10 ANEXOS

Comprobante de pago de la tasa de presentación de la solicitud
Documento que acredita la xistencia

representación legal cuando el solicitante sea per5
Poderes si fuere el caso Protocolo No. 17.398
ElDocumento de cesión de inventor al solicitante o a su causante ElDeclaraciones

Copia de la solicitud inter acional. (Resumen, descripciOn, reivindicaciones, dibuj Traducciôn de la solicituc internacional al castellano. (Resumen, descripción, rei Copia del examen prelim nar internacional efectuado por la Autoridad Internacion

LITraducciôn

Preliminar (IPEA).
del examen Freliminar internacional efectuado por la IPEA De ser el caso copia de c ontrato de acceso.
De ser el caso, documen o que acredite la licencia o autorizaciôn de uso de conc
de las comunidades mdl enas
De ser el caso, certificado de deposito del material biológico

LII Arte final l2Xl2.
De ser el caso, informaci n sobre otras solicitudes de patente o titulos obtenidos mismo titular a su causar te, relacionadas parcial o totalmente con la invención th
De ser el caso, modifica jones efectuadas a la solicitud internacional
Otros

Copia de la notifi ación de Is inscripciôn de un cam bio

de la Opinion E5

11 FIGURA GARACTE

Prot. 17.398

S)

ndicaciones, dibujos)
I de Examen

mientos tradicionales

n el extranjero par,
esta solicitud.

RECIBO OFICIAL DE CJA 04 - 26,405
FECHA MAR 70 31 DE 2004

iT 300176089-2

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CANT. RENTISTICO CONCEPTO TOTAL CONCEPTO ---

1 0005-01-01 SOLICITUDES I TRAMITES DE S0L DE PATENTE DC IN 422.000.00 TOTAL $ 422.000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RECIBU DE CAJA APLICADO AL EXPEDIENTE N.

ANEXOS

INVENTORES

I.) LIPTON, Allan
(Division of Oncology, Room C6830, Hershey Medical Center, Hershey, Pennsylvania 17033, Estados Unidos de America);

2.) WITTERS, Lois, Mary
(25 Fisher Road, York Haven, Pennsylvania 17370, Estados Unidos de AniØrica);

3.) GREEN, Jonathan
(Waldstrasse 12, CW4 144 Arlesheim, Suiza).

- 00

Solicito expresarnente a nombre de la sociedad NOVARTIS AG, sociedad constituida de conformidad con las leyes de Suiza, dorniciliada en Lichtstrasse 35, CH-4056 Basilea, Suiza, el otorgamiento de Patente para la invenciOn titulada "COMPOSICION

FARMACEUTICA PARA UTILIZARSE PARA EL TRATAMIENTO DE MALIGNIDADES, QUE COMPRENDE UNA COMBNACION DE BISFOSFONATOS, UN INHIBIDOR DE COX -2 Y UN TAXOL".
Clase: A61K31/663

U2L VLb2IL.
JIMENA OBAR URIB.E
C.C. 39.779.452 de Usaquen.
T.P. 68.228

63
RESUMEN

Se describe una composición farmacØutica para & tratamiento
de matignidades, en particular una enfermedad maligna, la cual estÆ
5 asociada con el desarrollo de metastasis ósea o reabsorciOn excesiva de huesos, que comprende en combinación un bisfosfonato,
un inhibidor de COX-2 y/o un taxol o derivado d& mismo, para uso simultÆneo, secuencial o separado. TambiØn se proporciona un mØtodo para tratar a un paciente que padece de una enfermedad
10 maligna, que comprende administrar al paciente una cantidad efectiva de un bisfosfonato, una cantidad efectiva de un inhibidor de COX-2 y/o una cantidad efectiva de un taxol o derivado del mismo.

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I
COMPOSICION FARMACEUTICA PARA UTILIZARSE PARA EL TRATAMIENTO DE MALIGNIDADES, QUE COMPRENDE UNA COMBINACION DE BISFOSFONATOS, UN INHIBIDOR DE COX -2 Y
UN TAXOL

DESCRIPCION DE LA INVENCION

Esta invenciOn se refiere a bisfosfonatos, en particular a
nuevos usos farmacØuticos de

composiciones que contienen
10 bisfosfonatos.

40 Los bisfosfonatos se utilizan ampliamente pars inhibir la

actividad de osteoclasto en una variedad de enfermedades tanto

benignas como malignas, que involucran la reabsorción ôsea
excesiva o inapropiada. Estos anâlogos de pirofosfato no solo
15 reducen la ocurrencia de eventos relacionados con el esqueleto, sino
que tambiØn proporcionan a los pacientes el beneficio clinico y supervivencia mejorada. Los bisfosfonatos son capaces de prevenir
la reabsorciôn Osea in vivo; Is eficacia terapØutica de los bisfosfonatos ha sido demostrada en el tratamiento de osteoporosis,
20 osteopenia, enfermedad de huesos de Paget, hipercalcemia inducida
por tumor (TIH) y, mªs recientemente, metastasis ósea (BM) y melanoma mUltiple (MM) (para revision, ver Fleisch H. 1997 Bisphosphonates clinical. In Busphosphonates in Bone Disease. From
the Laboratory to the Patient. Eds: The Pharthenon Publishing Group,
25 New York/London pâg. 68-163). Los mecanismos a travØs de los

