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As. 2652/PCT.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES
E. S. D.

Ref.: Expediente No. 04034537
Solicitud de Patente a nombre de
NOVARTIS AG

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Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogota, en la Carrera ii A No. 94-76 of. 305, obrando como apoderada dc Ia sociedad NOVARTIS AG, clomicthada en Basilea, Suiza, solicitante de la patente de la referencia, pido a usted quc se proceda a examinar si la invcnción, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial ci recibo No. 06-2,123 de 11 de enero de 2006, por la sun-ia dc $194.000,00, con lo cual queda cubicrta la tasa oficial correspondiente a dicho estudio.

SeæorSuperintendente,

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T.P. 68.228
Cod. 5376
JEU/mI.

SUPERINTENDENCIA DE INDUSTRIA V COHERCIO

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RECIBO OFICIAL DE CAJA: 06 2’,123 FECHA ENERO 11 DE 2006

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TOTAL $ 194000.00

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RECIBO DE CAJA APLICADO AL EXPEDIENIE N.

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Industria y Comercio
SUPERINTENDENCIA

DIVISION DE NUEVAS CREACIONES

RADICACION EXPEDIENTE No.04-34537

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 557

DE FECHA 31 DE OCTUBRE DEL 2005, EL TERMINO HABIL SEfIALADO POR

LA LEY EXPIRA EL 27 DE ENERO DEL 2006

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberÆ solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con 10 establecido en el Articulo 44 de la Decision 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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Bogota D.C., Noviembre de 2006

NO X

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION

International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification I I (11) International Publication Number: WO 00138730

A61K 45/06, 41/00, A61P 35/00 I A2 I (43) International Publication Date: 6 July 200(1(06.07.00)

(21) International Application Number: PCT/US99/30693

(22) International Filing Date: 22 December 1999 (22.12.99)

(30) Priority Data:
60/113,786 23 December 1998 (23.12.98) US

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, EQ, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE,
ES, Fl, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
KE, KG, K?, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, FL, PT, RO, RU,
SD, SE, SG, SI, 5K, SL, TJ, TM, TR, U, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, ARIPO patent (OH, GM, KB,
LS, MW, SD, SL, SZ. TZ, UG, ZW), Eurasian patent (AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT,
BE, CH, CY, DE, DK, ES, Fl, FR, GB, GR, III, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, Cl, CM,
GA, GN, OW, ML, MR, NE, SN, TD, TO).

Published

Without international search report and to be republished
upon receipt of that report.

(54) Title: METHOD OF USING A CYCLOOXYGENASE-2 INHIBITOR AND ONE OR MORE ANTINEOPLASTIC AGENTS AS A COMBINATION THERAPY IN THE TREATMENT OF NEOPLASIA

(57) Abstract

The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of a cyclooxygenase-2
:or and an antineoplastic agent.

WO 00/38730 - 10 - PCTS990693 animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.
The methods and combinations of the present
invention may be used for the treatment or prevention of
5 neoplasia disorders including acral lentiginous
melanoma, actinic keratoses, adenocarcinoma, adenoid
cycstic carcinoma, adenomas, adenosarcoma, adenosquamous
carcinoma, astrocytic tumors, bartholin gland carcinoma,
basal cell carcinoma, bronchial gland carcinomas,
. 10 capillary, carcinoids, carcinoma, carcinosarcoma,
cavernous, cholangiocarcinoma, chondosarcoma, choriod
plexus papilloma/carcinoma, clear cell carcinoma,
cystadenoma, endodermal sinus tumor, endometrial
hyperplasia, endometrial stromal sarcoma, endometriold
15 adenocarcinoma, ependymal, epitheloid, Ewing’s sarcoma,
fibrolamellar, focal nodular hyperplasia, gastrinoma,
germ cell tumors, glioblastoma, glucagonoma, hemangiblastomas, hemangloendothelioma, hemangiomas,
hepatic adenoma, hepatic adenomatosis, hepatocellular
20 carcinoma, insulinoma, intaepithelial neoplasia,
interepithelial neoplasia, invasive
squamous cell cell carcinoma,
leiomyosarcoma, lentigo maligna melanomas, malignant
melanoma, malignant mesothelial tumors, medulloblastoma,
25 medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular
melanoma, oat cell carcinoma, oligodendroglial,
osteosarcoma, pancreatic polypeptide, papillary serous
30 adenocarcinoma, pineal cell, pituitary tumors,
plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma,

