LLOREDA & CIA. S. A.
ABOGADOS

SUPLRINFENDENCIA DE INDUS TRIA Y COMERCIO

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Seæor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES
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Re: P1. -F. HOFFMANN-LA ROCHE AG.-Solicitud de Patente de Invención en Fase Nacional PCT para "TRATAMIENTO CON GEMCITABINA Y UN INHIBIDOR DEL EGRF".-Oase A61K 31/513.-Expediente nümero 06-129.585-

1. Me refiero a ml memorial de 19 de Septiembre de 2007.

2. De conformidad con lo dispuesto en el ArtIculo 5.2.12 de la Circular
Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial nümero 583 de 18 de Diciembre de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente

invenclon.

3. Por otro lado, atentamente me permito manifestar a usted que en el
extracto de la solicitud arriba nombrada, publicado en la Gaceta de la Propiedad Industrial niimero 583 de 18 de Diciembre de 2007, pÆgina 462, la reivindicación nümero 10 aparece publicada en forma equivocada, la reivindicación nmero 10 correcta es como sigue a continuación:

Reivindicación nümero 10 -

El mØtodo de cualquiera de las reivindicaciones 5 a 9, en el que el inhibidor de la actividad quinasa del EGER y la gemcitabina estn destinados a ser administrados al paciente por vIas diferentes.

LLOREDA & CIA. S. A.

4. En vista de lo anterior, muy comedidamente solicito a usted que las
aclaraciones correspondientes sean incluidas en la Fe de Erratas de la próxima Gaceta de la Propiedad Industrial.

5. Me permito recordar a usted, que tal como se informó en el Petitorlo de la
invención, la presente solicitud corresponde a CapItulo II.

6. Anexo me permito presentar recibo nimero 08-43.648, expedido por la
Superintendencia de Industria y Comercio, que acredita el pago de la tasa que

dicho examen causa.

7. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

SeæorSuperintendente,

LICI??LLOORE?DARICAUR?TE?
T.P. 53.215

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Industria y Comercio
S P E R I N T E N DE N C I A

DIVISION DE NUEVAS CREACIONES

RADICACION EXPEDIENTE No. 06129585

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCIÔN

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 583 DE

FECHA 18 DE DICIEMBRE DE 2007 EL TERMINO HABIL SEIcIALADO POR LA

LEY EXPIRA EL 14 DE MARZO DE 2008

NOTA: Dentro del plazo de los sets (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberâ solicitar y canceler el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el ArtIculo 44 de la DecisiOn 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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

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(71) Applicant: UAB RESEARCH FOUNDATION [[S/US]; 701 20th Street, /11 120-0 South, Birming-
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S

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Fat’ two-letter codes and other abbreviations. refer to the "Guid-
ance Notes on Codes andAhbrevialions" appearing at the begin-
ning o/’each regular issue ofthe PCT Gazelle.

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(54) Title: COMBINAFION RADIAI’ION THERAPY AND CHEMOTHERAPY IN CONJUCTION WITH ADMINISTRATION
I OF CROW’lll FACTOR RECEPTOR ANTIBODY

(57) Abstract: This invention comprises a method of inhibiting tumor growth in tumors having growth factor receptors compiSsing administering, about simultaneously, antibodies to the target growth factor receptors, at least one chemotherapeutic agent and radia-tion therapy.

