



No. 07-090237-00004-0000

Fecha: 2010-08-18 18:48:17 Dep. 2020 DIR.NUEVASC
Tra. 11 PATENTEYII Evo: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 14**FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES**

1

SOLICITUD DE:

Corrección de Error Material



Modificación a una solicitud

2

SOLICITANTENombre: **BAYER SCHERING PHARMA AG**
Sociedad constituida y existente bajo las leyes de
Alemania.Dirección: Muellerstrasse 178,
13353 Berlín,
Alemania.Domicilio: Berlín,
AlemaniaTeléfono: 546 09 70 Fax: 249 40 70
E-mail: clientes@cavelier.com**IDENTIFICACION**C.C. ☐ NIT ☐
C.E. ☐ Otro ☐

Número: _____

3

**REPRESENTANTE
O APODERADO**Nombre: **LUZ CLEMENCIA DE PÁEZ**
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.**IDENTIFICACIÓN**C.C. ☒ NIT ☐
C.E. ☐ Otro ☐

Cual _____

Número **35.456.344 T. P. 23.555**

4

Número de expediente: 07.090.237

5

Descripción de la corrección o modificación solicitada:

Atentamente solicito a ese Despacho ordenar la anotación en los libros de la Propiedad Industrial del cambio de nombre del solicitante **BAYER HEALTHCARE AG**, domiciliada en 51368 Leverkusen, Alemania a **BAYER SCHERING PHARMA AG**, domiciliada en Muellerstrasse 178, 13353 Berlín, Alemania.

Por lo tanto, solicito se sirva expedir el certificado de registro a favor de la Sociedad **BAYER SCHERING PHARMA AG**.

6

Comprobante de pago No. 10-62.528 Fecha: 2 de agosto de 2010

82
02

7

Anexos

- ☒ Comprobante de pago de la tasa por \$114.000, por concepto de modificaciones.
- ☒ Poderes, si fuere el caso
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.
- ☒ La copia auténtica del Documento que acredita el cambio de nombre solicitado esta siendo presentada en el Expediente **00.097.415**, radicada ante Su Despacho el día de hoy 18 de agosto de 2010, por lo tanto ya se encuentra en sus archivos. Por lo anterior solicito sea tenido en cuenta este documento al momento de emitir una decisión sobre la presente Solicitud de patente.

8

NOMBRE: LUZ CLEMENCIA DE PÁEZ

FIRMA: Luz Clemencia de Páez

C.C. 35.456.344 de Usaquén T.P.A. 23.555

JGG

RAF-MEK-ERK PATHWAY INHIBITORS TO TREAT CANCER

FIELD OF THE INVENTION

[0001] The invention described herein is in the field of cancer therapy, and preferably for the treatment of chronic myelogenous leukemia.

BACKGROUND OF THE INVENTION

[0002] A goal of modern cancer therapy is to identify molecules in signal transduction pathways that affect cell growth, and particularly those that cause a normal cell to become cancerous. One such pathway is the RAF-MEK-ERK pathway, and the up-regulation of one or more of its members is thought to be responsible for a number of cancers. For example, patients with chronic myelogenous leukemia, herein after referred to as CML, who are in either the chronic or blast phase typically achieve remissions in response to the marketed drug Gleevec™, also referred to as imatinib or ST1571 (*N. Eng. J. Med.* 244, 1031 [2001]; *N. Eng. J. Med.* 244, 1038 [2001]). CML is characterized by the Philadelphia chromosomal translocation (Ph+) resulting in a Bcr-Abl fusion protein. Imatinib treats CML by blocking Bcr-Abl kinase activity.

[0003] While the remissions achieved with imatinib during the chronic phase of CML are durable, patients with remissions achieved during the blast phase usually relapse within 2-6 months (*N. Eng. J. Med.* 244, 1038 [2001]). Resistance to Imatinib results in reactivation of Bcr-Abl kinase activity. Recently, it has been shown that these relapses are usually due to imatinib-resistance that occur either by over-expression of the translocated Bcr/Abl gene, or mutation of the imatinib target gene, namely the Abl kinase (*Science* 293, 876 [2001]). Resistance often correlates with mutations in the Abl kinase domain, including T315I and E255K.