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sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor,
squamous carcinoma, squamous cell carcinoma,
submesothelial, superficial spreading melanoma,
5 undifferentiated carcinoma, uveal melanoma, verrucous
carcinoma, viporna, well differentiated carcinoma, and

Wilm’s tumor.
The methods and combinations of the present
invention provide one or more benefits. Combinations of

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COX-2 inhibitors with the compounds, compositions,
agents and therapies of the present invention are useful
in treating and preventing neoplasia disorders.
Preferably, the COX-2 inhibitors and the compounds, compositions, agents and therapies of the present
15 invention are administered in combination at a low dose,
that is, at a dose lower than has been conventionally
used in clinical situations.

A benefit of lowering the dose of the compounds, compositions, agents and therapies of the present
20 invention administered to a mammal includes a decrease
in the incidence of adverse effects associated with
higher dosages. For example, by the lowering the dosage
of a chemotherapeutic agent such as mnethotrexate, a reduction in the frequency and the severity of nausea
25 and vomiting will result when compared to that observed
at higher dosages. Similar benefits are contemplated
for the compounds, compositions, agents and therapies in combination with the COX-2 inhibitors of the present invention.
30 By lowering the incidence of adverse effects, an improvement in the quality of life of a patient
undergoing treatment for cancer is contemplated.

WO 00/38730 - 16 - PCT1US99130693 administration are well and widely known in the pharmaceutical art.
Liquid dosage forms for oral administration can
include pharmaceutically acceptable emulsions,
5 solutions, suspensions, syrups, and elixirs containing
inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

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10 The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.
The present invention further includes kits
15 comprising a COX-2inhibitor and an antineoplastic agent.
The term "treatment" refers to any process, action,
application, therapy, or the like, wherein a mammal, including a human being, is subject to medical aid with
the object of improving the mammal’s condition, directly
20 or indirectly.
The term "inhibition," in the context of neoplasia,
tumor growth or tumor cell growth, may be assessed by delayed appearance of primary or secondary tumors,
slowed development of primary or secondary tumors,
25 decreased occurrence of primary or secondary tumors,
slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors,
among others. In the extreme, complete inhibition, is
referred to herein as prevention or chemoprevention.
30 The term "prevention" includes either preventing
the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of

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or in multiple, single capsules for each of the
therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent
can be effected by any appropriate route including, but
5 not limited to, oral routes, intravenous routes,
intramuscular routes, and direct absorption through
mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes.
For example, a first therapeutic agent of the
10 combination selected may be administered by intravenous
injection while the other therapeutic agents of the combination may be administered orally. Alternatively,
for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by
15 intravenous injection. The sequence in which the
therapeutic agents are administered is not narrowly
critical. "Combination therapy" also can embrace the
administration of the therapeutic agents as described
above in further combination with other biologically
20 active ingredients (such as, but not limited to, a
Ssecond and different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or
radiation treatment). Where the combination therapy
further comprises radiation treatment, the radiation
25 treatment may be conducted at any suitable time so long
as a beneficial effect from the CO -action of the combination of the therapeutic agents and radiation treatment is achieved. For example, in appropriate
cases, the beneficial effect is still achieved when the
30 radiation treatment is temporally removed from the
administration of the therapeutic agents, perhaps by
days or even weeks.