2
cuales los bisfosfonatos inhiben la reabsorción ósea aün no se han entendido por completo y parecen variar de acuerdo con los bisfosfonatos estudiados. Se ha mostrado que los bisfosfonatos se unen fuertemente a los cristales de hidroxiapatita de los huesos,
5 Para reducir la absorción y reabsorción ósea, Para disminuir los
niveles de hidroxiprolina o fosfatas alcalina en la sangre, y ademÆs
Para inhibir la formaciôn, reclutamiento, activación la actividad de
osteoclastos.
Los estudios recientes tambiØn han mostrado que algunos
10 bisfosfonatos pueden tener un efecto directo sobre cØlulas tumorales. De esta manera, por ejemplo, se ha encontrado que concentraciones relativamente altas de bisfosfonatos, incluyendo zoledronato, inducen apoptosis do carcinoma de pecho y de prôstata
y cØlulas do mieloma in vitro Senaratne y otros, Br. J. Cancer, 82:
15 1459-1468, 2000; Lee y otros, Cancer Res., 61:2602-2608, 2001,
Shipman y otros, Br. J. Cancer, 98:665-672 (1997).
Ahora so ha encontrado que si ciertos tipos de bisfosfonatos
son utilizados en combinación con ciertos tipos de inhibidores de ciclooxigenasa-2 (COX-2) Para tratar cØlulas cancerosas in vitro, que
20 mejoran, y en algunos casos sinergisticos, se logra la inhibición de
crecimiento de cØlula comparado con el uso ya sea de bisfosfonatos
a el inhibidor de COX-2 solo.
Por consiguierite, la presente invención proporciona una composición farmacØutica Para el tratamiento de malignidades, el
25 cual compreride una combinación de bisfosfonato y un inhibidor de

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COX-2 para uso smuItâneo, secuencial o separado.
AdemÆs, la invenciOn proporciona el uso de un inhibidor de
COX -2 para Is preparación de un medicamento, pare utilizarse en
combnación con un bisfosfonato para el tratamiento de una
5 enfermedad maligna.
En la alternativa, la invenciOn proporciona & uso de un bisfosfonato para la preparaciOn de un medicamento para utilizarse
en combinaciôn con inhibidor de COX -2 para el tratamiento de una enfermedad maligna.
10 En un aspecto mâs, Is invención proporciona un mØtodo para
tratar a un paciente que padece de una enfermedad maligna, que comprende administrar al paciente una cantidad efectiva de un bisfosfonato y una cantidad efectiva de un inhibidor de COX-2.
AUn mÆs, Ia invenciôn proporciona el uso de un inhibidor de
15 COX -2 en combinaciOn con un bisfosfonato para inhibir el
crecimiento de cØlulas cancerosas o inducir apoptosis de cØlula

cancerosa.

Por consiguiente, la presente invenciÆn tamblØn proporciona
una composición farmacØutica para inhibir & crecimiento de cØlula
20 cancerosa o inducir la apoptosis de cØlula cancerosa, el cual
comprende en combinación un bisfosfonato

un inhibidor de COX -2
pars uso simultÆneo, secuencial o separado.
AdemÆs, la invención proporciona el uso de un bisfosfonato
para la preparación de un medicamento, para utilizarse en
25 combinación con un inhibidor de COX -2 para inhibir el crecimiento de

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cØlulas cancerosas o inducir la apoptoSis de cØlulas cancerosas.
En modalidadeS preferidaS & bisfosfonato y el inhibidor de COX-2 se utilizan en combinación con taxol 0 Ufl derivado del mismo. Por consiguiente, en un aspecto mÆs, la presente inveflC’’

5 tambiØn proporciona una composiciOn tarmaceunca para ei tratamiento de malignidades, el cual comprende en combinaciôn, un bisfosfonato, taxol a un derivado del mismo, y un inhibidor de COX-2 para uso simultÆneo, secuencia a separado.
AdemÆs, la invenciOn proporciona el uso de un taxol a un
10 derivado del mismo para la preparación de un medicamento, para
usarse en combinación con bisfosfonato y un inhibidor de COX -2 para el tratamiento de una enfermedad maligna.
Aün mÆs, la invenciOn proporciona un mØtodo para tratar un
paciente que sufre de una enfermedad maligna, que comprende
15 administrar al paciente una cantidad efectiva de un bisfosfonato, una
cantidad efectiva de un inhibidor de COX-2 y una cantidad efectiva
de un taxol o un derivado del mismo.

De acuerdo con Is presente invenciôn Se ha encontrado que
todas las posibles dobles combinaciones de (a) bisfosfonatos, (b)
20 inhibidor de COX-2 y (c) taxol a derivado del mismo, segUn probado,
proporcionaron una inhibiciôn mejorada del crecimiento de cØlulas cancerosas cuando se comparô con el uso de cada agente, en forms separada.
De esta manera, en otras modalidades, Ia invención
25 proporciona:

5

un mØtodo para tratar un paciente que sufre de una enfermedad maligna, que comprende administrar al paciente una cantidad efectiva de un taxol o un derivado del mismo, en combinaciôn con una cantidad efectiva de un bisfosfonato o una cantidad efectiva de
5 un inhibidor de COX-2;
una composiciön farmacØutica correspondiente para uso
simultÆneo, secuencial o separado; y usos de las combinaciones
dobles correspond ientes, es decir, taxol o derivado del mismo + bisfosfonato, o taxol o derivado del mismo + inhibidor de COX-2,
10 para la preparación de medicamentos contra cancer.