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in vitro. IMC-C225, a chimeric monoclonal antibody to
epidermal growth factor receptor (EGFr), inhibits tumor cell proliferation and enhances cytotoxicity of drugs or radia-
tion. In an evaluation of interaction of 1MC-C225 combined
5 with gemcitabine (GEM) plus radiation therapy (RT) on EGFr
moderately expressing Mia-PaCa-2 human pancreatic cancer
cells it was found IMC-C225+GEM+RT and GEM+RT were equiva-
lent and produced greater inhibition of tumor cell prolifer-
ation as well as apoptosis in vitro compared to IMC-C225 (5
10 gg/ml), RT (3 Gy), GEM (27 riM), IMC-C225+RT, or IMC-C225+-
GEM. Similar clonogenic survival occurred following INC-
C225(5 g/ml)+RT(8 Gy) or IMC-C225+GEM (50 riM)+RT.
Studies were then done in vjyo to evaluate the same
active agents alone or in combination. Athyinic nude mice
15 were implanted subcutaneously with 2 x107Mia-PaCa-2 cells
mixed with Matrigel. Twenty-two days later, mice were
injected intraperitoneally with IMC-C225 (1 mg q3d x 12),
GEM (120 mg/kg q6d, starting 1 day after the first dose of
INC-C225), and RT to the tumor (3 Gy q6d, beginning at 1 day
20 after GEM). Combined treatment of mice bearing tumors
(n=8/group) showed enhancement of complete tumor regressions following treatment with IMC-C225+GEM+RT (8/8) compared to IMC-C225+RT (5/8), IMC-C225+GEM (0/8), GEM+RT (1/8), INC-

10

C225 (1/8), GEM (0/8), or RT (0/8). Animals treated with
25 IMC-C225, GEM, RT, IMC-C225+GEM, IMC-C225+RT, GEM+RT, or
IMC-C225+GEM+RT had mean tumor size doubling times of 46,
22, 35, 59, 201, 101, and 309 days, respectively. Surpris-
ingly, the in vivo data demonstrated greatly improved re-
sults when IMC-C225, GEM, and RT were used in combination, a
30 finding contra to the findings on in vitro studies disclosed
above.
In vitro cell proliferation:
Even though IMC-C225 bloc]cedEGF-.activate.d tyrosine
in pancreatic cancer cell lines, the ability
35 of IMC-C225 to inhibit cell proliferation vitrQ was
different between the two cell lines. After exposure for 96
h to IMC-C225, the BxPC-3 cells showed a 35% reduction in

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cell proliferation as compared to untreated cells. Under
the same conditions, 4iaI’aCa-2 cells did not show any inhib-
itory effect by IMC-C225. A 24 h exposure to the IC., dose
of gemcitabine inhibited approximately 55% of the BxPC-3
5 cell growth whereas approximately 45% inhibition was ob-
served with the MiaPaCa-2 coils. When IMC-C225 was included
24 h prior to the addition of gemcitabine, a modest decrease
in cell proliferation was observed in BxPC-3 cells when
compared to gemcitabine treatment alone. MiaPaCa-2 cells
10 were not affected by the addition of IMC-C225 24 h prior to
gemcitabine treatment compared to gemcitabine treatment
alone.
Radiation treatment (3 Gy) was given on day 2 either
alone or in combination with fllC-C225 and/or gemcitabine
15 treatment. When radiation was combined with IMC-C225, there
was a decrease in cell proliferation compared to radiation
or IMC-C225 treatment alone for the BxPC-3 cells, but not
for the MiaPaCa-2 cells. The combination of radiation and gemcitabine produced a decrease in cell proliferation both
20 for BxPC-3 and MiapaCa-2 cells and the addition of IMC-C225
treatment did not enhance this effect.
ppptotic cell death
The induction of apoptosis was determined using an
identical treatment schedule for cell cycle and cell prolif-
25 oration assays. For BxPC-3 cells, there was not a signifi-
cant increase in apoptosis among the IMC-C225 + gemcitabine
group, the geincitabine + radiation group and the three-agent combination of fl4C-C225 + genicitabine + radiation group.
However these three groups produced a significant increase
30 in apoptotic cell death as compared to all other treatment
groups (p-value<0.05).
For MiaPaCa-2 cells, the gemcitabine treatment resulted
in a small but significant increase in apoptotic cell death
which was not enhanced by any other treatment (p-value
3’ <0.05).
Animal-model tutor theraystudies
Female BALB/c athytnic nude mice, 4-6 weeks old, were

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head and neck cancer: cisplatin, 5-fluorouracil
colon cancer: 5-fluorouracil,. irinotecan (CPT-11),
cisplatin, paclitaxel
pancreatic cancer: gemcitabine, 5-fluorouracil, in -

