OLARTERAISBECK
OLARTE RMSBECK MOURE & CASTRO LmA.

2. a- El Examinador establece que la Solicitud Divisional presentada junto con la respuesta at primer examen de fondo, no es aceptada.

i) En respuesta at anterior planteamiento del Examinador, me permito
anotar que el ArtIculo 36 de Ia Decision 486 establece que:
"El solicitante podrÆ, encualguier momento del trªmite, dividir
su solicitud en dos o mÆs fraccionarias,pero ninguna de Østas
podrÆ implicar una ampliación de la protección que corresponda a la divulgaciôn contenida en la solicitud inicial.

A efectos de la division de una solicitud, el solicitante consignarÆ los documentos que fuesen necesarios para formar las solicitudes fraccionarias correspondientes." (mi subrayado y negrilla)

A su vez, el Manual Andino de Patentes confirma todo to anterior,’ ratificando que el onicol requisito necesario al momento de la presentación de una solicitud divisional es que el contenido de dicha divisional no amplie la materia originalmente contenida enla solicitud inicial. .4

AsI las cosas, sorprende enormemente que el Examinador en su concepto tØcnico No. 0107 realice objeciones ciue se apartan de to estrictamente establecido pot la legislación aplicable. Nada en la norma establece que para Ia aceptaciOn de una solicitud divisional debe realizarse un estudio de fondo para evaluar La conformidad de Østa en la claridad de su contenido, o aun, su patentabilidad. El Tribunal Andino de Justicia ha reafirmado to establecido por la Decision 486 y el Manual Andino de Patentes, adicionando que cada solicitud fraccionaria devengarÆ la tasa establecida,2 to que evidentemente implica que una solicitud divisional debe ser tramitada completamente, surtiendo cada una de las etapas de estudio de forma, publicaciOn y posterior estudio de fondo, con el fin de, en cada oportunidad procesal, adecuar su contenido a los requerimientos legales y establecer su patentabilidad (independientemente del trªmite de la solicitud inicial).

AsI las cosas, en el presente caso, insito en la presentación de una solicitud divisional de la presente solicitud.

’Manual para el Examen de Solicitudes de Patente de InvenciOn (Manual Andino de Patentes). OMPI, EPO,

Secretaria de la Comunidad Andina, 2004. ISBN: 9978-43-855-6. Sección 12.3.1. 2 Tribunal Andino de Justicia de la Comunidad Andina. PROCESO 156-IP-2006. PÆgina 16, lIneas34 a 36.
Page 2 of 9

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OLARTERAISBECK
OLARTF RAISECK MOURE & CASTRO LTOA,

v) Mn cuando el Examinador argumente que La preparación de tabletas
que comprenden compuestos activos en diferentes cantidades, de acuerdo con las necesidades diarias del paciente, resuitarla derivada del estado del arte, sin tener en cuenta de los problemas mencionados anteriormente, me permito resaltar que el Examinador precisamente tiene Ia carga de La prueba para demostrar por quØ ci desarrollo de una tahieta de aita dosis, que supera los inconvenientes mencionados, resulta trivial y no presenta

aitura inventiva.

Segiin la aproximación del Examinador, es claro que luego de desarrollar una formuiaciOn con las propiedades deseadas, la misma resuita obvia despuØs de preparada. Sin embargo, un anÆlisisen retrospectiva con ci anterior, o tipo "hindsight", debe evitarse estrictamente en ci anÆlisis de patentabilidad de una invención, ya que, en ci presente caso, antes que Ia invención fuera desarrollada, ci arte previo existente no se enfocaha en La solución de los problemas asociados a La formulación que contiene grandes cantidades de principio activo. Asimismo, no existe ninguna "rutina" convenciona’Y’que yna persona medianamente versada Page 8of9 t/

V Colombian Patent Application

No. 04-111.533
Our Ref: P2004/000184

IN THE COLOMBIAN PATENT OFFICE

Colombian Patent Application no. 04-111.533
Title: "HIGH DRUG LOAD TABLETS"
Applicant: NOVARTIS A.G.
International Counterpart: W003/090720

DECLARATION OF Dr. Jörg Ogorka

I, Jörg Ogorka, declare that all statements made herein are ofmy own knowledge and are true, and that the statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under the Colombian
Criminal Code and such willful false statements may jeopardize the validity ofthe
application or any patent issuing thereon; and I further declare that:

I am a Pharmacist with a PhD. in pharmaceutical chemistry.

