 capsules, syrups, suspensions or solutions, e.g. for injection.

[0004] Despite the progress described in the art with regard to kinase inhibitors, there remains a need for improved medicines for the treatment of cancer. In particular, there remains a need for improved oral pharmaceutical compositions which can be taken in easily and therefore would increase the patient's compliance. The oral pharmaceutical composition has to provide a plasma level of the active agent which is sufficient for an effective therapy. This is dependent on the
40 solubility and the release behavior of the active agent. In the case of a solid pharmaceutical composition the dissolution properties and chemical and mechanical stability are of importance. In order to support a high compliance the oral pharmaceutical composition should not have to be taken in more than three times a day, the less the better, and in the case of a tablet the dimensions of the tablet should not be too large to allow a good swallowing. The dimensions of a tablet are dependent on the amount of the active agent needed for an effective therapy and the amounts of the excipients.
45 Type and amount of the excipients in combination with the process for preparing are essential for release properties, bioavailability of the compound in mammals, stability and the industrial applicability of the manufacturing process of the pharmaceutical composition.

[0005] The objective of the present invention is to provide a pharmaceutical composition comprising the compound of formula (I) which should be applied no more than three times a day in order to achieve an effective plasma level of the compound of formula (I). In the case of a tablet or capsule as oral pharmaceutical composition it should not be too
50 large to provide good swallowing and no more than two should have to be taken in at the same time.

Description of the Invention

55 [0006] The present invention pertains to a pharmaceutical composition comprising the compound of the formula (I) in a high concentration and at least one pharmaceutically acceptable excipient, the use of the composition for the treatment of hyper-proliferative diseases, such as cancer, either as a sole agent, or in combination with other anti-cancer therapies, and the process for preparing of said composition.

[0007] Surprisingly the pharmaceutical composition according to the invention has a good bioavailability of the compound of the formula (I), and an effective plasma level is achieved. Furthermore the pharmaceutical composition according to the invention provides a good stability of the compound of the formula (I).

[0008] Although the tablets according to the invention are high concentrated on the compound of the formula (I), they surprisingly show good release properties, good bioavailability, high stability and a sufficient hardness. Due to the fact that the pharmaceutical composition according to the invention comprises the compound of the formula (I) in a high concentration dimensions of the composition can be realized which allow a good swallowing of the composition. Therefore the pharmaceutical composition can be taken in easily and supports a high compliance.

[0009] The term "the compound of formula (I)", "active agent" or "the compound of this invention" does not only refer to 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide as depicted in Formula I, but also refers to its polymorphs, solvates, hydrates, pharmaceutically acceptable salts, or a combination thereof.

[0010] Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid (tosylate salt), 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include salts of inorganic bases, such as salts containing alkaline cations (e.g., Li⁺ Na⁺ or K⁺), alkaline earth cations (e.g., Mg⁺², Ca⁺² or Ba⁺²), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

[0011] Solvates for the purposes of the invention are those forms of the compounds where solvent molecules form a complex in the solid state and include, but are not limited to for example ethanol and methanol. Hydrates are a specific form of solvates, where the solvent molecule is water.

[0012] Preferably used in the pharmaceutical composition according to the invention is the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide (tosylate salt of compound (I)). More preferably the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]phenoxy}-pyridine-2-carboxylic acid methyl amide exists for at least 80% in the stable polymorph I. Most preferably the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide exists for at least 80% in the stable polymorph I and in a micronized form.

[0013] Micronization can be achieved by standard milling methods, preferably by air chat milling, known to a skilled person. The micronized form can have a mean particle size of from 0.5 to 10 µm, preferably from 1 to 6 µm, more preferably from 1 to 3 µm. The indicated particle size is the mean of the particle size distribution measured by laser diffraction known to a skilled person (measuring device: HELOS, Sympatec).

[0014] The process for preparing the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide and its stable polymorph I are described in the patent applications EP 04023131.8 and EP 04023130.0.

[0015] The inventive pharmaceutical composition comprises the compound of formula (I) in a portion of at least 40%, preferably at least 45%, more preferably at least 50, most preferably at least 55% by weight of the composition.

[0016] Preference is given to a pharmaceutical composition comprising the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide in a portion of at least 55%, preferably at least 62%, more preferably at least 69%, most preferably at least 75% by weight of the composition.

[0017] The total amount of the active ingredient (compound of Formula I) to be administered preferably via the oral route using the pharmaceutical composition of the present invention will generally range from about 0.1 mg/kg to about 50 mg/kg body weight per day. Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the pharmaceutical compositions of this invention can readily be determined by those skilled in the art. The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

[0018] Preference is given to an amount of the compound of formula (I) in the pharmaceutical composition from 20 to 2000 mg, preferably from 40 to 800 mg, more preferably from 50 to 600 mg.

[0019] Particular preference is given to an amount of *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide in the pharmaceutical composition from 27 to 2740

mg, preferably from 54 to 1096, more preferably from 68 to 822 mg.

[0020] The pharmaceutical composition according to the invention is administered one or more, preferably up to three, more preferably up to two times per day. Preference is given to an administration via the oral route. With each administration the number of tablets or capsules taken in at the same time should not exceed two.

5 [0021] Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behavior toward the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

10 [0022] This pharmaceutical composition will be utilized to achieve the desired pharmacological effect by preferably oral administration to a patient in need thereof, and will have advantageous properties in terms of drug release, bioavailability, and/or compliance in mammals. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease.