5 notecan

brain cancer: gemcitabine, 5-fluorouracil
lung cancer: ininotecan
prostate: doxorubicin, cisplatin
Other malignancies wherein EGFr is expressed include breast
10 (often treated with doxorubicin or paclitaxel) and ovarian
(often treated using cisplatin or paclitaxel) malignancies.
The dosage for use with any therapeutic agent in the combi-
nation therapy would usually be on the order of that gener-
ally administered when the agent is used alone.
15 It would also be appropriate to use antibodies against growth factor receptors such as Her-2/neu or epidermal
growth factor receptor in combination with both radiation
therapy and two or more chemotherapy agents. The dosage
range for administration of antibodies to EGFr would be
20 about 100 to 3000 mg/kg. At the present time, in adults
receiving radiation treatment, an initial dosage of 400
mg/kg IMc-c225 is administered on day one with 250 mg/kg
being administered weekly thereafter. For administration in conjunction with both chemotherapy and radiation therapy,
25 the dosage would be continued during the entire period of
therapy. This often translates into 6-8 weeks of adminis-
tration during the usual term of treatment with radiation.
It is surprising that benefit seen in vivo when IMc-
C225+GEM+RT are administered simultaneously in comparison
30 with GEM+RT was not demonstrated in in vitro. It was only
in the intact animal that the benefits of the treatment
methods taught herein were demonstrated.
Studies using Herceptin:
Studies in accord with the studies described above
35 using Herceptin (obtained and available from the pharmacy,
University of Alabama at Birmingham Medical Center) in place
of IMC-C225 were conducted. Athymic nude mice were implant-

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What we claim is:

1. A method of inhibiting tumor growth in tumors having
growth factor receptors comprising administering, about
5 simultaneously, antibodies to the target growth factor
receptors, at least one chemotherapeutic agent and
radiation therapy.

2. The method of claim 1 wherein the first dose of anti-
10 bodies to target growth factor receptors is adminis-
tered before or at the time of administration of at
least one chemotherapeutic agent.

3. The method of claim 1 wherein the antibody is to a
15 epidermal growth factor receptor or a Her-2/neu recep-
tor.

4. The method of claim 1 wherein the chemotherapeutic
agent is chosen from among cisplatin, irinotecan (CPT--
20 11), paclitaxel, gemcitabine, 5-fluorouracil, and doxo-
rubicin.

5. The method of claim 1 wherein the tumor growth to be
inhibited is a pancreatic tumor.
25

6. The method of claim 1 wherein the tumor growth to be
inhibited is a colon tumor.

7. The method of claim 1 wherein the antibody administered
30 is one chosen from IMC-C225 and Herceptin.

8. The method of claim 7 wherein the antibody administered
is Herceptin.

35 9. The method of claim 2 wherein the antibody administered
is one chosen from INC-C225 and Herceptin.

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10. The method of claim 4 wherein the chemotherapeutic
agent is gemcitabine.

11. The method of claim 1 wherein the antibodies adminis-
5 tered are antibodies against epidermal growth factor
receptor.

12. The method of claim 1 wherein the course of treatment
is at least 6 weeks.

13. The method of claim 12 wherein the antibodies against a
growth factor receptor are administered at a higher
dosage at the first dose than at subsequent doses.

15

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Filed on 15 July 2002 (15.07.2002)

(is 601396,136 (CIP)
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Filed on 2 August 2002 (02.08.2002)
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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, 80, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, BC, BE, ES, Fl, GB, GD, GE, GE, (3M, HR, HU, ID, IL, IN, IS, JP,KE, KG, KP, KR, KZ, LC, LK, LR, LS, LI’, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, P1-I, FL, PT, SO, RU, SC, SD, SE. SG, 5K, SU, SY, TJ, TM, TN, TR, TI, TZ, IJA, UG, U’S, lIZ, VC, VN, YtJ, ZA, ZM, ZW.

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SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, OW, ML, MR, NE, SN, ID, TO).

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ance Notes on Codes and itbbreviallons" appearing at the bsy’in-

ning of each regular issue of the PCT Gazette.