[0004] The Abl kinase was chosen as a molecular target in the treatment against cancer since 95% of patients with CML have activation of the Abl pathway that occurs through chromosomal translocations that result in fusion of the Bcr and Abl genes. As mentioned above, a key pathway that is up-regulated in CML cells that are resistant to imatinib is the RAF-MEK-ERK pathway. Therefore, treatment with inhibitors of the RAF-MEK-ERK pathway should lead to remissions in patients with imatinib resistant CML.

SUMMARY OF THE INVENTION

[0005] The invention described herein presents methods and compositions for treating cancers that involve up-regulation of one or more molecules in the pathway: RAF-MEK-ERK.

[0006] An object of the invention is a description of inhibitors of the RAF-MEK-ERK pathway that are beneficially applied to the treatment of certain forms of cancer, preferably CML, and more preferably to those forms of CML that are resistant to Bcr-Abl kinase inhibitors, and most preferably to those forms of CML that are resistant to the Bcr-Abl kinase inhibitor, imatinib.

[0007] Another object of the invention is a description of RAF inhibitors, preferably Bay 43-9006, alone or in combination with Bcr-Abl kinase inhibitors, preferably imatinib, for the treatment of CML.

[0008] Still another object of the invention is a description of MEK inhibitors, preferably CI-1040, alone or in combination with Bcr-Abl kinase inhibitors, preferably imatinib, for the treatment of CML.

[0009] Another object of the invention is a description of methods and compositions for formulating and administering inhibitors of the RAF-MEK-ERK pathway, preferably in combination with Bcr-Abl kinase inhibitors and more preferably with the Bcr-Abl kinase inhibitor, imatinib.

[0010] These and other objects of the present invention will become apparent to a skilled practitioner of the art upon a full consideration of the invention.

BRIEF DESCRIPTION OF THE FIGURES

[0011] FIG. 1 shows the RAF-MEK-ERK pathway that becomes up-regulated in certain cancer cells, including chronic myelogenous leukemia. Also shown are the compounds BAY 43-9006, and CI-1040, and the proteins in the pathway that they affect, RAF and MEK, respectively.

[0012] FIG. 2 shows the structure of BAY 43-9006.

[0013] FIG. 3 shows the effects of the RAF kinase inhibitor, BAY 43-9006, and imatinib, on imatinib-resistant CML Cells.

[0014] FIG. 4 shows the effects of the RAF kinase inhibitor, BAY 43-9006, on imatinib-resistant CML Cells. The results are from 3 experiments.

[0015] FIG. 5 shows the effects of the RAF kinase inhibitor, BAY 43-9006, on ERK phosphorylation.

DESCRIPTION OF THE INVENTION

[0016] All publications, including patents and patent applications, mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

[0017] Based on the pathway shown in FIG. 1, it will be appreciated that in cancers where Raf, MEK, or ERK are up-regulated, compounds that inhibit the activities of these molecules will have beneficial effects for treating such cancers. An example of one such cancer, also shown in FIG. 1, is chronic myelogenous leukemia. Thus, treating patients with non-toxic doses of, preferably, 200-400 mg and higher of the Raf kinase inhibitor BAY 43-9006 (*Endocr. Relat. Cancer* 8, 219 [2001]) will result in remissions, or minimally stabilization of the growth of the cancer. Furthermore, treating patients with non-toxic doses of, preferably, 200-400 mg and higher of the MEK inhibitor PD184352 (now designated CI-1040, *Oncogene* 19, 6594 (2000)) will also lead to remissions or cancer growth stabilization in these patients.

[0018] Definitions

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures described below are those well known and commonly employed in the art.

[0020] BAY 43-9006 is described in U.S. patent application Ser. No. 09/425,228 and PCT/US00/00648, as are numerous other RAF kinase inhibitors.

[0021] The MEK inhibitor, CI-1040, is described in *Oncogene* 19, 6594 (2000).

[0022] Imatinib, or Gleevec,™ is described in U.S. Pat. No. 5,521,184.

[0023] By "up-regulated" or "up-regulation" of the RAF-MEK-ERK pathway is meant elevated levels, by whatever molecular mechanism, of one or more of the proteins, RAF MEK, or ERK, or increases in their enzymatic activity, or changes in their normal substrate affinity when compared to normal cells.