15 [0023] The pharmaceutical composition comprises suitable administration forms which deliver the compound of the invention in a rapid manner, for example tablets (uncoated or coated tablets), tablets which disintegrate rapidly in the oral cavity or capsules optionally filled with granules (for example hard or soft gelatin capsules), sugar-coated tablets, powders, sachets, granules, pellets, dragées, chewable tablets, dispersible tablets, troches and lozenges.

[0024] Preference is given to tablets, granules, capsules optionally filled with granules, pellets, dragées, chewable tablets, dispersible tablets, troches and lozenges. More preferably the application forms are tablets, granules and capsules optionally filled with granules. Most preferably the application form is a tablet.

20 [0025] The tablet according to the invention shows for example a hardness of more than 80 N, preferably more than or equal to 100 N.

[0026] The pharmaceutical composition according to the invention preferably a tablet or a capsule has dimensions which allows good swallowing. Good swallowing depends also on the used format. The longest dimension for example of an oval tablet or capsule is less than or equal to 25 mm. For example a round tablet should have a diameter less than or equal to 13 mm.

[0027] The pharmaceutical composition according to the invention shows good release properties. Furthermore preference is given to administration forms wherein the compound of the invention is delivered in a rapid manner also known as "immediate release" administration form. According to the present invention immediate release administration forms having a Q-value (30 minutes) of 75% due to USP-release method with device 2 (paddle, 75 rpm, in 0.1M HCl + 1% sodium dodecylsulfate).

30 [0028] The pharmaceutical composition according to the invention is stable for more than 18 months.

[0029] A pharmaceutically acceptable excipient is any excipient which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the excipient do not vitiate the beneficial effects of the active ingredient. Pharmaceutically acceptable excipients according to the invention are for example disintegrants, binders, lubricants, fillers, plasticizers, surfactants and wetting agents, film-forming agents and coating materials, and coloring agents for example pigments.

35 [0030] Disintegrants include, but are not limited to croscarmellose sodium, crospovidone, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, microcrystalline cellulose, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycolate, partially hydrolysed starch, sodium carboxymethyl starch and starch. Preference is given to croscarmellose sodium and/or cross-linked polyvinylpyrrolidone, more preference is given to croscarmellose sodium.

[0031] The amount of the disintegrant contained in the pharmaceutical composition can be from 0 to 15%, preferably from 5 to 12% by the total weight of the composition.

45 [0032] Binders include, but are not limited to hydroxypropyl cellulose, hypromellose (hydroxypropyl methylcellulose, HPMC), microcrystalline cellulose, acacia, alginic acid, carboxymethylcellulose, ethylcellulose, methylcellulose, hydroxyethylcellulose, ethylhydroxyethylcellulose, polyvinyl alcohol, polyacrylates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, polyvinyl pyrrolidone and pregelatinized starch. Preference is given to a hydrophilic binder which are soluble in the granulation liquid, more preference is given to hypromellose (hydroxypropyl methylcellulose, HPMC) and/or polyvinylpyrrolidone, most preference is given to hypromellose.

[0033] The amount of the binder contained in the pharmaceutical composition can be from 0 to 15%, preferably from 0.5 to 8% by the total weight of the composition.

55 [0034] Lubricants include, but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid, fumaric acid, sodium stearyl fumarate, zinc stearate and polyethyleneglycol. Preference is given to magnesium stearate.

[0035] The amount of the lubricant contained in the pharmaceutical composition can be from 0 to 2%, preferably from 0.2 to 0.8% by the total weight of the composition.

[0036] Fillers include, but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline

cellulose, silicated microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, magnesium trisilicate, mannitol, maltitol, sorbitol, xylitol, lactose for example the anhydrous form or the hydrate form such as the monohydrate form, dextrose, maltose, saccharose, glucose, fructose or maltodextrine, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate and starch. Preference is given to microcrystalline cellulose, mannitol, lactose and/or dicalcium phosphate, more preference is given to microcrystalline cellulose.

[0037] The amount of the filler contained in the pharmaceutical composition can be from 0 to 60%, preferably from 3 to 20 % by the total weight of the composition.

[0038] Surfactants and Wetting agents include, but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, polyoxyethylene stearate, polyoxyethylene sorbitan monolaurate, benzalkonium chloride, nonoxynol 10, octoxynol 9, polysorbates for example 20, 40, 60 or 80, sorbitan mono-palmitate, sodium salts of fatty alcohol-sulfates such as sodium lauryl sulfate, sodium dodecylsulfate, sodium salts of sulfosuccinates such as sodium dioctylsulfosuccinate, partially esters of fatty acids with alcohols such as glycerine monostearate, partially esters of fatty acids with sorbitans such as sorbitan monolaurate, partially esters of fatty acids with polyhydroxyethylene sorbitans such as polyethyleneglycol sorbitan monolaurate, -monostearate or -monooleate, ethers of fatty alcohols with polyhydroxyethylene, esters of fatty acids with polyhydroxyethylene, copolymers of ethylenoxide and propylenoxide (Pluronic®) and ethoxylated triglycerides. Preference is given to sodium lauryl sulfate.

[0039] The amount of the surfactant contained in the pharmaceutical composition can be from 0 to 5 %, preferably from 0.1 to 2 % by the total weight of the composition.

[0040] Film-forming agents and coating materials include, but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose, HPMC), methylcellulose, ethylcellulose, cellulose acetate phthalate, shellac, polyvinylpyrrolidone, copolymers of vinylpyrrolidone and vinylacetate such as Kollidon® VA64 BASF, copolymers of acrylic-and/or methacrylic acid esters with trimethylammoniummethylacrylate, copolymers of dimethylaminomethacrylic acid and neutral methacrylic acid esters, polymers of methacrylic acid or methacrylic acid esters, copolymers of acrylic acid ethylester and methacrylic acid methyl ester, and copolymers of acrylic acid and acrylic acid methylester. Preference is given to hydroxypropyl methylcellulose (hypromellose, HPMC) as film-forming agent.