10 En la presente descripciOn, el tØrmino "tratamiento" incluye

tanto tratamiento profilÆctico como preventivo, asi como un
tratamiento curativo o de modificaciOn de enfermedad, incluyendo el
tratamiento de pacientes con riesgo de contraer la enfermedad o con
15 sospecha de tener la enfermedad ya contraida, asI como pacientes
enfermos.
La invención en general Se puede aplicar al tratamiento de
enfermedades malignas para las cuales se indica un tratamiento con bisfosfonato. De esta manera, tipicamente Is enfermedad es una
S20 enfermedad maligna, la cual estª asociada con el desarrollo de
metastasis ósea o reabsorciôn excesiva de huesos. Ejemplos de
dichas enfermedades incluyen cªnceres, tales como cânceres de
pecho y prôstata, mieloma multiple (MM), hipertensión inducida por
tumor (TIH) y enfermedades y condiciones similares. En particular, la
25 invenciªn es aplicable al tratamiento de metastasis ósea (BM)

asociadas con cânceres tales como cancer de pecho, cancer do pulmôn, cancer de colon o cancer de próstata.
Las composiciones, usos y mØtodos de la presente invención representan una mejora a Is terapia existente de enfermedades
5 malignas, en donde se utilizan bisfosfonatos para prevenir o inhibir & desarrollo de metastasis ósea o reabsorción excesva de huesos, y
en donde (como so ha descubierto de acuerdo con la presente invenciOn) el tratamento do bisfosfonato tambiØn inhibe el crecimiento de cØtulas cancerosas o induce la apoptosis de cØlulas
10 cancerosas. La combinación de un bisfosfonato con un inhibidor de COX-2, especialmente tambiØn con un taxol o un derivado del mismo, ventajosamente da surgimiento a niveles mejorados, o sUn sinergisticos, de inhibiciôn de crecimiento de cØlula cancerosa o apoptosis de cØlula cancerosa.
15 Los bisfosfonatos para utilizarse en la presente invención son preferiblemente N-bisfosfonatos.
Pars los propósitos de la presente descripcion, un N-bisfosfonato es un compuesto quo ademÆs de la porcón bisfosfato geminal caracteristica, comprende una cadena lateral que contiene

10 20 nitrOgeno, por ejemplo, un compuesto do la formula (I):
R
P(OA)2

Ax I X

25

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en donde:

X es hidrógeno, hidroxilo, amino, alcanoilo, 0 Un grupo amino substituido por aiquilo de 1 a 4 Ætomos de carbono, a alcanoilo;
R es hidrógeno a alquilo de 1 a 4 âtomos de carbono, y
5 Rx es una cadena lateral que contiene un grupo amino
opcionalmente substituido, 0 Ufl heterociclo que contiene nitrôgeno
(incluyendo, heterociclos que contienen nitrôgeno aromÆtico),

SUS

sales farmacØuticamente aceptables a cualquier hidrato de los mismos.
10 De esta manera, par ejemplo, los N-bisfosfonatos adecuados
para utilizarse en la invención pueden incluir los siguientes compuestos o una sal farm acØuticamente aceptable de los mismos, a cualquier hidrato de los mismos: Æcido 3-amino-i -hidroxipropan-1 1-
difosfOnico (Æcido pamidrónico), por ejemplo, pamidronato (APD);
15 ªcido 3-(N,N-dimetilamino)-1-hidroxipropan-1,1-difosfônico, por
ejemplo, dimetil-APD; Æcido 4-amino-i-hidroxibutan-1,1-difosfônico
(Æcido alendrOæico), por ejemplo, alendronato; âcido 1-hidroxi-3-
(metilpentilam ino)-propiliden-bisfosfOnico, Æcido ibandrón icc par
ejemplo, bandronato; Æcido 6-amino-1-hidroxihexan-1,1-difosfônico,
20 por ejemplo, amino-hexil-BP; Æcido 3-(N-metil-N-n-pentilamino)-1--
hidroxipropan-1,1-difosfónico, por ejemplo, metil-peritil-APD (=BM
210955); Æcido 1 -hidroxi-2-(imidazol- 1 -il)etan-1 1 -difasfOnico, por
ejemplo, Æcido zoledrónico; Æcido 1-hidroxi-2-(3-piridil)etan-1,1-
difosfónico (âcido risedrónica), par ejemplo, risedronato incuyendo
25 las sales de N-metil piridinio de los mismos, por ejemplo yoduro de