(54) Title: MF,TT-IODS FOR THE TREATMENT OF NEOPLASMS

(57) Abstract: The invention features a method for treating a patient having a cancer or other neoplasm by administering to the patient a n,iclosarnide, or a structural or functional analog thereof, and, optionally, one or more antiproliferative agents in an amount effective to inhibit the growth of the neoplasrn.

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Other include brain cancer, breast cancer, cervical cancer, colon
cancer, gastric cancer, kidney cancer, leukemia, liver cancer, lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, sarcoma, skin cancer, testicular cancer, and uterine cancer. These cancers, like lung cancer, are
5 sometimes treated with chemotherapy.
Antiproliferative agents currently in use or in clinical trials include
paclitaxel, docetaxel, tamoxifen, vinoreibme, geincitabme, cisplatm, etoposide, topotecan, irinotecan, anastrozole, rituximab, trastuzumab, fludarabine, cyclopliosphamide, gentuzurnab, carboplatin, interferon, and doxorubicin. The
10 most commonly used antiproliferative agent is paclitaxel, which is used alone or
in combination with other antiproliferative agents such as: 5 -FU, doxorubicin, vinorelbine, cytoxan, and cisplatin.

Summary of the Invention
15 We have discovered that niclosaniide, a salicylanilide compound, acts
an antiproliferative agent against cancer cells, and enhances the activity of antiproliferative agents when used in combination therewith. Structural and functional analogs of nielosamide are known and can also be used alone or in combination with antiproliferative agents in the methods ofthe invention.
20 Accordingly, the invention features a method for treating a patient who has a neoplasm or is at risk for developing a neoplasm by administering to the patient

10 a compound having formula I:
R7

R1 DNR5

EF_ R2., R3

I

25 or a salt thereof. In formula ID is N or CR9; E is N or CR’°; F is Nor CR11; and
R’ is H, halide, OR12, NR14R’, or described by one ofthe formulas:

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Endothellu A atraentan (Abbott) YM-598 (Yamanouchi)
receptor antagonist ZD-4054 (AstraZeneca)

Retinoic acid fenretinide (Johnson Johnson) alitretinoin (Ligand)
receptor agonists LOD1550 (Ligand)

Immuno- interferon dexosome therapy (Anosys)
modulators orteophege (Antigenics) peutrix (Australian Cancer Technology)
UM1I((Progenies) ISF-154 (Tragen)
adenocarcinoma vaccine (iomira) cancer vaccine (Intercell)
CTP-37 (AVI BioPharina) norelin (Biostar)
{RX-2 (Immuno-Rx) BLP-25 (Biomira)
PEP-005 (Poplin Biotech) MGV (Progenies)
syrichrovax vaccines (CTL Immuno) il-alethine (Dovetail)
melanoma vaccine (CTL Immuno) CLL therapy (Vasogen)
p21 RAS vaccine (UernVax)

Hormonal and estrogens prednisone
antihormonal conjugated estrogens methyiprednisolone
agents ethinyl estradiol prednisolone
chlortrianisen aminoglutethimide
idenestrol leuprolide
hydroxyprogesterone caproate goserelin
medroxyprogesterone leuporelin
testosterone bicalutamide

testosterone propionate; flutamide
fluoxymesterone octreotide
mcthyltcstosterone nilutamide
diethylstilbestrol mitotane
megestrol P-04 (Novogen)
tamoxifen 2-methoxyestradiol (EntreMed)
toremofine arzoxifene (Eli Lilly)
dexamethasone

Photodynamic talaporfiui (Light Sciences) Pd-bacteriopheophorbide (Yeda)
agents Theralux (Theratechnologies) lutetium texaphyrin (Pharmacyclics)
motexafin gadolinium (Pharrnaeyclics) hypericin