[0041] Plasticizers include, but are not limited to polyethylene glycol, diethyl phthalate and glycerol. Preference is given to polyethylene glycol.

[0042] Coloring agents include, but are not limited to pigments, inorganic pigments, FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel, ferric oxide red, ferric oxide yellow and titanium dioxide. Preference is given to ferric oxide red, ferric oxide yellow and titanium dioxide. Further commonly used pharmaceutical excipients which can be used as appropriate to formulate the composition for its intended route of administration include, but is not limited to: Acidifying agents for example acetic acid, citric acid, fumaric acid, hydrochloric acid and nitric acid; alkalinizing agents for example ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine and triethylamine; adsorbents for example powdered cellulose and activated charcoal; stabilizers and antioxidants for example ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate and sodium metabisulfite; other binding materials for example block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers; buffering agents for examples potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate hydrates; encapsulating agents for example gelatin, starch and cellulose derivatives); flavorants, masking agents and odors for example anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin; humectants for example glycerol, propylene glycol and sorbitol; sweeteners for example aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose; anti-adherents for example magnesium stearate and talc; direct compression excipients for example dibasic calcium phosphate, lactose and microcrystalline cellulose; tablet polishing agents for example carnauba wax and white wax.

[0043] Preference is given to a pharmaceutical composition comprising the compound of the formula (I) in a portion of at least 40%, a filler in a portion of from 0 to 60 %, a disintegrant in a portion of from 0 to 15 %, a binder in a portion of from 0 to 15 %, a lubricant in a portion of from 0 to 2 % and a surfactant in a portion of from 0 to 5 % by weight of the composition.

[0044] Also preference is given to a pharmaceutical composition comprising the p-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide in a portion of at least 55%, microcrystalline cellulose as a filler in a portion of from 0 to 60 %, croscarmellose sodium as a disintegrant in a portion of from 0 to 15 %, hypromellose as a binder in a portion of from 0 to 15 %, magnesium stearate as a lubricant in a portion of from 0 to 2 % and sodium lauryl sulfate as a surfactant in a portion of from 0 to 5 % by weight of the composition.

[0045] Particular preference is given to a pharmaceutical composition comprising the compound of the formula (I) in a portion of at least 55%, a filler in a portion of from 3 to 20 %, a disintegrant in a portion of from 5 to 12 %, a binder in a portion of from 0.5 to 8 %, a lubricant in a portion of from 0.2 to 0.8 % and a surfactant in a portion of from 0.1 to 2 %

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by weight of the composition.

[0046] Also particular preference is given to a pharmaceutical composition comprising the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}pyridine-2-carboxylic acid methyl amide in a portion of at least 75%, microcrystalline cellulose as a filler in a portion of from 3 to 20 %, croscarmellose sodium as a disintegrant in a portion of from 5 to 12 %, hypromellose as a binder in a portion of from 0.5 to 8 %, magnesium stearate as a lubricant in a portion of from 0.2 to 8 % and sodium lauryl sulfate as a surfactant in a portion of from 0.1 to 2 % by weight of the composition.

[0047] The pharmaceutical composition according to the invention comprising water in an amount of less than or equal to 6 %, preferably less than or equal to 3 %, more preferably less than or equal to 1.5 % by weight of the composition. The water content of the composition is determined by the Karl-Fischer method which is known to a skilled person.

Process for manufacturing

[0048] The present invention also relates to a process for the manufacturing of a solid and oral pharmaceutical composition according to the invention, wherein the compound of formula (I) is blended with at least one pharmaceutically acceptable excipient.

[0049] Preference is given to a process for the manufacturing of a solid and oral pharmaceutical composition according to the invention, wherein

a) the compound of formula (I) and at least one pharmaceutically acceptable excipient are wet granulated,

b) the granulate is blended with the lubricant and optionally with one or more further pharmaceutically acceptable excipient,

c) the post blend granulate is subdivided into single units ,

d) and the product of step c) is optionally coated with one or more further pharmaceutically acceptable excipients.

Step a: Wet granulation

[0050] The compound of formula (I), the filler, preferably microcrystalline cellulose, the binder, preferably hypromellose, the wetting agent, preferably sodium lauryl sulfate and optionally the disintegrant, preferably croscarmellose sodium are granulated in the granulation liquid in terms of a wet granulation. The granulation process is finished when the granulate achieves a "snow ball like consistency". The wet granulation mass is optionally sized and then dried in a suitable device for example in a fluidized bed dryer at an inlet air temperature at a range from 50 to 120 °C, preferably from 80 to 100 °C until a residual moisture of less than or equal to 3 % preferably then or equal to 1.5 % (loss on drying) is reached. The dry granules are optionally sieved for example using a sieve size from 1 to 2 mm.

[0051] The wet granulation process can be carried out in a high-shear mixer or in a fluidized bed granulator, preferably in a high-shear mixer for wet granulation. The compound of formula (I) can be initially charged as solid in the receiver or is dissolved and/or suspended in the granulation liquid.

[0052] Preference is given to a wet granulation process wherein the wetting agent is first dissolved in the granulation liquid and then the blend comprising the compound of formula (I), the filler, the binder and a portion of the disintegrant is added. The blend is mixed before granulation for 1 to 10 minutes, preferably for 1 to 5 minutes.