N-metil piridinio tales como NE -10244 o NE -10446; Æcido 3-[N-[N-(2-. -(2 - fenniltioetil)-N-metilamina]-1 i Itioetil)-N-meti lam ino]- 1 -hidroxipropari-1,1-difosfOnico; Æcido 1-hidroxi-3-(pirrolidin-1-il)propan-1, 1-difosfónico, por ejemplo, EB 1053
(Leo); Æcido 1-(N-fenilaminotiocarbonil)metan-1,1 -difosfOnico, par
5 ejemplo FR 78844 (Fujisawa); ester tetraetilico de âcido 5-benzoil-
3,4-dihidro-2H-pirazol-3,3-difosf6nico, por ejemplo U-81581 (Upjhon);
y Æcido 1.-hidroxi-2-(imidazo[1,2-a]piridin-3-il)etan-1,1-difosfÆnico, par ejemplo, YM 529.
En una modalidad, un N-bisfosfonato particularmente preferido
10 para utiJzarse en la invenciOn comprende un compuesto de la
formula It:

P(OR)2

Het-A X1111
15 (OR)2
0

en donde:
Het es un radical imidazol, oxazol, isoxazol, oxadiazol, tiazol,
20 tiadiazol, piridina, 1,2,3-triazol, 1,2,4-triazol o benzimidazol, el cual
estâ opcionalmente substituido par alquilo, alcoxi, halôgeno, hidroxilo, carboxilo, un grupo amino opcionalmente substituido por radicales alquilo a atcanoilo a un radical bencilo opcionalmente substituido por alquilo, nitro, amino a aminoalquilo;
25 A es una porciOn de hidrocarburo saturada a insaturada, de

cadena recta o ramificada que contiene de I a 8 Ætomos de carbono;
X es un Ætomo de hidrôgeno, opcionalmente substituido por alcanoilo, o un grupo amino opcionalmente substituido por radicales alquilo o alcanoilo, y
5 R es un Ætomo de hidrOgeno o un radical alquilo,
y SUS sales farmacologicamente aceptables.
En una modalidad mÆs, un bisfosfonato particularmente preferido para utilizarse en la invenciOn comprende un compuesto de
la formula Ill:
10

Het’ - I
5(OR)2
0
15 en donde:
Het’ es un anillo de 5 miembros, heteroaromÆtico, substituido o
no substituido seleccionado del grupo que consiste de imidazolilo, imidazohnilo, isoxazolilo, oxazolilo, oxazolinilo, tiazolilo, tiazolinilo, triazolilo, oxadiazolilo y tiadiazolilo, en donde el anillo puede ser
20 parcialmente hidrogenado y en donde dichos substituyentes se
seleccionan de por lo menos uno del grupo que consiste de alquilo
de 1 a 4 Ætomos de carbono, alcoxi de 1 a 4 Ætomos de carbono,
fenilo, ciclohexilo, ciclohexilmetilo, halOgeno y amino, y en donde un substituyente es alquilo adyacente de Het en conjunto pueden formar
25 un segundo anillo;

10

Y as halôgeno o alquilo de I a 4 Ætomos de carbono;
X" es hidrOgeno, hidroxilo, amino, o un grupo amino substituido
por alquilo de I a 4 Ætomos de carbono, y
R es hidrógeno o alquilo de I a 4 Ætomos de carbono;
5 asI como sus sales e isómeros farmacológicamente aceptables.
En otra modalidad mÆs, un bisfosfonato particularmente preferido pars utilizarse en la invención comprende un compuesto de
la fOrmula IV:

11
10 P(OR)2

HetH’-C I R2 IV
H2 I
(OR)2
0
en donde:
15 Het" es un radical imidazolilo, 2H-1,2,3-, 1H-1,2,4,- o 41-1-1,2,4-triazolilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiazolilo o tiadiazolilo, el cual estÆ no substituido o mono- o di-substituido por alquilo inferior, por alcoxi inferior, por feriilo, el cual
a su vez puede estar mono- o disubstituido por alquilo inferior, alcoxi
20 inferior y/o halOgeno, por hidroxi, por alquilamino di-inferior, por alquiltio inferior y/o por halógeno y estÆ N-substituido en un Ætomo N-substituible por alquilo inferior o fenilalquilo inferior, el cual a su
vez puede estar mono- o di-substituido en la porción fenilo por alquilo inferior, alcoxi inferior y/o halôgeno, y
25 R2 es hidrOgeno, hidroxi, amino, alquiltio inferior o halógeno,

11

radicales inferiores que henen hasta e incluyen 7 Ætomos de carbono,
o una sal farmacolôgicamente aceptable de los mismos.
Ejemplos de N-bisfosfonatos prefendos para utilizarse en la
5 invenciôn son:
Acido 2-(1-metilimidazol-2 l)-1hidroxietan1,1-difosfónico;
Acido 2-(1-bencilimidazol-2il)-1-hidroxietan-1 1-difosf6nico;
Acido 2-(lmetiIimidazol4il)-1-hidroxietan-1,1-difosfOnico;
Acido 1amino-2-(l-metilimidazoI-4l)etan-1,1difosfonico;
10 Acido 1amino2-(l-bencilimidazot4-il)etan-1,1-difosfónico;
Acido 2-(1-metilimidazol-2l)etan-1,1difosf6nico;
Acido 2(l-bencilimidazoI-2-il)etan1,1 -difosfOnico;
Acido 2-(imidazol-1-ii)-1hdroxietan-1,1-difosfónico;
Acido 2-(imidazol-1-il)etan-1,1-difosfOnico;
15 Acido 2-(4H-1,2,4-triazol4il)-1 -hid rox!etan-1,1-difosfônico;
Acido 2-(tiazol2il)etan-1,1-difosf6nico;
Acido 2-(imidazol-2-il)etari-1,1-difosf6nico;
Acido 2-(2-metilimidazol-4(5)-il)etan1,1difosfOnico;
Acido 2-(2fenilimidazol4(5)-il)etan-1,1-difosfónico;
20 Acido 2-(4,5-dimetilimidazol1ii)-1-hidroxietan-1,1-difosfOnico, y
Acido 2(2metilimidazol4(5)-il)-1-hidroxietan-1,1-difosfOnico,
y sus sales farm acológicamente aceptables.
El Nbisfosfonato muy preferido para utilizarse en la invención
es Æcido 2-(imidazol-1 -il)-1 -hidroxietan-1, I -difosfônico (Æcido
25 zoledrónico) una sal farmacolôgicamente aceptable del mismo,