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production of angiogenic factors such as vascular endothelial growth factor.
Consequently, the administration of a COX-2
inhibitor in combination with an anti HER-2/neu
5 antibodies such as trastuzumab (Herceptinfi) and other
therapies directed at inhibiting HER-2/neu is contemplated to treat cancers in which HER-2/neu is overexpressed -
Also, it is contemplated that COX-2 levels are
10 elevated in tumors with amplification and/or
overexpression of other oncogenes including but not
limited to c-myc, -myc, L-myc, K-ras, H-ras, N-ras.
Products of COX-2 activity stimulate cell proliferation, inhibit immune surveillance, increase invasiveness of
15 malignant cells, and promote angiogenesis. Consequently,
the administration of a COX-2 inhibitor in combination
with an agent or agents that inhibits or suppresses oncogenes is contemplated to prevent or treat cancers in which oncogenes are overexpressed.
20 Accordingly, there is a need for a method of treating or preventing cancer in a patient that overexpresses COX-2 and/or an oncogene. Methods for the production of anti- ErbB2 antibodies are described in WO 99/31140.
25 Specific COX-2 inhibitors are useful for the treatment of cancer (W098/16227) and in several animal models reduce angiogenesis driven by various growth
factors (W098/22101). Anti-angiogenesis was achieved
with a COX-2 inhibitor in rats implanted with bFGF,
30 vascular endothelium growth factor (VEGF) or
carrageenan, proteins with well-known angiogenic properties. (Masferrer, et al., 89 Annual Meeting of

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4- t5- (4-chorophenyl) -3- (trifluoromethyl) -1H-pyrazole-1-yll benzenesulfonamide;

Still more preferably, the COX-2 inhibitors that
may be used in the present invention include, but are not limited to celecoxib, valdecoxib, parecoxib, rofecoxib, and Japan Tobacco JTE-522.
Also included in the combination of the invention
are the isomeric forms and tautomers of the described compounds and the pharmaceutically-acceptable salts thereof. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propioriic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, funtaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, ernbonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, b-hydroxybutyric, galactaric and galacturonic acids.
Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include

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cells with F-araA is associated with the accumulation of cells at the Cl/S phase boundary and in S phase; thus,
it is a cell cycle S phase-specific drug. InCorp of the
active metabolite, F-araATP, retards DNA chain
5 elongation. F-araA is also a potent inhibitor of
ribonucleotide reductase, the key enzyme responsible for the formation of dATP. 2-Chiorodeoxyadenosine is useful
in the treatment of low grade B-cell neoplasms such as chronic lymphocytic leukemia, non-Hodgkins’ lymphoma,
10 and hairy-cell leukemia. The spectrum of activity is
similar to that of Fludara. The compound inhibits DNA synthesis in growing cells and inhibits DNA repair in resting cells.
A fifth family of antineoplastic agents which may
15 be used in combination with the present invention
consists of hormonal agents. Suitable hormonal -type
antineoplastic agents that may be used in the present
invention include, but are not limited to Abarelix;
Abbott A-84861; Abiraterone acetate; Axninoglutethimide;
20 anastrozole; Asta Medica AN-207; Antide; Chugai AG-041R;
SAvorelin; aseranox; Sensus B2036 -PEG; Bicalutamide; buserelin; BTC CB-7598; BTG CB-7630; Casodex; cetrolix;
clastroban; clodronate disodium; Cosudex; Rotta Research
CR-1505; cytadren; crinone; deslorelin; droloxifene;
25 dutasteride; Eliinina; Laval University EM-800; Laval
University EM-652; epitiostanol; epristeride; Mediolanum
EP-23904; EntreMed 2 -ME; exemestane; fadrozole;
finasteride; flutamide; formestane; Pharmacia & Upjohn FCE-24304; ganirelix; goserelin; Shire gonadorelin
30 agonist; Glaxo Wellcome GW-5638; Hoechst Marion Roussel
Hoe-766; NCI hCG; idoxifene; isocordoin; Zeneca ICI -
182780; Zeneca ICI -118630; Tulane University J015X;

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Table No. 10.
agents.