[0053] Alternatively the wetting agent can be added to the dry blend and/or the binder can be dissolved and/or suspended in the granulation liquid.

[0054] In the wet granulation process the amount of the granulation liquid is preferably from 40 to 70 %, more preferably from 50 to 60 % by weight of the dry powder blend.

[0055] Preferably the compound of formula (I) is used in the crystalline form, more preferably in a micronized form. The micronized form can have a mean particle size of from 0.5 to 10 µm, preferably from 1 to 6 µm, more preferably from 1 to 3 µm.

[0056] The wet granulation mass is preferably sized through a rasp from 2 to 8 mm, preferably from 4 to 6 mm.

[0057] Solvents such as granulation liquids and film-coating liquids include, but are not limited to ethanol, acetone, glycerol, isopropanol, purified water and mixtures thereof. Preferably the granulation liquids are purified water, ethanol, acetone or mixtures thereof, more preferably purified water.

[0058] Preference is given to a process for the manufacturing of a solid and oral pharmaceutical composition according to the invention, wherein the disintegrant is partly used in the granulation process described under a) and the blending process described under b). More preferably an amount of the disintegrant from 3 to 6 % by the total weight of the composition is used in step a) and the remaining is used in step b).

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Step b: Blending

[0059] The granulate is blended with the lubricant, preferably magnesium stearate and with the remaining disintegrant, preferably croscarmellose sodium, using a suitable device for example a tumbler blender for from 5 to 10 minutes.

Step c: Subdividing/Tablet compression

[0060] The blend is subdivided into single units and further processed to the desired administration form known to the person skilled in the art for example filling into sachets or capsules. Optionally one or more further pharmaceutically acceptable excipients are added. Preferably the blend is subdivided into single units and compressed to tablets using for example a standard rotary tablet press at typical tableting speeds of 25,000 - 250,000 tablets / hour.

Step d: Film-coating

[0061] The product of step c) is coated with one or more further pharmaceutically acceptable excipients.

[0062] Preference is given to a process for the manufacturing of a solid and oral pharmaceutical composition according to the invention, wherein the one or more further pharmaceutically acceptable excipients is selected from the group of plasticizer, film-forming agents and colorants. The plasticizer, preferably polyethylene glycol, the film-forming agent, preferably hypromellose and the colorants, preferably ferric oxide red and/or yellow, are combined with film-coating liquids, preferably purified water to result in a homogeneous coating suspension which is brought up to, preferably sprayed on the product of step c), preferably on the tablets in a suitable coating device for example a perforated drum coater. Other pigments or water soluble dyes or combinations thereof can be used to modify the color of the coating.

[0063] Alternative methods for manufacture of a solid oral pharmaceutical composition according to the invention are:

- The compound of formula (I) and at least one pharmaceutically acceptable excipient are blended without granulation and directly compressed to tablets or filled into capsules or sachets. Further excipients may be utilized to result in the formulation. Optionally, the product can be coated with one or more further pharmaceutically acceptable excipients.

[0064] The compound of formula (I) alone or the compound of formula (I) and at least one pharmaceutically acceptable excipient are treated by a dry granulation method and then compressed to tablets or filled into capsules or sachets. Further excipients may be utilized in the formulation. Optionally, the product can be coated with one or more further pharmaceutically acceptable excipients.

Method of treating hyper-proliferative disorders

[0065] The present invention also relates to a method for using the pharmaceutical composition according to the invention to treat mammalian hyper-proliferative disorders, including cancer. This method comprises administering the pharmaceutical composition preferably via the oral route to a mammal in need thereof, including a human, an amount which is effective to treat the disorder. The term "hyper-proliferative disorders" and/or "cancer" not only refers to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases, but also includes lymphomas, sarcomas, and leukemias.

[0066] Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma *in situ*, and lobular carcinoma *in situ*.

[0067] Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

[0068] Examples of brain cancers include, but are not limited to brain stem and hypophtalamic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

[0069] Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

[0070] Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small intestine, and salivary gland cancers.

[0071] Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

[0072] Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

[0073] Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with

or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

[0074] Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

[0075] Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer.

[0076] Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

[0077] Sarcomas include, but are not limited to sarcoma of the soft tissue, fibrosarcoma, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

[0078] Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

[0079] These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering the pharmaceutical compositions of the present invention. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Combination therapy

[0080] The pharmaceutical compositions of this invention can be administered as the sole agent or in combination with one or more other therapies where the combination causes no unacceptable adverse effects. For example, they can be combined with cytotoxic agents, signal transduction inhibitors, or with other anti-cancer agents or therapies, as well as with admixtures and combinations thereof.

[0081] In one embodiment, the pharmaceutical compositions of the present invention can be combined with cytotoxic anti-cancer agents. Examples of such agents can be found in the 11th Edition of the Merck Index (1996). These agents include, by no way of limitation, asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycin), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

[0082] Other cytotoxic drugs suitable for use with the pharmaceutical compositions of the invention include, but are not limited to, those compounds acknowledged to be used in the treatment of neoplastic diseases in Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ninth Edition, 1996, McGraw-Hill). These agents include, by no way of limitation, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

[0083] Other cytotoxic anti-cancer agents suitable for use in combination with the compositions of the invention also include newly discovered cytotoxic principles such as oxaliplatin, gemcitabine, capecitabine, epothilone and its natural or synthetic derivatives, temozolomide (Quinn et al., J. Clin. Oncology 2003, 21(4), 646-651), tositumomab (Bexxar), trabectedin (Vidal et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3181), and the inhibitors of the kinesin spindle protein Eg5 (Wood et al., Curr. Opin. Pharmacol. 2001, 1, 370-377).