Tyrosinc Kinase imatinib (Novartis) kahalide F (PharmaMar)
Inhibitors leflunomide (Sugcn/Pharrnacia) CEP-701 (Cephalon)
ZD 1539 (AstraZeneca) CEP-751 (Cephalon)
erlotinjh(Oncogenc Science) MLN518 (Milleniurn)
cariertinib (Pfizer) PKC4 12 (Novartis)
squalarnine (Genaera) phenoxodiol (Novogen)
SU54 16 (Pharmacia) trastuzumab (Genentech)
$U6668 (Pharmacia C225 (ImClone)
ZD4190 (AstraZeneca) rhu-Mab (Genentech)
ZD6474 (AstraZeneca) MDX-H210 (Medarex)
vatalanib (Novartis) 2C4 (Genentech)
PKI 166 (Novartis) MDX-447 (Medarex)
GW2016 (GlaxoSmithiCline) ABX-EGF (Abgenix)
EIC13-509 (Wyeth) IMC-1C1 1 (ImClorie)
gKB-569 (Wyeth)

WO 2004I00906

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Miscellaneous agents

SR-27897 (CCK A inhibitor, Sanofi-Synthelabo) tocladesinc (cyclic AMP agonist, Ribapharrn) alvocidib (COK inhibitor, Aventis)
CV-247 (COX-2 inhibitor, Ivy Medical)
P54 (COX-2 inhibitor, Phytopharm)
CapCelliM (CYP450 stimulant, Bavarian Nordic) GCS-100 (gal3 antagonist, GlycoGenesys)
GI7DT immunogen (gastric inhibitor, Aphton) efaproxiral (oxygenator, Allos Therapeutics) P1-88 (heparanase inhibitor, Progen)
tesmilifene (histamine antagonist, YM
BioSciences)
histamine (histamine H2 receptor agonist, Maxim) tiazoflirin (IMPDH inhibitor, Ribaphann)
cilengitide (integrin antagonist, Merck KGaA) SR-31747 (IL-i antagonist, Sanofi-Synthelabo) CCI-779 (rnTOR kinase inhibitor, Wyeth)
exisulind (P1DB V inhibitor, Cell Pathways) CP-461 (PDE V inhibitor, Cell Pathways)
AG-2037 (GART inhibitor, Pfizer)
WX-UK1 (plasminogen activator inhibitor, Wilex) P31-1402 (PMN stimulant, ProMetic LifeSciences) boitinoriiib (proteasome inhibitor, Millennium) SRL-172 (T cell stimulant, SR Pharma)
TLK-286 (giutatbione S transferase inhibitor, Telik)
PT- 100 (growth factor agonist, Point Therapeutics) midostaurin (PKC inhibitor, Novartis)
bryostatin-1 (PKC stimulant, (IPC Biotech) CDA-II (apoptosis promotor, Everlife)
SDX- 101 (apoptosis promotor, Salmedix)
cetlatonin (apoptosis promoter, ChemGen ax)

PCT/US2003/022026

BCX-1777 (PNP inhibitor, BioCryst)
ranpirnase (ribonueleae stimulant, Alfacell) galarubicin (RNA synthesis inhibitor, Dong-A) tirapazamine (reducing agent, SRI International) N-acetylcysteine (reducing agent, Zambori) R-flurbiprofen (NF-kappa3 inhibitor, Encore) 3CPA (NF-kappaB inhibitor, Active Biotech) seocalcitol (vitamin D receptor agonist, Leo)
131 -1-TM-601 (DNA antagonist, TransMolecular) eflornithine (ODC inhibitor, ILEX Oncology) minodronic acid (osteolast inhibitor, Yamanouchi) indisulam (p53 stimulant, Eisai)
aplidine (PPT inhibitor, PharmaMar)
rituximab (CD20 antibody, Genentech)
gemtuzumab (CD33 antibody, Wyeth Ayerst)

P02 (hematopoiesis enhancer, Pharmagenesis) ImmunolTM (triclosan oral rinse, Endo)
triacetyluridine (uridine prodrug, Welistat) SN-407 1 (sarcoma agent, Signature BioScience) TransMID107rM (immunotoxin, KS Biomedix) PCK-3 145 (apoptosis promotor, Procyon)
doranidazole (apoptosis promotor, Pola)
CHS-828 (cytotoxic agent, Leo)
trans-retinoic acid (differentiator, NIH)
MX6 (apoptosis promoter, MAXIA)
apomine (apoptosis promotor, ILEX Oncology)
urocidin (apoptosis promotor, Bioniche)
Ro-3 1-745 3 (apoptosis promotor, LaRoche)
brostallicin (apoptosis promotor, Pharmacia)