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Median dosages for selected cancer

NAME OF CHEMOTHERAPEUTIC
5 AGENT MEDIAN DOSAGE

Asparaginase 10,000 units
Bleoinycin Sulfate 15 units
Carboplatin 50-450 mg.
10 Carmustine 100 mg.
Cisplatin 10-50 mg.
Cladribine 10 mg.
Cyclophosphamide 100 mg. -2 gm.
(lyophilized)
15 Cyclophosphaxnide (non- 100 mg. -2 gin.
lyophilized)
Cytarabine (lyophilized 100 mg. -2 gin.
powder)
Dacarbazine 100 mg. -200 mg.
20 Dactinomycin 0.5 mg.
SDaunorubicin 20
Diethylstilbestrol 250 mg.
Doxorubicin 10-150 mg.
Etidronate 300 mg.
25 Etoposide 100 mg
Floxuridine 500 mg.
Fludarabine Phosphate 50 mg.
Fluorouracil 500 Mg. -5 gin.
Goserelin 3.6 mg.
30 Granisetron Hydrochloride 1 mg.
Idarubicin 5-10 mg.
Ifosfamide 1-3 gm.

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Leucovorin Calcium 50-350 mg.
Leuprolide 3.75-7.5 mg.
1,.lechlorethamine 10 mg.
MedroxyprogesterOfle 1 gin.
Meiphalan 50 gin.
Methotrexate 20 mg. -1 gin.
Mitomycin 5-40 mg.
Mitoxantrone 20-30 mg.
Ondansetrori Hydrochloride 40 mg.
Paclitaxel 30 mg.
Paxnidronate Disodium 30-90 mg.

Pegaspargase 750 units
Plicamyciri 2,500 mcgm.
Streptozocin 1 gm.
Thiotepa 15 mg.
Teniposide 50 mg.
Vinbiastine 10 mg.
Vincristine 1-5 mg.
Aldesleukin 22 million units
Epoetin Alfa 2,000-10,000 units
Filgrastim 300-480 incgm.
Immune Globulin 500 mg. -10 gin.
Interferon Alpha-2a 3-36 million units
Interferon Alpha-2b 3-50 million units
Levamisole 50 mg. Octreotide 1,000-5,000 mncgm. Srgramostim 250-500 mccun.

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present invention can be prepared in the manner set
forth in EP 00/095,875. The vinorelbine used in the
therapeutic combinations of the present invention can be prepared in the manner set forth in EP 00/010,458. The
5 sulindac sulfone used in the therapeutic combinations of
the present invention can be prepared in the manner set
forth in U.S. Patent No. 5,858,694. The selenium
(selenomethionine) used in the therapeutic combinations
of the present invention can be prepared in the manner
10 set forth in EP 08/04,927. The ursodeoxycholic acid
used in the therapeutic combinations of.the present invention can be prepared in the manner set forth in WO 97/34,608. Ursodeoxycholic acid can also be prepared according to the manner set forth in EP 05/99,282.
15 Finally, ursodeoxycholic acid can be prepared according
to the manner set forth in U.S. Patent No. 5,843,929.
Still more preferred antineoplastic agents include:
anastrozole, calcium carbonate, capecitabine,
carboplatin, cisplatin, Cell Pathways CP-461,
20 cyclophosphaxnide, docetaxel, doxorubicin, etoposide,
Exisulindfi, fluorouracil (5 -FU), fluoxymestrine,
gemcitabine, goserelin, irinotecan, ketoconazole,
letrozol, leucovorin, levamisole, megestrol,
mitoxantrone, paclitaxel, raloxifene, retinoic acid,
25 tamoxifen, thiotepa, topotecan, toremifene, vinorelbine,
vinbiastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac suifone and eflornithine (DFMO).
The phrase "taxane" includes a family of diterpene
30 alkaloids all of which contain a particular eight (8)
member ’taxane" ring structure. Taxanes such as
paclitaxel prevent the normal post division breakdown of