2. In my current position I head the Cardiovascular & Metabolism Franchise within
Technical Research & Development at Novartis.

40 3. 1 am an Inventor ofthe invention claimed by the Colombian Patent Application
no. 04-111.533.

4. 1 was asked to provide clarification regarding the patentability of the claims filed
with Colombian Patent application No. 04-111.533. I hereby submit that present
invention solves the problems associated with the production of small tablets
containing high amounts of Imatinib (40-65%) and relatively small quantities of
excipients overcoming the issues of stickiness (during tabletting), poor friability and poor abrasion resistance, all of which become more problematic the higher the
drug load of the tablets. The problems encountered during the development of the
tablets had been unexpected and the measures to overcome these technical hurdles
heave not been obvious.

5. In addition to the proper support, I consider that the claimed subject matter is
patentable. Specifically, the invention presented surprising and unexpected results
. that serve to demonstrate its inventive step. The closest prior art related to the
present invention is W001/47507 and US552 1184, references cited by the
Examiner. Nothing in said prior art provides teachings leading to expect these
unexpected results.

Sep 4, 2009

Date

Dr. JorJgorka

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WO 01/47507

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preferably due to high AGP levels in blood plasma) or may have developed or Is developing during treatment with an abl-, PDGF-R- and/or Kit receptor-tyrosine kinase inhibitor as described in the present disclosure.

The present invention preferably relates to a combination preparation comprising (a) at least one abl-, PDGF-R- and/or Kit receptor-tyrosine kinase inhibitor and (b) at least one organic compound capable of binding to a1 -acidic glycoprotein (AGP); or pharmaceutically accept-able salts of any component (a), (b) or (a) and (b) if at least one salt-forming group is

.

present.

The invention also relates to a method for treating a proliferative disease that can be trea-ted by administration of an abl-, PDGF-R- and/or Kit receptor-tyrosine kinase inhibitor,

wherein

(a) at least one abl-, PDGF-R- and/or Kit receptor-tyrosine kinase Inhibitor and
(b) at least one organic compound capable of binding to 1 -acidic glycoprotein (AGP)
are administered to a mammal in combination in a quantity which is jointly therapeutically effective against a proliferative disease that can be treated by administration of an abl-, PDGF-R- and/or Kit receptor-tyrosine kinase inhibitor, wherein any component (a) and/or (b) can also be present in the form of a pharmaceutically acceptable salt, if at least one salt-forming group is present.

The invention also relates to a product which comprises
(a) at least one abl-, PDGF-R- and/or Kit receptor-tyrosine kinase inhibitor and
(b) at least one organic compound capable of binding to a1 -acidic glycoprotein (AGP), wherein any component (a) and/or (b) can also be present in the form of a pharmaceutically acceptable salt, if at least one salt-forming group is present,
in the presence or absence of one or more pharmaceutically acceptable carrier materials, as a combination preparation for simultaneous or chronologically staggered use within a period of time which is small enough for the active compounds both of component (a) and of component (b) to enhance antiproliferative activity of compound (a) against proliferating cells, especially in a patient, for treating a proliferative disease which responds to such a compound.

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Preferably, a combination according to the present invention is used in the treatment of a warm-blooded animal, especially a human, that has a proliferative disease which (especially
due to higher than normal AGP levels) is or, during treatment with an abi-, PDGF-R- and/or
Kit receptor-tyrosine kiriase inhibitor, is becoming or has become completely or partially re-
sistant to such treatment, such warm-blooded animals representing a special group of pro-
bationers.