Furthennore, the invention also features a composition, that icludes (i) a compound described above (e.g., offormula (I), an antihelminthic agent, or otherwise listed above) and (ii) an antiproliferative agent,

The invention also features a method for identifying combinations of compounds useful for treating a patient having a neoplasm. The method includes the steps of (a) contacting cancer cells in vitro with (i) niclosamide or an antiproliferative agent and (ii) a candidate compound, and (b) determining whether the combination of niclosamide or an antiproliferative and the candidate compound reduces growth ofthe cancer cells relative to cancer cells contacted with niclosamide or an antiproliferative agent but riotcontacted with the candidate compound, or cancer cells contacted with the candidate compound but

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’1)

WO 2004/00ft906 PCTIUS2003/022026

Any of a number of strategies can h pursued in order toobtain controlled
release in which the rate ofrelease outweighs the rate ofmetabolism ofthe compound in question. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients,
S including, e.g., various types of controlled release compositions and coatings.
Thus, the drug is formulated with appropriate excipients into a pharmaceutical composition that, upon administration, releases the drug in a controlled manner. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, in. icrospheres, nanoparticles,
10 patches, and liposomes.

Solid Dosage Forms For Oral Use
Formulations for oral use include tablets containing the active ingredient(s)
in a mixture with non-toxic pharmaceutically acceptable excipients.. These
15 excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol,
sugar, maimitol, microcrystalline cellulose, starches including potato starch,
calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate,
or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch,
20 croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose,
glucose, sorhitol, acacia, alginic acid, sodium alginate, gelatin, starch,
pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulos c, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating
25 agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic
acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.
The tablets may be uncoated or they may, be coated by known techniques,
30 optionally to delay disintegration and absorption in the gastrointestinal tract and
thereby providing a sustained action over a longer period. The coating may be

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIRECCION DE NUEVAS CREACIONES

2020

Bogota, D.C.

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO RadicaciÆn 06-129585
TrÆmite 011
Evento 379
Actuaciôn 411
Oficio
Folios 016

Patente de InvenciOn Patente de Modelo de Utilidad LIII

Via Nacional El

Via PCT (fase nacional) j Cap.I EJ Cap, II
No, Sol. Internacional PCT/EP2005/005735

Fecha de Presentación Internal, 27/05/05

Como resultado del examen de fondo, realizado con fundamento en el articulo 45
de la Decision 486 de la Comisión de la Comunidad Andiria, se le comunica:

1. Documentos estudiados

S1.1, Descripción: Folios: 52 a 127 como se radicO inicialmente

1.2. Reivindicaciones: Folios: 25 a 29 como se radicó inicialmente
Folios: 128 a 131 modificado.

1.3. Prioridad: 03/06/04; US;60/576541

2. Objeto de la invención

Titulo de la invenciOn: TfATAMIENTO CON GEMCITABINA Y UN INHIBIDOR DE
EGFR,

Problema TØcnico Planteado: Necesidad de tratamientos mas eficaces frente a la neoplasia y a otros tratamientos proliferativos.

SoluciOn: Composicion segün la reivindicaciOn 1, su mØtodo de elaboraciOn.

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IPC: A61 K31/513, 31/517, 31/5377, 31/519, 31/4706, A61 p35/00

De la solicitud de Patente

2.1. ReMndicaciones (artIculo 30 D 486)

Reivindicaciôn 1, no esta sustentada con un ejemplo de una composiciOn que contenga los dos principios activos, un inhibidor de la actividad quinasa del EGFR (erlotinib) y gemcitabina en concentraciones especificas, que muestren claramente un efecto tØcnico inesperado, como una posible sinergia; ya que de las composiciones solo se hace mención. En la descripción.