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microtubules which form to pull and separate the newly duplicated chromosome pairs to opposite poles of the
cell prior to cell division. In cancer cells which are
rapidly dividing, taxane therapy causes the microtubules
S to accumulate which ultimately prevents further division
of the cancer cell. Thxane therapy also affects other
cell processes dependant on microtubules such as cell motility, cell shape and intracellular transport. The major adverse side-effects associated with taxane
S10 therapy can be classified into cardiac effects,
neurotoxicity, haematological toxicity, and
hypersensitivity reactions. (See Exp. Opin. Thera.
Patents (1998) 8(5), hereby incorporated by reference). Specific adverse side-effects include neutropenia,
15 alopecia, bradycardia, cardiac conduction defects, acute
hypersensitivity reactions, neuropathy, mucositis,
dermatitis, extravascular fluid accumulation,
arthraj.gias, and myalgias. Various treatment regimens
have been developed in an effort to minimize the side
20 effects of taxane therapy, but adverse side-effects
remain the limiting factor in taxane therapy.
It has been recently discovered in vitro that COX-2 expression is elevated in cells treated with taxanes. Elevated levels of COX-2 expression are associated with
25 inflammation and generation of other COX-2 derived
prostaglandin side effects. Consequently, when taxane
therapy is provided to a patient, the administration of
a COX-2 inhibitor is contemplated to reduce the inflammatory and other COX-2 derived prostaglandin side
30 effects associated with taxane therapy.
Taxane derivatives have been found to be useful in treating refractory ovarian carcinoma, urothelial

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cancer, breast carcinoma, melanoma, non-small -cell lung
carcinoma, gastric, and colon carcinomas, squamous
carcinoma of the head and neck, lymphoblastic,
rnyeloblastic leukemia, and carcinoma of the esophagus.
5 Paclitaxel is typically administered in a 15-420

mg/m2dose over a 6 to 24 hour infusion. For renal cell
carcinoma, squamous carcinoma of head and neck,
carcinoma of esophagus, small and non-small cell lung
cancer, and breast cancer, paclitaxel is typically
10 administered as a 250 mg/rn224 hour infusion every 3
weeks. For refractory ovarian cancer paclitaxel is
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typically dose escalated starting at 110 mg/rn

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Docetaxel is typically administered in a 60 - 100 mg/M
Lv. over 1 hour, every three weeks. It should be
15 noted, however, that specific dose regimen depends upon
dosing considerations based upon a variety of factors including the type of neoplasia; the stage of the
neoplasm; the age, weight, sex, and medical condition of
the patient; the route of administration; the renal and
20 hepatic function of the patient; and the particular
agents and combination employed.
In one embodiment, paclitaxel is used in the
present invention in combination with a cyclooxygenase-2 inhibitor and with cisplatin, cyclophosphamide, or
25 doxorubicin for the treatment of breast cancer. In
another embodiment paciltaxel is used in combination
with a cyclooxygenase-2 inhibitor, cisplatin or
carboplatin, and ifosfamide for the treatment of ovarian

cancer.

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metastat, celecoxib, rofecoxib, JTE-522, EMD-121974, and D-2163 (BMS-275291)

Cryotherapy
5 Cryotherapy recently has been applied to the
treatment of some cancers. Methods and compositions of
the present invention also could be used in conjunction
with an effective therapy of this type.
. All of the various cell types of the body can be
10 transformed into benign or malignant neoplasia or tumor
cells and are contemplated as objects of the invention.
A "benign" tumor cell denotes the non-invasive and non-metastasized state of a neoplasm. In man the most
frequent neoplasia site is lung, followed by colorectal,
15 breast, prostate, bladder, pancreas, and then ovary.
Other prevalent types of cancer include leukemia,
central nervous system cancers, including brain cancer, melanoma, lymphoma, erythroleukemia, uterine cancer, and head and neck cancer. Examples 1 through 9 are provided

40

20 to illustrate contemplated therapeutic combinations, and
are not intended to limit the scope of the invention.

Illustrations

25 The following non-limiting illustrative examples
describe various cancer diseases and therapeutic
approaches that may be used in the present invention,
and are for illustrative purposes only. Preferred COX-2 inhibitors of the below non-limiting illustrations
30 include but are not limited to celecoxib, rofecoxib, and

JTE-522.