In another preferred embodiment of the present Invention, the combination is used aiming
. at a warm-blooded animal, especially a human, in order to already prophylactically avoid the emerging of a partial or complete resistance during treatment of a proliferative disease with
an abi-, PDGF-R- and/or Kit receptor-tyrosine kinase inhibitor.

Pharmaceutical Compositions (= Preparations) and Processes:
Where in the following "component (a) and/or (b)" is mentioned, this is intended to mean
any’&or more of the compounds defined above as component (a) and component (b) as
such or a pharmaceutically acceptable salt of one or more of the respective components.

The pharmaceutical compositions that can find use in a combination according to the inven-tion are comprising either one or more of the components (a) and (b) with the properties ac-cording to the invention as active ingredient. The combinations can be used alon (e.g. as fixed combination) or as kit of parts. Especially preferred are compositions for enteral, especially oral, or pareriteral administration. The compositions comprise one or more of the components (a) and (b) or combinations thereof as such or, preferably, together with a pharmaceutically acceptable carrier. The dose of any active ingredient depends on the disease to be treated and on the species, age, weight and individual condition, as well as the method of administration.

Preferred is a pharmaceutical composition or combination that Is suitable for administration to a warm-blooded animal, especially a human, suffering from any disease mentioned herein; preferably any disease is meant that responds to an abl-, PDGF-R- and/or Kit recep-tor-tyrosinekinase inhibitor; especially, a proliferative disease selected from a cancer disea-se, especially a tumor disease or leukemia, or a non-malignant proliferative disease, e.g. atherosclerosis, thrombosis, psoriasis, scierodermitis or fibrosis, Is meant; more preferably, a disease selected from the group consisting of CIVIL (chronic myelold leukemia) and ALL

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(acute lymphobiastic leukemia), or a solid tumor, especially selected from lung cancer, especially non-small cell lung cancer, and from cancer of the prostate, is meant; most
preferably, any of the diseases just mentioned that has become or is becoming resistant to
treatment with one or more of the mentioned tyrosine kinase inhibitors, or was resistant to
such treatment already before the treatment with any such tyrosine kinase inhibitor, espe-
cially due to higher AGP concentrations being present in the blood plasma of the individual
to be treated, is meant.

. The pharmaceutical compositions comprise from approximately 0.0001 % to approximately 95 % of any component

and/or (b), dosage forms that are in single dose form preferably
comprising from approximately 10 % to approximately 90 % of component (a) or (b), and
dosage forms that are not in single dose form preferably comprising from approximately 10
% to approximately 60 % of each component. Unit dose forms, such as dragØes, tablets,
ampoules or capsules, comprise from approximately 5 mg to approximately 1.5 g of com-ponent (a) and/or component (b), preferably from 5 mg to approximately 1 g.

The pharmaceutical compositions are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising pro-cesses. For example pharmaceutical compositions for oral administration can be obtained by combining component (a) and/or (b) with one or more solid or liquid carriers, where necessary granulating a resulting mixture and processing the mixture or the granules, If desired or appropriate with the addition of further excipients, to form tablets or dragØe cores or solutions, respectively.

Suitable carriers are especially fillers, such as sugars, e.g. lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, e.g. tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starches, e.g. corn, wheat, rice or pota-to starch, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcollulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, and also carboxymethyl starch, crosslinked polyviriylpyrrolidono or alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditio-ners and lubricants, e.g. silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

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Crystal modification of a N-12henyl-2pvrimidineamine derivative, łrocesses for its manufacture and its use

The invention relates to a particular form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1 -ylmethyl)-N-(4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl-
berizamide, comprising certain crystals, processes for the preparation thereof, pharma-
ceutical compositions containing this crystal form, and their use in diagnostic methods or
preferably for the therapeutic treatment of warm-blooded animals, especially humans, or
. their use for the preparation of pharmaceutical preparations for use in diagnostic methods or preferably for the therapeutic treatment of warm-blooded animals, especially humans.