Reivindicación 4, no esta sustentada con un ejemplo de una composición que contenga los principios activos: 1) un inhibidor de la actividad quinasa del EGFR (erlotinib) 2) gemcitabina y 3) ademÆs uno ma’s agentes antineoplÆsicos diferentes; en concentraciones determinadas, que muestren claramente un efecto tØcnico inesperado, como una posible sinergia. AdemÆs tampoco existe
concision en esta reivindicación al mencionar ’uno 0 mÆs agentes
antineoplÆsicosdiferentes", ya que la expresiOn anterior se refiere a una categorla farmacolOgica de compuestos muy general, que presentan esta actividad.

La reivindicación 5, reclama un mØtodo de elaboración de un medicamento caracterizado per utilizar un inhibidor de la actividad quinasa del EGFR y gemcitabina. Dicha reivindicación de mØtodo de elaboraciOn se debe caracterizar por las etapas y condiciones del mismo, y en esta, solo se mencionan los componentes que se utilizan en dicho mØtodo; ademÆs "un inhibidor de la
actividad quinasa del EGFR’, se refiere a una categorla farmacologica de compuestos que presentan esta actividad.

La reivindicaciOn 6, que se refiere a un mØtodo tambiØn adolece de falta de
claridad, ademÆs no agrega ninguna caracteristica esencial de un mØtodo de elaboraciÆn.

. Las reivindicaciones 22-24, no estÆn sqstentadas con LJfl ejemplo de una composiciôn que contenga los dos principios activos, un inhibidor de la actividad
quinasa del EGFR y gemcitabina y concentraciones especIficas, que muestren
claramente un efecto tØcnico logrado, como una posible sinergia

La reivindicaciOn 23, menciona el tØrmino el "subterapØutico" el cual no es
conciso.

3. Determinación del Estado de la TØcnica

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

Fecha de presentaciôn de la solicitud prioritaria: 03/06/04.

Teniendo en cuenta la fecha indicada se realizO la bUsqueda en el estado de la tØcnica de documentos relacionados con la solicitud encontrÆndose los siguientes documentos ms relevantes:

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NO Documento Titulo

Combination radiation therapy

Fecha de
publicación*

Dl W00245653 and chemotherapy in conjunction Junio 13 de 2002 with administration of growth
factor receptor antibody

02 W02004006906 Methods for the treatment of Enero 22 de 2004 neoplasms
Dl (folios: 158-163); D2 (folios: 164-168)

4. Anàlisis de patentabilidad (articulo 14 D486)

4.1 Novedad (artIculo 16 D486)

La reivindicación 1, reclama una composición farmacØutica, que comprende: Un
inhibidor de la quinasa del EGFR y gemcitabina, con un vehIculo farmacØuticamente aceptable.

Dl (W00245653), divulga la combinación de un inhibidor de quinasa del EGFR y
. gemcitabina (folios 159-161; pg 4, linea 33; pg 5, lInea 14; reivindicaciones 1, 4,10).

Comparando elemento por elemento se observa que las caracteristicas tØcnicas
esenciales de la presente reivindicaciôn ya se divulgaban en Dl, por lo tanto se
concluye que la materia reclamada no es nueva.

La reivindicación 4, reclama una composición farmacØutica, de acuerdo a Ia reivindicación 1: que ademÆs comprende uno mÆs agentes antineoplÆsicos diferentes.

D2 (W02004006906) da a conocer composiciones farmacØuticas, que sirven para el cancer (folio 165, pg2, lineas 1-4; folio 167, pg 10; folio 168, pg 32 lineas 13-
15) y ademÆs logran disminuir la toxicidad de los antiproliferativos (reivindicación 25), que incluyen:

un compuesto de formula (I), que actüa como agente antirol iferativo.
-agentes antiproliferativos: (gemcitabina, folio 165, pg 2), Un inhibidor de tirosina quinasa (inhibidor de EGFR, erlotinib, folio 166, pg 9).
- un vehIculo (folio 168, pg 32).