12
Todos los denvados de Æcido N-bisfosfônico mencionados anteriormente son bien conocidos en la literature. Esta incluye su
fabricación (ver, por ejemplo EP -A-513760, pªgs. 13-48). Por
ejemplo, el ªcido 3-amino-i -hidroxipropan-1, I -difosfónico se prepare
5 como se describe en por ejemplo, la patente de E. U. A. 3,962,432
asI como la sal disôdica como en las patentes de E. U. A. 4,639,338
y 4,711,880, y el Æcido 1-hidroxi-2-(imidazol-1-il) etan-1 1-
difosfónico se prepara como se describe en, por ejemplo, la patente
de E. U. A. 4,939,130, Ver tamblØn patentes de E. U. A. 4,777,163
10 4,587,767.
Los N-bisfosfonatos se pueden utilizar en la forms de un
isómero o una mezcla de isómeros cuando as apropiado, tipicamente como isómeros ópticos tales como enantiOmeros 0
diaestereoisômeros o isômeros geomØtricos, tipicamente isómeros
15 cis -trans. Los isómeros ópticos se obtienen en la forma de antIpodos
puros y/o como racematos.
Los N-bisfosfonatos tambiØn se pueden utilizar en la forma de
sus hidratos o incluir otros solventes usados pare su cristalización.
Los inhibidores de COX-2 utilizados en las composiciones
20 farmacØuticas y mØtodos de tratamiento de la presente invención son
tipicamente aquellos que tienen un valor IC50 para la inhibiciôn de COX-2 menor que aproximadamente 2 iM y una IC50 pars la inhibición de COX-1 mayor que aproximadamente 5 pM, por ejemplo, cuando se mide en los ensayos descritos por Brideau y otros, in
25 lnflamm. Res. 45:68-74:68-74 (1996). De preferencia, el inhibidor de

13

COX-2 tiene una relación de selectivdad de por lo menos 10, muy preferiblemente de por 10 menos 40 para la inhibicióri de COX -2 con respecto a la inhibición de COX-1.
De esta manera, por ejemplo, los inhibidores adecuados de
5 COX-2 para utilizarse en la invención pueden irihibir los siguientes
compuestos o sus derivados o una sal farmacØuticamente aceptable
de los mismos, o cualquier hidrato de los mismos: rofecoxib, etoricoxib, etoricoxib, celecoxib, valdecoxib, parecoxib, 0 Ufl inhibidor de COX-2 del derivado de Æcido 5-alquil-2-
10 arilaminofenilacØtico, por ejemplo, de la formula V como se define a
continuaciOn.
En una modalidad, un inhibidor de COX-2 para utilizarse en la
presente invención comprende un compuesto de la formula V:

15 R CHCQOH

NH (V)

RI R5 R24R4

A3
 20

en donde R es metilo 0 etilo;
R1 es cloro o fluoro;
R2 es hidrógeno o fluoro;
R3 es hidrôgeno, fluoro, cloro, metilo, etilo, metoxi, etoxi o
25 hidroxi;

14

R4 es hidrOgeno o fluoro; y
R5 es cloro, fluoro, trifluorometilo a metilo;
y sus sales farmacØuticamente aceptables; y
sus Østeres de profÆrmacofarmacØuticamente aceptable s.
5 Los compuestos particulares de la formula

son aquellos en
donde R es metilo a etilo; R1 es cloro a fluoro; R2 es hidrógena; R3
es hidrôgerio, fluoro, cloro, metilo o hidroxi; R4 es hidrOgeno; y R5 es cloro, fluoro a metilo; sus sales farmacØutcamente aceptables; y sus Østeres de profÆrmaco farmacOuticamente aceptables.
10 Una modalidad particular se refiere a los compuestos de la
fOrmula V, en donde R es metilo o etilo; R1 es fluoro; R2 es hidrOgeno; R3 es hidrOgeno, fluoro, a hidroxi; R4 es hidrOgeno; y R5
es cloro; sus sales farmacØuticamente aceptables; y sus Østeres de profÆrmaco farmacØuticamente aceptables.
15 Otra modalidad particular de la invenciOn se refiere a
compuestos de la formula V, en donde R es metilo a etilo; R1 es fluoro; R2 es hidrOgeno a fluoro; R3 es hidrOgeno, fluoro, etoxi a hidroxi; R4 es hidrOgeno o fluoro; y R5 es cloro, fluoro o metilo; sus sales farmacØuticamente aceptables; y sus Østeres de profÆrmaco
20 farmacØuticamente aceptables.
Ademâs hay compuestos en donde R es metilo a etilo; R1 es a
fluoro; R2 -R4 es hidrôgeno a fluoro; y R5 es cloro o fluoro; sus sales farmacØuticamente aceptables; y sus Østeres de profªrmaco farmacØuticamente aceptables.
25 Una modalidad mÆs de la invención se refiere a los compuestos