Background to the invention:
The preparation of 4-(4-methylpiperazin-1 -ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyfjbenzamide and the use thereof, especially as an anti-tumour agent, are
described in Example 21 of EP-A-0 564 409, which was published on 6 October 1993, and
in equivalent applications in numerous other Countries. This compound is exemplified in these publications only in free form (not as a salt).

It has now been surprisingly found that a crystal form may under certain conditions be found in the methanesulfonate salt of this compound, which is described hereinafter as 3-crystal form, and which has very advantageous properties.

Detailed description of the invention
The invention is described in more detail in the following with the help of drawings and other aids:

Description of the drawing
Fig. 1f3 shows the X-ray diffraction diagram of the a-crystal form of the methanesulfonic acid addition salt of a compound of formula I.
Fig. 2/3 shows the X-ray diffraction diagram of the -crystal form of the methanesulfonic acid addition salt of a compound of formula I.
Fig. 3/3 shows the crystals above of the a-crystal form and below of the 3-crystal form of 4-(4-methylpiperazin-1 -ylmethyl).N-(4-methyt-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenylj-

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benzamide methanesulfonate (= of the methanesulfonic acid addition salt of a compound of formula I).

In both X-ray diagrams, the angle of refraction 2theta is plotted on the horizontal axis (x-axis) and the relative line intensity (background-corrected peak intensity) on the vertical (y-axis). The diagrams are obtained as follows: first, the x-ray diffraction diagram is recorded on film using a Guinier camera (Enraf-Nonius FR 552 model) with a Guinier 258-94c film and copper radiation (Kc1 radiation, wavelength? = 1.54060 Angstrom). The optical density of the lines on the film is proportional to the light intensity. The film is then scanned in using a line scanner (LS 18, Johansson, Täby, Sweden) with SCANPI software.

In accordance with Fig. 2/3 there are lines having a relative line intensity of 20 or more at the following angles of refraction 2theta (relative line intensities given in parentheses): 9.70 (40), 13.9° (26), 14.7° (23), 17.5° (57), 18.20 (90), 20.00 (65), 20.6° (76), 21.1° (100), 22.1° (89), 22.7° (38), 23.8° (44), 29.8° (23) and 30.8° (20). The fact that in Fig. 2/3 the relative line intensity of the line at 30.80 seems to be higher than that of the line at 29.80 is due to a close by further line at 31.0° having a relative line intensity of 13.

Melting points are determined by means of a DSC thermogram using a Mettler-Toledo TA8000. DSC (’differential scanning calorimetry") is the technique of dynamic differential calorimetry. Using this technique, the melting temperature both of the ct-crystal form and of the 3-crystal form can be measured by heating the samples until a thermal, i.e. an endothermic or exothermic, reaction is detected by means of ultrasensitive sensors, The melting points indicated in this text are determined using a Mettler-Toledo TA8000 apparatus, about 5.5 to 6.5 mg of each sample being measured in an aluminium crucible with a perforated lid under a quiescent atmosphere of air at a heating rate of 10°C/mm (starting at 200C).

The cL-crystal form of 4-(4-methylpiperazin-1 -ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimi-din-2’ylamino)phenyl}benzamide methanesulfonate is characterised by needle-shaped crystals and is hygroscopic. In this form, the crystals are not particularly well-suited to pharmaceutical formulation as solid dosage forms, because their physical properties, for exampletheirflow characteristics, are unfavourable. Under certain conditions, however, it is

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One of the advantages of the p-crystal form is especially its more compact crystal form, which results in substantially more beneficial flow properties and thus in better processability of the methanesulfonic acid addition salt of a compound of formula I in the 3-crystal form versus the a-crystal form, for example in the manufacture of pharmaceutical preparations.

It is true to say that the a-crystal form of the methanesulfonic acid addition salt of a compound of formula I is metastable at room temperature. However, the 3-crystal form of the methanesulfonic acid addition salt of a compound of formula I is the thermodynamically stable form at room temperature. Greater stability is thus to be expected.