[0024] It will be appreciated that the compounds that affect RAF, MEK, or ERK may be used alone, or in combination. They may also be used in combination with other compounds known to affect particular cancers where the RAF-MEK-ERK pathway is up-regulated. For example, the drug imatinib (Gleevec™) is used to treat CML patients; thus, imatinib resistance that develops in certain advanced staged CML patients that causes up-regulation of the RAF-MEK-ERK pathway can be treated with the appropriate compounds that control the up-regulation of the appropriate molecules in the RAF-MEK-ERK pathway. Such compounds can be combined with imatinib for treatment of a CML patient before imatinib resistance develops, or without imatinib after resistance has developed. The pathway in question and the sites of action of BAY 43-9006, CI-1040 and imatinib are illustrated in FIG. 1.

[0025] There are several important rationale for applying inhibitors to the RAF-MEK-ERK pathway for the treatment of CML. First, cells from leukemia patients (Ph+) have elevated phospho-ERK levels at least in part due to elevated, or up-regulated, RAF kinase activity. Second, imatinib treatment results in decreased phospho-ERK levels. Also, cells from imatinib-resistant patients have re-elevated phospho-ERK levels.

[0026] **Pharmaceutical Compositions and Modes of Administration**

[0027] The present invention also relates to pharmaceutical compositions for administration to humans that comprise an inhibitor of the RAF-MEK-ERK pathway alone, or in combination with imatinib. Such would include compositions for enteral administration, such as nasal, buccal, rectal or, especially, oral, and parenteral administration, such as intravenous, intramuscular or subcutaneous. The compositions comprise the inhibitor on its own or, preferably, together with a pharmaceutically acceptable carrier. The dose of inhibitor depends on the disease to be treated, preferably CML, and more preferably imatinib resistant CML, and the age, weight and individual condition of a patient, and the mode of administration.

[0028] The invention relates also to processes, and to the use of inhibitors of the RAF-MEK-ERK pathway in the preparation of pharmaceutical compositions alone, or in combination with imatinib. Preference is given to a pharmaceutical composition that is suitable for administration to a human suffering from a cancer that is responsive to inhibition of a protein tyrosine kinase. Preferably the cancer is CML, and more preferably it is imatinib resistant CML

which composition comprises an inhibitor, or a salt thereof where salt-forming groups are present, in an amount that is effective in inhibiting the protein tyrosine kinase, together with at least one pharmaceutically acceptable carrier.

[0029] Preference is also given to a pharmaceutical composition for the prophylactic or, especially, therapeutic treatment of preferably CML, and more preferably imatinib-resistant CML, which composition comprises as active ingredient an inhibitor, or a pharmaceutically acceptable salt thereof, in an amount that is prophylactically or, especially, therapeutically effective against the mentioned diseases.

[0030] The pharmaceutical compositions comprise from approximately 1% to approximately 95% of the appropriate inhibitor, dosage forms that are in single dose form preferably comprising from approximately 20% to approximately 90% active ingredient, and dosage forms that are not in single dose form preferably comprising from approximately 5% to approximately 20% active ingredient. Unit dose forms are, for example, dragees, tablets, ampoules, vials, suppositories or capsules. Other dosage forms are, for example, ointments, creams, pastes, foams, drops, sprays, dispersions, etc. The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes.

[0031] There are preferably solutions that can be used with the appropriate inhibitor, including suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions, which, for example in the case of lyophilized compositions comprising the active ingredient on its own or together with a carrier, e.g. mannitol, may be prepared before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known per se, for example by means of conventional dissolving or lyophilising processes. The said solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin, or also solubilisers, for example RIM-Tween 80 polyoxyethylene(20) sorbitan monooleate; trademark of ICI Americas, Inc, USA.

[0032] Synthetic or semi-synthetic oils as are known in the art may be used for injection of the appropriate inhibitor. Particularly useful can be liquid fatty acid esters which contain a long-chain fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms.

[0033] Pharmaceutical compositions will preferably be used in oral form, and can be obtained, for example, by combining a RAF-MEK-ERK pathway inhibitor, with or without a Bcr-Abl tyrosine kinase inhibitor, with one or more solid carriers, granulating a resulting mixture, where appropriate, and processing the mixture or granules, if desired, where appropriate with the addition of additional excipients, to form tablets or dragees. Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tri-calcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, floc or potato starch, methylcellulose, hydroxypropylmethylcellulose, sodium

95
97

96

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.

Abogada
/ **LUZ CLEMENCIA DE PAEZ**

ASUNTO	Radicación	07-90237
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	
	Folios	006 05872

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (Fase Nacional)	☒	Cap. I	☒
		Cap. II	☐

No. Sol. Internacional	<u>PCT/EP2006/001574</u>
Fecha de Presentación Internacional.	<u>22/02/2006</u>

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios 35 a 57 como se radicó inicialmente.