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A preferred therapy for the treatment of maligant glioma is a combination of therapeutically effective amounts of one or more COX-2 inhibitors in combination with the following combinations of therapies and antineoplastic agents:: 1) radiation therapy, BCNU (carmustine); 2) radiation therapy, methyl CCNU (lomustine); 3) radiation therapy, medol; 4) radiation therapy, procarbazine; 5) radiation therapy, BCNU, medrol; 6) hyperfraction radiation therapy, BCNU; 7) radiation therapy, misonidazole, BCNU; 8) radiation therapy, streptozotocin; 9) radiation therapy, BCNU, procarbazine; 10) radiation therapy, BCNU, hydroxyurea, procarbazine, VM-26; 11) radiation therapy, BNCU, 5-flourouacil; 12) radiation therapy, Methyl CCNU, dacarbazine; 13) radiation therapy, misonidazole, BCNU;
14) diaziquone; 15) radiation therapy, PCNU; 16) procarbazine (matulane), CCNU, vincristine. A preferred dose of radiation therapy is about 5,500 to about 6,000 cGY. Preferred radiosensitizers include misonidazole, intra-arterial Budr and intravenous iododeoxyuridine (IUdR). It is also contemplated that radiosurgery may be used in combinations with antiangiogenesis agents. Example 9
Additional examples of combinations are listed in Table No 19.

Table No. 19. Combination therapy examples

COX-2
Inhibitor

Antineoplastic
Agents

Indication

Celecoxib Anastrozole Breast
Celecoxib Capecitabine Breast
Celecoxib Docetaxel Breast
Celecoxib Gemcitabine Breast,

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Pancreas
Celecoxib Letrozole Breast
Celecoxib Megestrol Breast
Celecoxib Paclitaxel Breast
Celecoxib Tamoxiten Breast
Celecoxib Toremifene Breast
Celecoxib Vinorelbine Breast, Lung
Celecoxib Topotecan Lung
Celecoxib Etoposide Lung
Celecoxib Fluorouracil Colon
Celecoxib Irinotecari (CPT-
11)

Colon, Bladder

Celecoxib Retinoids Colon
Celecoxib DFMO Colon
Celecoxib Ursodeoxycholic
acid

Colon

Celecoxib Calcium carbonate Colon
Celecoxib Selenium Colon
Celecoxib Sulindac sulfone Colon
Celecoxib Carboplatin Brain
Celecoxib Goserelin Acetate Prostate
Celecoxib Cisplatin
Celecoxib Ketoconazole Prostate
Rofecoxib Anastrozole Breast
Rofecoxib Capecitabine Breast
Rofecoxib Docetaxel Breast
Rofecoxib Geiucitabjne Breast,

Pancreas
Rofecoxib Letrozole Breast
Rofecoxib Megestrol Breast
Rofecoxib Paclitaxel Breast
Rofecoxib Tamoxifen Breast
Rofecoxib Toremifene Breast
Rofecoxib Vinorelbine Breast, Lung
Rofecoxib Topotecan Lung
Rofecoxib Etoposide Lung
Rofecoxib Fluorouracil Colon

Rofecoxib Irinotecan (CPT-
11)

Colon, Bladder

Celecoxib Retinoids Colon
Celecoxib]DFMO Colon
Celecoxib Ursodeoxycholic
acid

Colon

Celecoxib Calcium carbonate Colon
Celecoxib Selenium Colon

WO 00/38730 PcTIUS99/30693

AS

Celecoxib Sulindac suifone Colon
Rofecoxib Carboplatin Brain
Rofecoxib Goserelin Acetate Prostate
Rofecoxib Cisplatin
Rofecoxib Ketoconazole Prostate
JTE-522 Anastrozole Breast
JTE-522 Capecitabine Breast
JTE-522 JDocetaxel Breast
JTE-522 Geincitabine Breast,
Pancreas
TTE-522 Letrozole Breast
3TE-522 Megestrol Breast
JTE-522 Paclitaxel Breast
JTE-522 Tainoxifen Breast
JTE-522 Toremifene Breast
JTE--522 Vinorelbine Breast, Lung
rTE-522 Topotecan Lung
JTE-522 Etoposide Lung
JTE-522 rluorouracil Colon
JTE-522 Irinotecari (CPT-
11)

Colon, Bladder

Celecoxib Retinoids Colon
Celecoxib DFMO Colon
Celecoxib Ursodeoxycholic
acid

Colon

Celecoxib Calcium carbonate Colon
Celecoxib Selenium Colon
Celecoxib Sulindac suifone Colon
JTE-522 Carboplatin Brain
JTE-522 Goserelin Acetate Prostate
JTE-522 Cisplatin
JTE-522 Ketoconazole Prostate

Additional examples of combinations are listed in Table No 20.