Finally, the -crystal form is less hygroscopic than the a-crystal form of the methanesulfonic acid addition salt of a compound of formula I, as can be shown by the following table:

On measurement of the crystal forms

to the point where equilibrium is reached (no
further adsorption) in a glass climatic chamber at 25°C and at the humidities shown below, the following water content values are found (the % values for the final water content refer to dry weight):

Relative humidity Final water content on adsorption
(%) a-crystal form -crystal form
(%) (molar) (%) (molar)
12 0.14 0.05 0.08 0.02
33 0.18 0.06 0.10 0.03
46 014 0.05
54 0.13 0.04 0.14 0.05
66 0.07 0.02 0.09 0.03
75 0.49 0.16
85 0.18 0.06 0.16 0.05
93 40 13.1 0.15 0.05
97 63 20.8 23 7.5
100

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SUPERINTENDENCIA DE INDUSTRIA V COMERCIO DIRECCION DE NUEVAS CREACIONES

2020

Bogota, D.C.,

Abogado
CARLOS R. OLARTE
Apoderado

ASUNTO

Patente de lnvención

Via Nacional

Via POT (fase nacional)

Radicación 04-111533
TrÆmite 002
Evento 001
Actuación 430
Oficio
Folios

14

fl Patente de Modelo de Utilidad

No. Sal, Internacional
Fecha de Presentación Internal

Cap.l Cap. II

PCT/EP03/041 51
22de Abril de2003

Coma resultado del examen de fonda, realizado con fundamento en el artIculo 45 de la Decision 486 de la ComisiOn de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descrición: Folios: 5 a 31 y 36 como se radicO inicialmente

Reivindicaciones: Folios 32 a 35 como Se radicO inicialmente

4 Folios 79 a 82 modificaciones fase internacional
Folios 97 a 98 modificaciones fase nacional
Folios 118 a 119 mod ificaciones fase nacional
Folios 208 a 209 modificaciones fase nacional
Prioridad: Folios: 01
23 de Abril de 2002, Reino Unido, 0209265.8

Respuesta del solicitante: Folios 113 y 117; Folios 199 a 207

2. AnÆlisisde la Prioridad

La fecha de prioridad del 23 de Abril de 2002 y su correspondiente documento, son aceptados Para el estudio de patentabilidad.

3. Modificaciones

Se acepta la presentaciOn de la correspondiente solicitud divisional a este estudio de patentabilidad.

4. Objeto de la invención

. Titulo de la solicitud: "TABLETA CON ALTA CARGA DE FARMACO" Folio 1.

El objeto de la presente solicitud de patente de invenciôn consiste en una tableta del compuesto de fOrmula I.

El problema planteado en esta solicitud es obtener una tableta de alta carga del fÆrmaco deformula I con una proporciOn entre 30-80% en peso de la fracciOn activa.

Para solucionar este problema tØcnico Ia solicitud en estudio proporciona una tableta del compuesto de fOrmula I o sus sales farmacØuticamente aceptables.

Clasificación Internacional de Patentes (IPC): A61K9/16, A61K9/26, A61K9/28, A61K47/32, A61K47/38, A61K31/505

5. Determinación del Estado de la TØcnica

La fecha que se ha tenido en cuenta para determinar el Estado de la TØcnica es:

Fecha de presentaciOn de la solicitud prioritaria: 23 de Abril de 2002

Considerando que la fecha de presentaciOn de la primera solicitud de patente de la cual se reivindica prioridad es: 23/04/2002 se encontraron los siguientes documeritos del estado de la tØcnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

NO Documento TItulo Fecha de

publicación
Combinations of a receptor

Dl WO 01/47507 tyrosine kinase with an organic 05/07/2001 compound capable of binding to
a1-acidic_glycoprotein
Crystal modification of a N-phenyl-

D3 WO 99/03854 2-pyrimidineamine derivative, 28/01/1999

processes for its manufacture and
its use I

6. AnÆlisis depatentabilidad (articulo 14 D486)

Nivel inventivo (articulo18 D486)

La reivindicaciOn I Se refiere a una tableta que comprende una cantidad farmacológicamente efectiva de un compuesto de formula (I)

114 NTh LN
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