[0084] In another embodiment, the pharmaceutical compositions of the present invention can be combined with other signal transduction inhibitors. Of particular interest are signal transduction inhibitors which target the EGFR family, such as EGFR, HER-2, and HER-4 (Raymond et al., Drugs 2000, 60 (Suppl.1), 15-23; Harari et al., Oncogene 2000, 19 (53), 6102-6114), and their respective ligands. Examples of such agents include, by no way of limitation, antibody therapies such as Herceptin (trastuzumab), Erbitux (cetuximab), and penuzumab. Examples of such therapies also include, by no way of limitation, small-molecule kinase inhibitors such as ZD-1839 / Iressa (Baselga et al., Drugs 2000, 60 (Suppl. 1), 33-40), OSI-774 / Tarceva (Pollack et al. J. Pharm. Exp. Ther. 1999, 291(2), 739-748), CI-1033 (Bridges, Curr. Med. Chem. 1999, 6, 825-843), GW-2016 (Lackey et al., 92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 4582), CP-724,714 (Jani et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3122), HKI-272 (Rabindran et al., Cancer Res. 2004, 64, 3958-3965), and EKB-569 (Greenberger et al., 11th NCI-EORTC-AACR Symposium on New Drugs in Cancer Therapy, Amsterdam, November 7-10, 2000, abstract 388).

[0085] In another embodiment, the pharmaceutical compositions of the present invention can be combined with other signal transduction inhibitors targeting receptor kinases of the split-kinase domain families (VEGFR, FGFR, PDGFR, flt-3, c-kit, c-fms, and the like), and their respective ligands. These agents include, by no way of limitation, antibodies such as Avastin (bevacizumab). These agents also include, by no way of limitation, small-molecule inhibitors such as STI-571 / Gleevec (Zelebail, Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs 2000, 2(1), 74-82), PTK-787 (Wood et al., Cancer Res. 2000, 60(8), 2178-2189), SU-11248 (Demetri et al., Proceedings of the American Society for Clinical

Oncology 2004, 23, abstract 3001), ZD-6474 (Hennequin et al., 92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 3152), AG-13736 (Herbst et al., Clin. Cancer Res. 2003, 9, 16 (suppl 1), abstract C253), KRN-951 (Taguchi et al., 95th AACR Meeting, Orlando, FL, 2004, abstract 2575), CP-547,632 (Beebe et al., Cancer Res. 2003, 63, 7301-7309), CP-673,451 (Roberts et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3989), CHIR-258 (Lee et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 2130), MLN-518 (Shen et al., Blood 2003, 102, 11, abstract 476), and AZD-2171 (Hennequin et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 4539).

[0086] In another embodiment, the pharmaceutical compositions of the present invention can be combined with inhibitors of the Raf/MEK/ERK transduction pathway (Avruch et al., Recent Prog. Horm. Res. 2001, 56, 127-155), or the PKB (akt) pathway (Lawlor et al., J. Cell Sci. 2001, 114, 2903-2910). These include, by no way of limitation, PD-325901 (Sebolt-Leopold et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 4003), and ARRY-142886 (Wallace et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3891).

[0087] In another embodiment, the pharmaceutical compositions of the present invention can be combined with inhibitors of histone deacetylase. Examples of such agents include, by no way of limitation, suberoylanilide hydroxamic acid (SAHA), LAQ-824 (Ottmann et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3024), LBH-589 (Beck et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3025), MS-275 (Ryan et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 2452), and FR-901228 (Piekarczyk et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3028).

[0088] In another embodiment, the pharmaceutical compositions of the present invention can be combined with other anti-cancer agents such as proteasome inhibitors, and m-TOR inhibitors. These include, by no way of limitation, bortezomib (Mackay et al., Proceedings of the American Society for Clinical Oncology 2004, 23, Abstract 3109), and CCI-779 (Wu et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3 849).

[0089] Generally, the use of cytotoxic and/or cytostatic anti-cancer agents in combination with the pharmaceutical compositions of the present invention will serve to:

(1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered agents,

(3) provide for a chemotherapeutic treatment protocol that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(7) provide a longer time for tumor progression, and/or

(8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects. It is believed that one skilled in the art, using the preceding information and information available in the art, can utilize the present invention to its fullest extent.

[0090] The weight data are, unless stated otherwise, percentages by weight and parts are parts by weight.

Examples:

Example 1: Immediate release tablet containing the tosylate salt of compound of formula (I) and optionally subsequent film-coating

1.1 Composition of tablets containing the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenoxy)-pyridine-2-carboxylic acid methyl amide (tosylate salt of compound (I))

[0091]