5 ,J W.LGNo. zu. combination therapy examples
COX-2
inhibitor

A.ntineoplastic Indication
Agents
Celecoxib Doxorubicin and Breast
Cyc lophasphamide
Celecoxib Cyclophosphamide, Breast
Doxorubicin, and
Fluorouraci].

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

202075

Bogota, D.C., (04 de Septiembre de 2007)

Abogado
JIMENA ESCOBAR URIBE.
Solicitante: NOVARTIS A.G.

ASUNTO RadicaciOn
Tram ite
Evento
Actuación
Oficio
Folios

04034537
002
001
430

11ii
021

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Como resultado del examen de fondo, realizado con fundamento en el artIculo 45 de la DecisiOn 486 de la ComisiOn de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descnción: Folios: 1 a 64 como se radicO inicialmente

1.2. Reivindicaciones: Folios: 65 a 67 coma se radicO inicialmente

1.3. Prioridad: Folios: 74 a 74 (19 de Octubre de 2001, US60/345,921).

2. Objeto de la invención

TItulo de la solicitud: Una composiciOn farmacOutica para utilizarse en el tratamiento de malignidades, que comprende una combinaciôn de bisfosfonatos, un inhibidor de COX-2 y un taxol.

El objeto de (a presente solicitud de patente de invenciOrt consiste en:

Una composiciOn farmacØutica para utilizarse en el tratamiento de malignidades, que comprende una combinaciOn de bisfosfonatos, un inhibidor de COX-2 y un taxol.

Reivindicaciones 1,4,11
ReivindicaciOn 2.
Reivindicaciones 3-10

ComposiciOn farmacØutica.
Uso.

MØtodo terapØutico.

El problema planteado en esta solicitud es el tratamiento de malignidades asociadas con el desarrollo de metastasis ósea o reabsorción excesiva de huesos.

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Para solucionar este problema tŁcnicola solicitud en estudlo proporciona una composiciOn farmacØutica de bisfosfonato y un inhibidor de COX-2.

El objeto de la invenciOn definido anteriormente se clasifico de acuerdo con la Clasificación Internacional de Patentes (IPC) A61K31/663, A611<31/635, A61 K31/644, A61 K31/365, A61 P5/50, A61 K31/337, A61 K31/196, A61 P29/00.

3. De la solicitud de Patente

3.1. Descripción (artIculo 28 D. 486)

Teniendo en cuenta la definiciôn de materia que realiza el interesado en los
folios (65-67) acerca de la cornposición farmacØutica esta Dependencia se
permite senalar que la invenciOn, no se encuentra debidamente sustentada en
el aparte descriptivo de la solicitud. Al observar los datos reportados en los

I folios (59-64) encontramos que solo una pequena parte de 10 reivindicado

presenta datos en los cuales no se yen las ventajas de combinar un COX-2,
un bisfosfonato y un taxol o un efecto sinØrgico inesperado.

3.2. Reivindicaciones (artIculo 30 D 486)

La reivindicaciôn I y en consecuencia sus dependientes, no son claras ni
concisas ya que resulta amplias y especulativas en el sentido que existen
mUltiples posibilidades de composiciones farmacØuticas obtenidas de la combinación de "lnhibidores de COX-2 "con "bisfosfonatos". Por este motivo
la caracteristica esencial de la composiciOn farmacØutica no es
representativa. Se le requiere al interesado definir o especificar las
composiciones que son relevantes para la invenciOn.

La reivindicaciôn 1 no estâ claramente definida, ya que inicialmente se indica
que la combinaciOn del bisfosfonato y el inhibidor COX-2 estÆn presentes

Sen la misma composiciOn. Sin embargo tambiØn se habla de un "uso

secuencial o separado" de la composición dicha. Asi las dos limitaciones son
confusas cuando estÆn tomadasjuntas, porque no se entiende silos agentes
estân en la misma composiciOn (y podria por lo tanto no ser administrado por
separado) segUn lo sugerido posteriormente en la reivindicación. Se solicita
aclaraciOn 0 correcciOn al respecto.