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de la formula V, en donde R es metilo o etilo; R1 es fluoro; R2 es fluoro; R3 es hidrOgeno, etoxi o hidrox; R4 es fluoro;

R5 es fluoro;
sus sales farmacØuticamente aceptables;

sus Østeres de
profÆrmaco farmacØuticamente aceptables.
5 Otra modalidad de la invención se refiere a los compuestos de
la fOrmula V, en donde R es metilo; R1 es fluoro; R2 es hidrOgeno; R3
es hidrOgeno o fluoro; R4 es hidrOgeno;

R5 es cloro; sus sales
farmacØuticamente aceptables;

sus Østeres de profârmaco
farmacØuticamente aceptables.
10 Las modalidades particulares de la invenciOn se refieren a
compuestos de la fOrmula V:
a) en donde R es metilo, R1 es fluoro; R2 es hidrogeno; R3
es hidrógeno; R4 es hidrageno;

R5 es cloro; sus sales
farmacØuticamente aceptables;

sus Østeres de profÆrmaco
15 farmacØuticamente aceptables;
b) en donde R es metilo; R1 es fluoro; R2 es hidrOgeno; R3
es fluoro; R4 es hidrOgeno;

R5 cloro; sus sales farm acØuticamente
aceptables;

sus Østeres de profârmaco farmacØuticamente
aceptables;
20 c) en donde R es etilo; R1 es fluoro; R2 es fluoro; R3 es
hidrógeno; R4 es fluoro;

R5 es fluoro; sus sales farmacØuticamente
aceptables;

sus Østeres de profÆrmaco farmacØuticamente
aceptables;
d) en donde R es etilo; R, es cloro; R2 es hidrôgeno; R3 es
25 cloro; R4 es hidrógeno;

R5 es metilo; sus sales farmacØuticamente

16

aceptables; y sus Østeres de profârmaco farm acØuticamente aceptables.
Las sales farmacolOgicamente aceptables de los bisfosfonatos
e inhibidores de COX-2 son preferiblemente sales con bases,
5 convenientemente sales metªlicas derivadas de los grupos la, lb, ha
y hib de la Tabla Penódca de los Elementos, incluyendo sales de metal alcalino, por ejemplo, sales de potasio, y especialmente sales
de sodio, o sales de metal alcalino tØrreo, preferiblemente sales de calcio o de magneslo, y tambiØn sales de amonlo con amoniaco a
10 aminas orgÆnicas.
Las sales farm acØuticamente aceptables especialmente preferidas de los N-bisfosfonatos son aquellas en donde 1 2, 3 o 4,
en particular 1 0 2 de los hidrogenos Æcidos del Æcido bisfosfônico
son reemplazados por un cation farmacOuticamente aceptable, en
15 particular sodio, potasio o amonio, en primer casa sodio.
Un grupo muy preferido de sales farmacØuticamente aceptables
de los N-bisfosfonatos se caracterizan por tener un hidrógeno Æcido
y un cation farmacØuticamente aceptable, especialmente sodio, en cada uno de los grupos de Æcido fosfOnico.
20 Una clase alternativa de compuestos inhibidores de COX-2 para utihizarse en ha invenciOn es ha chase de inhibidores de metal sulfonanihida, de los cuales NS -398, flosuhida, nimesulida y (i) son miembros ilustrativos,

25

NHSO CH

NO2

5 NS-398

NO2

17

Nlmesulida

HSO2CH3

1 15:1

0

(i),X=S
Flosulide, X = 0

F

Una clase adicional de inhibidores de COX-2 es la clase inhibidora triciclica, la cual ademÆs se puede dividir en las sub -
10 clases de inhibidores triciclicos con un anillo carbociclico central (los ejemplos incluyen SC -57666, I y 2); aquellas con un anillo heterociclico monociclico central (los ejemplos incluyen DuP 697,
SC -58125, SC -58125, SC -58635; SC 236 y 3, 4 y 5); y aquellas con
un anillo heterociclico biciclico central (los ejemplos incluyen 6, 7, 8,
15 9 y 10). Los compuestos 3, 4 y 5 se describen en la patente de E. U. A. 5,474,995.

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SC-57666

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DuP697

H2NSO2,,-,

NN

SC-.236

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CH3S02 NH2SO2,

H3C

SC-58125 SC58635, celeoxth

3 4

CH3S02. CH3S02,. CH3SO2

F I O

II>N

I \N

0 F)1 -

CH3SO2

5

NH..ScI._.

8 9

F

7

CH3O
10

CF3

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10

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Una clase mÆs de inhibidores de COX-2 puede ser denOmifl ada como aquellOS que son NSAIDS estruCturalmente modIficados, e incluye 11 a y la estruCtura 1 lb comO ejemPlOS iIustratV0s.