Comparando elemento por elemento se observa que las caracterIsticas tØcnicas esenciales de la presente reivindicación ya se divulgaban en D2, por lo tanto Se concluye que la materia reclamada no es nueva.

4.2 Nivel inventivo (artIculo18 D486)

La reivindicación 2, reclama una composicion farmacØutica, que comprende: Un inhibidor de la quinasa del EGFR, erlotinib, y gemcitabina, con un vehiculo farmacØuticamente aceptable.

El Estado de la TØcnica mÆs cercano es D2 (W02004006906) da a conocer composiciones farmacØuticas, que sirven para el cancer (folio 165, pg2, lineas 1-4; folio 167, pg 10; folio 168, pg 32 lineas 13-15) y ademÆs logran disminuir la toxicidad de los antiproliferativos (reivindicación 25), que incluyen:

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un compuesto de formula (I), que actüa como agente anti roliferativo.
-agentes antiproliferativos: (gemcitabina, folio 165, pg 2), un inhibidor de tirosina quinasa (inhibidor de EGFR, erlotinib, folio 166, pg 9).
- un vehIculo (folio 168, pg 32).

La composición reclamada en esta reivindicación, se diferencia de las composiciones de D2, en que esta, contiene solo dos agentes antiproliferativos.

El hecho de que la composiciOn reclamada contenga el compuesto inhibidor de EGFR y la gemcitabina, no da evidencia de un efecto tØcnico inesperado.

El Problema TØcnico Objetivo era "cômo obtener composiciones coma alternativa, a las ya existentes en D2".

Ademâs, en ausencia de un ejemplo de una composiciôn que contenga los dos principios activos (Erlotinib y gemcitabina) y concentraciones especificas, que mediante un ensayos muestren claramente un efecto tØcnico inesperado, como una po&ble sinergia; se concluye que, La presente reivindicaciÆn, es obvia, porque el Experto en la Materia enfrentado al problema de "coma obtener composiciones coma alternativa, a las ya existentes en D2", tomarla las enseæanzas ya divulgadas, logrando de esta forma la composicion objeto de esta solicitud.

Por Ia tanto las reivindicaciones 2 y sus dependientes 3, 19-20.

La reivindicaciOn 5, reclama un mØtodo de elaboración de un medicamento caracterizado porque se utilizan un inhibidor de la quinasa de EGFR y gemcitabina. Dicha reivindicación no esta caracterizada por las etapas y condiciones, de un metodo de elaboracion de un medicamento y solo menciona
los componentes que se utilizan en el mismO.

Los documentos Dl y D2, que se refieren a composiciones anticancerIgenas,
muestran los principios activos mediante los cuales estÆ caracterizado el mØtodo
de elaboraciOn, por lo tanto la presente reivindicación, no tiene nivel inventivo, asI
coma las reivindicaciones 6-18 y 21, que reclaman un mØtodo de elaboraciOn de

S un medicamento, de acuerdo con la reiviridicaciOn 5, que no agregan ninguna

caracteristica esencial de un mØtodo de elaboraciOn de un medicamento,

5. Conclusion:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados
asi:

= INo Documento N Reivindicaciones Requisito que afecta afectadas
Dl W00245653 1 Novedad
3 5,6,8, 19-21 Nivel Inventivo

W02004006906 4 D2 Novedad
3, 5,6,8, 19-21 Nivel Inventivo

En cumplimiento del artIculo 45 de la Decision 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de

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sesenta dIas contados a partir de la fecha de notificación de (a presente comunicaciôn. En caso de no dar respuesta al presente requerimiento, 0 Sj a pesar de la respuesta subsistieran los impedimentos para la coricesión, se denegarÆ lapatente.

NotifIquese el presente oficio conforme a Ia dispuesto en el numeral 5.2, literal e), del capitulo quinto del jitulo ppifero de la Circular Linica N° 10 de 2001.

ALIX CARMENZA/CESPEDES DE VERGEL

Directora de NuØvas Creaciones (C)

El anterior requerirniento fue notificado par fijación en lista, de fecha

CONCEPTO TECNICO No.1704 EXAMINADOR TECNICO
Codigo No.202078

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