El tØrmino "uso" simultaneo.... o separado, de la reivindicaciôn I debe ser eliminado.

Para la reivindicación 11 se encuentran el tØrmino "o cualquier otro derivado adecuado del taxol " el cual debe ser eliminado o sustentado ya que los grupos estructurales o las caracteristicas que lo conforman no pueden ser claramente identificados. Se solicita realizar la corrección o aclaraciôn respectiva o en su defecto definir los compuestos de taxol que son relevantes para la invenciOn.

La reivindicaciôn 4, no es clara ya que, no se define si se desea reivindicar una composiciôn farmacØutica de acuerdo con la reivindicaciOn 1,el uso de acuerdo con la reivindicaciOn 2 o a un mØtodo de acuerdo a la reivindicaciôn
3. Se solicita realizar aclaraciOn al respecto.

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4. Excepción a la patentabilidad (articulo 20 0486 literal a)-d)) (segUn causal)

Se aclara que, de acuerdo al Art 20 literal d) el mØtodo terapØutico de las reivindicaciones 3-10 no son patentables.

5. Reivindicaciones relativas a un uso o a un uso distinto (artIculos 14 y21 0 486)

Se aclara que, de acuerdo con el Art 14, no se puede otorgar patente al uso de la reMndicaciOn 2 porque no es un producto ni un procedimiento tecnolôgico.

6. Determinación del Estado de la TØcnica

Considerando que la fecha de presentaciôn de la primera solicitud de patente de la cual se reivindica prioridad es 19 de Octubre de 2001, se consultaron las bases de

datos

y los archivos con que cuenta la entidad con fecha de publicaciOn anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No Documento TItulo Fecha de

Publicación*
METHOD OF USING A
CYCLOOXYGENASE- 2-

INHIBITOR AND ONE OR MORE 6 DE Julio de DI W000/38730 ANTINEOPLASTIC AGENTS AS 2000. A COMBINATION THERAPY IN

THE TREATMENT OF
NEOPLASIA.

7. AnÆlisisde patentabilidad (articulo 14 D486)

Comparando elemento por elemento el objeto de esta solicitud con Jo mencionado en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No. 04034537, se refiere a:
Una composición farmacØutica para utilizarse en el tratamiento de malignidades, que comprende una combinaciOn de bisfosfonatos, un inhibidor de COX-2 y un taxol.

Dl (Folios 145-161) enseæa mØtodosde tratamiento o prevenciôn de desOrdenes de neoplasia usando una combinaciôn de COX-2 y un agente antineplÆsico.

bisfosfonatos
COX-2 con Clodronato disódico. (Folio 152
COX-2 con Etidronato (Folio 153
COX-2 con Pamidronato disódico (Folio 154

[1

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Estas composiciones especIficas de la anterioridad DI (W00038730) son iguales a [as composiciones farmaceUticas de la presente solicitud

Como se observa, el elemento caracterIstico de la composición farmacØutica reivindicada en 1,4,11 era conocida en Dl y estÆ comprendido en elestado de la tØcnica, con lo cual se considera que NO cumple con el requisito de Novedad.

8. Conclusion:

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

No Documento No Reivindicaciones Requisito que Afecta Afectadas 1
I DI W00038730 I 1,4,11 Novedad _J

En cumplimiento del articulo 45 de la Decision 486 de la ComisiOn de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de sesenta dIas contados a partir de la fecha de notificación de la presente comunicaciOn. En caso de no dar respuesta al presente requerimiento, 0 Si a pesar de la respuesta subsistieran los impedimentos para la concesiôn, se denegarÆ Iapatente.

NotifIquese el presente oficio conforme a lo dispuesto en el artIculo 8 de Is resoluciOn reglamentaria No. 00210 del 15 de enero de 2001, advirtiendo que contra ØI no procede recurso aguno en la ia gubernativa.

1

ALIX CARMENZA AISPEDES DE VERGEL
Jefe de DivisiOn de Nuevas Creaciones

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

CONCEPTO TECNICO No.
1532

EXAMINADOR TECNICO

Codigo No.202075