Br",&

lib

AdemÆs de las clases estructurales, sub-clases, ejemplos de compuestos inhibidores de COX-2 especIficos, ejemplos de
15 compuestos que selectivamente inhiben cictooxigenasa-2 tamblØn
han sido descntos en las siguientes publicaciones de patente, todas
estas se incorporan aqul por referenda: patentes de E. U. A. Nos,
5,344,991, 5,380,738, 5,393,790, 5,409,944, 5,434,178, 5,436,265,
5,466,823, 5,474,995, 5,510,368, 5,536,752, 5,550,142, 5,552,422,

40 20 5,604,253, 5,604,260, 5,639,780; y especificaciones de patente
internacional Nos. 94/13635, 94/15932, 94/20480, 94/26731,
94/27980, 95/00501, 95/15316, 96/03387, 96/03388, 96/06840; y publicaciones internacionales Nos. WO 94/20480, WO 96/21667, WO
96/31509, WO 96/36623, WO 97/14691, WO 97/16435.
25 Los compuestos inhibidores de COX -2 adicionales que se

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incuyen en el acance de esta invención incuyen:

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CI

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N

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Algunos de los compuestos anteriores pueden ser identificados
a travØs de los siguientes nombres qulmicos:
3: 3-fenil-4-(4-(metilsulfonil)fenil)-2-(5H)-furanona;
20 4: 3-(3,4-difluorofenil)-4-(4-(metilsulfonil)fenil)-2-(5H)-furanoria;
5:5, 5-d imetil-4-(4-(metilsulfori iI)fenhl)-3-(3-fluorofen iI)-H-fu ran -2-o na;
12: 5,5-dimetil-4-(4-(metilsulfonil)fenil)-3-(2-propoxi)-5H-furan-2-ona;
13: 5-cloro-3-(4-(metilsulfonhl)fenil)-2-(2-metil-5-piridinhl) piridina;
1 4:2-(3, 5-difluorofenil)-3-(4-(metilsulfonil)fenil)-2-ciclopenten-1 -ona;
25 15: 5(S)-5-etil-5-metil-4-(4-metilsulfonil)fenhl)-3-(2-propoxi)-5H-furan-

22
2-ona;
16: 5-etiI-5-meti l-4-(4-(metilsulfonI)fen I)-3-(34-difIuorofen il)-5H-furan-2-ona;
17: 3-((2-tiazolil)metoxi)-4-(4-metilsulfonil)fen il)-5, 5.-d i met iI-5 H-
5 furan-2-ona;
18: 3 -prop oxi-4-(4-metilsulfonil)fenil)-5,5-dimetil-5H-furan-2-ona;
19: 3-(1 -cicIopropiletox)-5, 5-dmetÆl-4-(4-metiIsuIfonil)fenil)-5H-
furan-2-ona;
20: 2-(4-clorofen I)-3-(4-metIsulfonil)feniI)-4-oxo-2-pentenoato de
10 sodio;
21: 3-(cicIopropilmetoxi)-5,5-dmeflI-4-(4-metiIsuIfonH)feniI)- 5H-
furan-2-ona;
22: 3-(ciclopropilmetoxi)-5, 5-dmeti1-4-(4-metUsuIfofflI)fenil)-2, 5-
dhidrofuran-2-oI;
15 23: 3-isopropox-55-dimetil-4-(4-metilsulfonhI)feniI)-2,5-dihdrofuran-
2-01;
24: 5,5-dimetU-3-(3-fluorofeniI)-2-hidrox-4-(4-metiIsulfoniI)feriiI)-2,5-dihdrofurano;
25: 5-Cloro-3-(4-metilsulfonil)fenil)-2-(3-piridinhl)piridina.
20 Las siguientes publicaciones describen y/o proporcionari
mØtodos para hacer los compuestos como se indica: compuestos 12,
15, 17, 18, 19 y 21, WO 97/14691; compuestos 22, 23 y 24, WO 97/16435; compuesto 20, WO 96/36623; compuesto 14, patente de E.U.A. No. 5,536,752; compuesto 16, patente de E. U. A. No.
25 5,474,995. Ver ejemplos aqul para los compuestos 13 y 25. TambiØn

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meorporados aqul por referenc;a son aquelios compuestos descritos
en WO 96/41645 teniendo la forma estructural VI, mostrada a continuaciôn, y Is definiciôn y definiciones preferidas y especies descritas ahi:

Los compuestos particularmente prefendos de la formula (VI)
10 incluyen:
5-(4-c!orofeni I)-1 -[4-(metilsulfonhl)fenit]-3-(trifluorometil)pirazol; 4-(4-clorofenil)-5-[4-(metilsulfonil)fenil]- l -fenil-3-(trifluorometil)
prazoI;
4-(5-(4-clorofenhI)-.3-(4-metodoxifeniI)l H-pirazol-1 -ii)
15 bencensulfonamida;
4-(3, 5-bis(4-metilfenil)-1 HpirazoI-1 -iI)bencensulfonamida; 4-(5-(4-clorofentl)-.3-fenil- 1 H-pirazol-1 -iI)bencensulfonamida;
4-(3, 5-bis(4.-metoxifenil)-1 H-pirazol- I -I)bencensuIfonamida; 4-(5-(4-clorofenhl).3-(4-metilfenil)-1 H-pirazoI 1 -II)
20 bencensulfonamida;
4(5-(4-cIorofeniI)-3-(4-nitrofentI)-1H-pirazoII-iI) bencensulfonamida; 4-(5-(4-clorofenil).-3-(5-cloro-2-tienil)-1 H-pirazol-1 -II)
bencensulfonamida;
4-(4-cloro-3,5-difenil-1 H-pirazoI1-iI) bencensulfonamida;
25 4-(5-(4-clorofenil)-3-(trifluorometil)-1 H-pirazol-1 -