Reivindicaciones: Folios 58 a 60 como se radicó inicialmente.

Prioridad: Folio 1 US 60/658,827 del 07/03/2005.

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad dado que esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486), y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título: COMPOSICION FARMACEUTICA QUE COMPRENDE UNA DIFENILUREA SUSTITUIDA CON OMEGA-CARBOXIARILLO PARA EL TRATAMIENTO DEL CANCER.

Objeto: La solicitud consiste en composiciones farmacéuticas orales de liberación inmediata de metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico, (BAY 43-9006 o sorafenib) sus solvatos, hidratos y sales farmacéuticamente aceptables.

El problema planteado es la necesidad de proveer composiciones farmacéuticas orales de liberación inmediata de metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico, sus solvatos, hidratos y sales aceptables con propiedades mejoradas en cuanto a biodisponibilidad y estabilidad.

Para solucionar este problema técnico la solicitud proporciona composiciones farmacéuticas orales de liberación inmediata de dicho compuesto activo.

Se clasificó la invención según la IPC en las categorías: A61K 9/22 y A61P 35/00.

4. Reivindicaciones relativas a uso o a uso distinto (artículos 14 y 21 D 486)

La reivindicación 22 se refiere al uso de las composiciones farmacéuticas de la invención, lo cual corresponde a materia no patentable.

5. De la solicitud de Patente

Título: El título se debe modificar de forma tal que se indique el compuesto específico (sorafenib) que caracteriza las composiciones farmacéuticas de la invención.

Reivindicaciones (artículo 30 D 486)

En el pliego reivindicatorio, para indicar el porcentaje en peso del agente activo, se emplea con frecuencia el término "al menos", que no es conciso.

La reivindicación 9 se refiere a composiciones farmacéuticas caracterizadas por su uso, lo cual no las hace diferentes, ni les otorga ninguna característica adicional.

La reivindicación 15 no es concisa al indicar "agentes citotóxicos" y además reclama composiciones farmacéuticas que no hacen parte de la invención de acuerdo a lo sustentado en la descripción, dado que allí no se menciona ninguna composición específica que contenga dos o más fármacos ni se evidencia el efecto que exhiben.

El procedimiento de la reivindicación 16 corresponde al procedimiento rutinario y conocido por el técnico medio para preparar una composición farmacéutica, que es mezclar el principio activo con excipientes aceptables.

6. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad 07/03/2005 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de publicación
D1	US 2003125359	RAF-MEK-ERK pathway inhibitors to treat cancer	03/07/2003

7. Análisis de patentabilidad (artículo 14 D 486)

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial para establecer la patentabilidad de la invención reivindicada en la solicitud.

Novedad: (artículo 16 D 486)

Las reivindicaciones 1 a 14 reclaman una composición farmacéutica que comprende:

- Metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-fenoxi}-piridin-2-carboxílico (BAY 43-9006) sus solvatos, hidratos o sales aceptables en una parte de al menos el 40% en peso de la composición y
- Al menos un excipiente farmacéuticamente aceptable.

El documento D1 describe composiciones farmacéuticas que comprenden:

- ✓ BAY 43-9006 (párrafo 7) en un porcentaje del 20 al 90% (párrafo 30) y
- ✓ excipientes aceptables.

Las reivindicaciones 16 a 21 reclaman procesos de granulación vía húmeda y vía seca para fabricar las composiciones farmacéuticas de las reivindicaciones 1 a 14.

D1 enseña que las composiciones farmacéuticas pueden ser preparadas por métodos convencionales como granulación vía húmeda y vía seca, empleando para ello los auxiliares de formulación y excipientes apropiados (párrafos 31 a 34).

Así las cosas, D1 divulga composiciones farmacéuticas de BAY 43-9006 y sus procedimientos de fabricación idénticos a las de la presente solicitud, por lo tanto el objeto reivindicado no cumple con el requisito de novedad.

8. Conclusión

Los requisitos de patentabilidad de la presente invención se encuentran afectados así

Nº	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	US 2003125359	1 a 21	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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.


JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento, fue notificado por fijación en lista, de fecha

01 ABR. 2011

CONCEPTO TECNICO No. 519	EXAMINADOR TECNICO Código No. 202077
--------------------------	---