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	Composition [mg/ tablet]	Tablet A 50 mg	Tablet B 200 mg	Tablet C 200 mg	Tablet D 400 mg
5	Tablet core:	step a), b)	step a), b), c) ii	Step a), b) c) i	Step a), b) c) i
	Tosylate salt of compound (I) micronized	68.5 mg	274.0 mg	274.0 mg	548.0 mg
10	Microcrystalline cellulose	4.0 mg	16.0 mg	16.0 mg	32.0 mg
	Croscannellose sodium	9.1 mg	36.4 mg	36.4 mg	72.8 mg
	Hypromellose (5 cP)	2.55 mg	10.2 mg	10.2 mg	20.4 mg
15	Magnesium stearate	0.425 mg	1.7 mg	2.55 mg ^{#1} (1.70 - 2.55 mg)	5.10 mg
	Sodium lauryl sulfate	0.425 mg	1.7 mg	1.7 mg	3.4 mg
	Weight	85.0 mg	340.0 mg	340.85 mg (340.0 - 340.85 mg)	681.70 mg
20	Film-coating:				
	Opadry Red YS2-15531 ^{#3}	----	10.0 mg	--#2--	--#2--
	Hypromellose (15 cP)	----	----	6.00 mg (4.8 - 7.2 mg)	9.0 mg (7.2-10.8 mg)
25	Macrogol 3350	----	----	2.00 mg (1.6 - 2.4 mg)	3.0 mg (2.4-3.6 mg)
	polyethylene glycol)			1.73 mg (1.384 - 2.076 mg)	1.6 mg (1.28-1.92 mg)
	Titanium dioxide	----	----	0.27 mg (0.216 - 0.324 mg)	----
30	Ferric oxide (red)	----	----		1.4 mg (1.12-1.68 mg)
	Ferric oxide (yellow)	----	----	----	15.0 mg (12.0 -18.0 mg)
	Weight of film coat	----	10.0 mg	10.0 mg (8.0 -12.0 mg)	696.7 mg (348.0-352.85 mg)
35	Total tablet weight	85.0 mg	350.0 mg	350.85 mg (348 - 352.85 mg)	
	Tablet format	Round	round	round	oval
	Dimensions of the tablet	diameter: 6 mm	diameter: 10 mm, height: 4.5 mm	diameter: 10 mm, ±0.3)height: 4.5 (±0.3) mm,	length: 18 mm, width: 8 mm
40					
45	#1 Range for Mg stearate may apply according to manufacturing conditions				
	#2 Range for film coat may apply according to manufacturing conditions Fixed ratio of coating components 60 % (hypromellose) - 20 % (polyethylene glycol) - 17.3 % (titanium dioxide) - 2.7 % ferric oxide				
	#3 Opadry Red YS-15531 ready to use commercial coating system.				

1.2 Process for manufacturing

Step a) Granulation

[0092] 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-uieido]-phenoxy}-pyridine-2-carboxylic acid methyl amide (tosylate salt of compound (I) micronized, microcrystalline cellulose, croscarmellose sodium, and hypromellose are mixed for 2 minutes in a high shear mixer in order to obtain a powder blend. Sodium lauryl sulfate is dissolved in water. The powder blend is granulated with the solution in a wet granulation process using a high-shear mixer. The granulation process is finished when the granulate achieves a "snow ball like consistency". The wet granulation mass is sized using a 4 mm rasp and then dried in a fluidized bed dryer at an inlet air temperature of 80 - 100 °C until a residual moisture of 0.3 up to 0.7% by weight (loss on drying) is reached. The dry granules are sieved using a 2 mm sieve size.

Step b) Tablet compression

[0093] The granulate is blended with magnesium stearate and croscarmellose sodium using a tumbler blender for from 5 to 10 minutes. The blend is subdivided into single units and compressed to tablets using a standard rotary tablet press at typical tableting speeds of from 25,000 to 250,000 tablets / hour.

Step c) Film-coating

Alternative i:

[0094] Hypromellose, polyethylene glycol (Macrogol), titanium dioxide and ferric oxide red are combined with purified water to result in a homogenous coating suspension which is sprayed on the tablets in a perforated drum coater.

Alternative ii:

[0095] The commercially available Opadry Red YS-15531 is combined with purified water to result in a homogenous coating suspension which is sprayed on the tablets in a perforated drum coater.

1.3 Properties of the tablets

[0096]

Tab. 1: Study of release of compound of formula (I) from tablets B and C

Release of the compound of the formula (I) in % by total weight of the composition.				
	15 min	30 min	45 min	60 min
Tablet B	94	97	97	97
Tablet C	96	99	99	99

[0097] Each value represents the mean of 6 single results. USP apparatus 2, 900 ml 0.1 N HCl + 1% Sodium Lauryl Sulfate, 100 rpm

[0098] The tablets have a stability of more than 18 months (real time stability data) and a hardness of more than 100 N.

[0099] The water content of the tablets is less then 1.5 % by weight of the composition (determination: Karl-Fischer method)

Claims

1. A pharmaceutical composition which is a tablet comprising the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide as active agent in a portion of at least 55% by weight of the composition.
2. The pharmaceutical composition of claim 1 comprising the active agent in a portion of at least 75% by weight of the composition.
3. The pharmaceutical composition of claim 1 comprising a filler in a portion of from 3 to 20 %, a disintegrant in a portion of from 5 to 12 %, a binder in a portion of from 0.5 to 8 %, a lubricant in a portion of from 0.2 to 0.8 % and a surfactant in a portion of from 0.1 to 2 % by weight of the composition.
4. The pharmaceutical composition of claim 2 comprising microcrystalline cellulose as a filler in a portion of from 3 to 20 %, croscarmellose sodium as a disintegrant in a portion of from 5 to 12 %, hypromellose as a binder in a portion of from 0.5 to 8 %, magnesium stearate as a lubricant in a portion of from 0.2 to 8 % and sodium lauryl sulfate as a surfactant in a portion of from 0.1 to 2 % by weight of the composition.
5. The pharmaceutical composition of any of claims 1 to 4 is an immediate release tablet.

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6. The pharmaceutical composition of any of claims 1 to 5 wherein the active agent is micronized.
7. The pharmaceutical composition of claim 6 wherein the micronized form has a particle size of from 0.5 to 10 μm .
- 5 8. The pharmaceutical composition of any of claims 1 to 7 comprising water in an amount of less than or equal to 6 % by weight of the composition.
9. The pharmaceutical composition of any of claims 1 to 8 showing a hardness of more than 80 N.
- 10 10. The pharmaceutical composition of any of claims 1 to 9 which is an oval tablet with a longest dimension of less than or equal to 25 mm.
11. The pharmaceutical composition of any of claims 1 to 9 which is a round tablet with a diameter of less than or equal to 13 mm.
- 15 12. The pharmaceutical composition of any of claims 1 to 11 wherein the amount of the active agent is from 54 mg to 1096 mg.
13. The pharmaceutical composition of any of claims 1 to 12 for oral administration.
- 20 14. The pharmaceutical composition according to any of claims 1 to 13 in combination with one or more cytotoxic agents, signal transduction inhibitors, or with other anti-cancer agents or therapies, as well as with admixtures and combinations thereof.
- 25 15. A process for manufacturing a pharmaceutical composition according to any of claims 1 to 14 wherein the active agent is blended with at least one pharmaceutically acceptable excipient.
16. The process of claim 15 wherein:
 - 30 a) the active agent and at least one pharmaceutically acceptable excipient are wet granulated,
 - b) the granulate is blended with the lubricant and optionally with one or more further pharmaceutically acceptable excipient,
 - c) the post blend granulate is subdivided into single units ,
 - d) and the product of step c) is optionally coated with one or more further pharmaceutically acceptable excipients.
- 35 17. The process of any of claims 15 or 16 wherein the product of step c) is coated with one or more further pharmaceutically acceptable excipients
18. The process of claim 15 wherein the active agent and at least one pharmaceutically acceptable excipient are blended without granulation and directly compressed to tablets.
- 40 19. The process of claim 15 wherein the active agent alone or the active agent and at least one pharmaceutically acceptable excipient are treated by a dry granulation method and then compressed to tablets.
- 45 20. Use of a pharmaceutical composition according to any of claims 1 to 14 for the manufacture of a medicament to treat mammalian hyper-proliferative disorders, including cancer.

Patentansprüche

- 50 1. Pharmazeutische Zusammensetzung, die eine Tablette ist, umfassend das *p*-Toluolsulfonsäuresalz von 4-{4-[3-(4-Chlor-3-trifluormethylphenyl)ureido]phenoxy}pyridin-2-carbonsäuremethylester als Wirkstoff mit einem Anteil von wenigstens 55 Gew.-% der Zusammensetzung.
- 55 2. Pharmazeutische Zusammensetzung gemäß Anspruch 1, umfassend den Wirkstoff mit einem Anteil von wenigstens 75 Gew.-% der Zusammensetzung.
3. Pharmazeutische Zusammensetzung gemäß Anspruch 1, umfassend einen Füllstoff mit einem Anteil von 3 bis 20

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%, ein Sprengmittel mit einem Anteil von 5 bis 12 %, ein Bindemittel mit einem Anteil von 0,5 bis 8 %, ein Gleitmittel mit einem Anteil von 0,2 bis 0,8 % und ein grenzflächenaktives Mittel mit einem Anteil von 0,1 bis 2 Gew.-% der Zusammensetzung.

- 5 4. Pharmazeutische Zusammensetzung gemäß Anspruch 2, umfassend mikrokristalline Cellulose als Füllstoff mit einem Anteil von 3 bis 20 %, Natriumcroscarmellose als Sprengmittel mit einem Anteil von 5 bis 12 %, Hypromellose als Bindemittel mit einem Anteil von 0,5 bis 8 %, Magnesiumstearat als Gleitmittel mit einem Anteil von 0,2 bis 8 %, und Natriumlaurylsulfat als grenzflächenaktives Mittel mit einem Anteil von 0,1 bis 2 Gew.-% der Zusammensetzung.
- 10 5. Pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 4 als Tablette mit sofortiger Freisetzung.
6. Pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 5, wobei der Wirkstoff mikronisiert ist.
- 15 7. Pharmazeutische Zusammensetzung gemäß Anspruch 6, wobei die mikronisierte Form eine Teilchengröße von 0,5 bis 10 µm aufweist.
8. Pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 7, umfassend Wasser in einer Menge von weniger oder gleich 6 Gew.-% der Zusammensetzung.
- 20 9. Pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 8, die eine Härte von mehr als 80 N aufweist.
10. Pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 9, die eine ovale Tablette mit einer längsten Abmessung von weniger oder gleich 25 mm ist.
- 25 11. Pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 9, die eine runde Tablette mit einem Durchmesser von weniger oder gleich 13 mm ist.
12. Pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 11, wobei die Menge des Wirkstoffs 54 mg bis 1096 mg beträgt.
- 30 13. Pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 12 für die orale Verabreichung.
14. Pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 13 in Kombination mit einem oder mehreren zytotoxischen Mitteln, Signalweiterleitungshemmern oder mit anderen Antikrebsmitteln oder -therapien, sowie mit Gemischen und Kombinationen davon.
- 35 15. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung gemäß einem der Ansprüche 1 bis 14, wobei der Wirkstoff mit wenigstens einem pharmazeutisch verträglichen Exzipienten gemischt wird.
- 40 16. Verfahren gemäß Anspruch 15, wobei:
 - a) der Wirkstoff und wenigstens ein pharmazeutisch verträglicher Exzipient nassgranuliert werden,
 - b) das Granulat mit dem Gleitmittel und gegebenenfalls mit einem oder mehreren weiteren pharmazeutisch verträglichen Exzipienten gemischt wird,
 - 45 c) das Granulat nach dem Mischen in einzelne Einheiten aufgetrennt wird,
 - d) und das Produkt von Schritt c) gegebenenfalls mit einem oder mehreren weiteren pharmazeutisch verträglichen Exzipienten überzogen wird.
- 50 17. Verfahren gemäß einem der Ansprüche 15 oder 16, wobei das Produkt von Schritt c) mit einem oder mehreren weiteren pharmazeutisch verträglichen Exzipienten überzogen wird.
18. Verfahren gemäß Anspruch 15, wobei der Wirkstoff und wenigstens ein pharmazeutisch verträglicher Exzipient ohne Granulation gemischt und direkt zu Tabletten komprimiert werden.
- 55 19. Verfahren gemäß Anspruch 15, wobei der Wirkstoff allein oder der Wirkstoff und wenigstens ein pharmazeutisch verträglicher Exzipient durch ein Trockengranulationsverfahren behandelt und dann zu Tabletten komprimiert werden.

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20. Verwendung einer pharmazeutischen Zusammensetzung gemäß einem der Ansprüche 1 bis 14 für die Herstellung eines Medikaments zum Behandeln von hyperproliferativen Störungen bei Säugern, einschließlich Krebs.

5 Revendications

1. Composition pharmaceutique qui est un comprimé comprenant le sel d'acide *p*-toluènesulfonique du méthylamide de l'acide 4{4-[3-(4-chloro-3-trifluorométhylphényl)-uréido]-phénoxy}-pyridine-2-carboxylique au titre de principe actif à une teneur d'au moins 55 % en masse de la composition.
2. Composition pharmaceutique conforme à la revendication 1 comprenant le principe actif à une teneur d'au moins 75 % en masse de la composition.
3. Composition pharmaceutique conforme à la revendication 1 comprenant une charge à une teneur comprise entre 3 et 20 %, un agent délitant à une teneur comprise entre 5 et 12 %, un agent liant à une teneur comprise entre 0,5 et 8 %, un lubrifiant à une teneur comprise entre 0,2 et 0,8 % et un tensioactif à une teneur comprise entre 0,1 et 2 % en masse de la composition.
4. Composition pharmaceutique conforme à la revendication 2 comprenant de la cellulose microcristalline au titre de charge à une teneur comprise entre 3 et 20 %, du croscarmellose sodium au titre d'agent délitant à une teneur comprise entre 5 et 12 %, de l'hypromellose au titre d'agent liant à une teneur comprise entre 0,5 et 8 %, du stéarate de magnésium au titre de lubrifiant à une teneur comprise entre 0,2 et 8 % et du laurylsulfate de sodium au titre de tensioactif à une teneur comprise entre 0,1 et 2 % en masse de la composition.
5. Composition pharmaceutique conforme à l'une quelconque des revendications 1 à 4 sous forme de comprimé à libération immédiate.
6. Composition pharmaceutique conforme à l'une quelconque des revendications 1 à 5 où le principe actif est micronisé.
7. Composition pharmaceutique conforme à la revendication 6 où la forme micronisée présente une granulométrie comprise entre 0,5 et 10 µm.
8. Composition pharmaceutique conforme à l'une quelconque des revendications 1 à 7 comprenant de l'eau à une teneur inférieure ou égale à 6 % en masse de la composition.
9. Composition pharmaceutique conforme à l'une quelconque des revendications 1 à 8 présentant une dureté supérieure à 80 N.
10. Composition pharmaceutique conforme à l'une quelconque des revendications 1 à 9 qui est un comprimé ovale dont la plus grande dimension est inférieure ou égale à 25 mm.
11. Composition pharmaceutique conforme à l'une quelconque des revendications 1 à 9 qui est un comprimé rond de diamètre inférieur ou égal à 13 mm.
12. Composition pharmaceutique conforme à l'une quelconque des revendications 1 à 11 où la teneur en principe actif est comprise entre 54 et 1096 mg.
13. Composition pharmaceutique conforme à l'une quelconque des revendications 1 à 12 pour administration orale.
14. Composition pharmaceutique conforme à l'une quelconque des revendications 1 à 13 en combinaison avec un ou plusieurs agents cytotoxiques, inhibiteurs de transduction du signal ou avec d'autres agents ou traitements anticancéreux, ainsi qu'avec des mélanges et des combinaisons de ces agents.
15. Procédé de fabrication d'une composition pharmaceutique conforme à l'une quelconque des revendications 1 à 14, le principe actif étant mélangé à au moins un excipient de qualité pharmaceutique.
16. Procédé conforme à la revendication 15, où :

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- a) le principe actif et au moins un excipient de qualité pharmaceutique sont granulés par voie humide,
- b) le granulat est mélangé au lubrifiant et éventuellement à un ou plusieurs excipients de qualité pharmaceutique supplémentaires,
- c) le granulat post-mélange est divisé en doses unitaires,
- d) et le produit de l'étape c) est éventuellement revêtu d'un ou de plusieurs excipients de qualité pharmaceutique supplémentaires.

- 17. Procédé conforme à l'une quelconque des revendications 15 ou 16 où le produit de l'étape c) est revêtu d'un ou de plusieurs excipients de qualité pharmaceutique supplémentaires.
- 18. Procédé conforme à la revendication 15 où le principe actif et au moins un excipient de qualité pharmaceutique sont mélangés sans granulation et directement compressés en comprimés.
- 19. Procédé conforme à la revendication 15 où le principe actif seul ou le principe actif et au moins un excipient de qualité pharmaceutique sont traités par granulation sèche avant d'être compressés en comprimés.
- 20. Emploi d'une composition pharmaceutique conforme à l'une quelconque des revendications 1 à 14 dans la fabrication d'un médicament destiné au traitement des troubles hyper-prolifératifs des mammifères, y compris le cancer.

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REFERENCES CITED IN THE DESCRIPTION

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