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i) bence nsu If on amid a
4-(5-fenil)-3-(trifluorometil)-1 H-pirazol-1 -iI)bencensulfonamida; 4-(5-(4-fluorofenil)-3-(trifluorometil)-1 H-pirazol- I -if) bencensulfonamida;
5 4-(5-(4-metoxifenil)-3-(trifluorometil)- l H-pirazol-1 -ii)
bencensulfonamida;
4-(5-(4-clorofen iI)-3-(difluorometil)-1 H-pirazol- I -ii) bencensulfonamida;
4-(5-(4-metilfenil)-3-(trifluorometi)- l H-pirazol- 1-il)
10 bencensulfonamida;
4-(4-cloro-5-(4-clorofenil)-3-(trifluorometil)-1 H-pirazol-1 -ii) bencensulfonamida;
4-(3-(difIuorometiI)-5(4-metiIfeniI)-1 H-pirazol- 1-il) bencensulfonamida;
15 4-(3.-(difluorometil)-5-fenil-1 H-pirazol- 1 -iI)bencensulfonamida;
4-(3-(difluorometil)-5-(4-metoxifenil)-1 H-pirazol-1 -ii) bencensulfonamida;
4-(3-.ciano-5-(4-clorofenhl)-1 H-pirazol-1 -iI)bencensulfonamida; 4-(3-(difIuorometiI)-5-(3-fIuoro4-metodoxifeniI)-1 HpirazoI- 1-il)
20 bencensulfonamida;
4-(5-(3-fluoro-4-metoxifenil)-3-(trifluorometil)-1 H-pirazol- I -II)
be n ce n s u I fo n amid a;
4-(4-cloro-5-fenil-1 H-pirazol-1.-iI)bencensulfonamida; 4-(5-(4-clorofenil)-3-hidroxifenhl)-IH-pirazol-1 -ii) bencensulfonamida;
25 4-(5-(N,N-dimetilamino)fenil)-3-(trifluorometil)-1 H-pirazol-I -ii)

25
ben ce ns u If on am ida
5-(4-fIuorofeniI)-6-(4-metiIsuIfoniI)fen hI)espiro[2.4]hept-5-eno; 4-(6-(4-fluorofenil)espiro[2,4]hept-5-en-511)bencensulfon amid a; 6-(4fIuorofeniI)-7-(4-(metiIsuIfoniI)fen iI)espiro[3,4]oct.-6-ene;
5 5-(3-cloro.4-metoxifeni I)-6-(4-(metilsulfonit)fenil)espiro[2 4]hept-5-

eno;

4-(6-(3..cIoro-4-metoxifeniI)espiro(24]he pt- 5-en-5iI) bencensulfonamida;
5-(3 5-dicloro-4-metodoxifeni1)-6-(4-(metilsulfonil)feni1)espiro[2 Al
10 hept-5-eno;

40 5-(3-cIoro-4-fIuorofeniI)-6(4-(metiIsuIfoniI)fenhI)espiro[2.4]hept-5-

eno;

4-(6-(34-dicIorofeniI)espiro[2,4]hept5-en-5-iI) bencensulfonamida; 2-(3-cIoro-4-fIuorofeniI)-4-(4-fIuorofenhI)-5-(4-metiIsuIfoniIfen ii)
15 tiazol;
2-(2-clorofen iI).-4(4-fIuorofen iI)-.5-(4-m etils ulfon lIfe n iI)tiazol; 5-(4-fluorofeni1)-4-(4-metilsulfonilfeni1)-2-metiltiazo1; 4-(4-fluorofenil)-5-(4-metilsulfonhlfenil)-2-trifluorometiltiazol;
4-(4-fI uo rofen I)-5(4-metiIsu Ifo n I Ifenhl)-2-(2-tien I)tiazo I;
20 4-(4-fIuorofen iI)-5-(4-metilsulfonilfenil)-2-- ben censulfon amid a;
4 -(4 -flu orofen iI)-5-(4-m etilsulfo n lIfe n iI)-2-(1 -prop ilam ino)tiazol;
2-((3, 5-diclorofenoxi)metil)-4-(4-fluorofeni1)-5-(4-(metilsulfon iI)fen II) tiazol;
5-(4-fIu orofen I I)-4-(4-meti Is u Ifon I Ifeni I)-2-trifl uorometi Itiazol;
25 1 -metilsulfonil-4-(1 I -dim etil-4-(4-fluorofenhl)ciclopenta-2,4-dien-3-

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iI)benceno;
4-(4-(4-fluorofenil-1, I -dim etilcicloperita-2,4-dien-3-il) bencensulfonamida;
5-(4-fluorofenil)-6-(4-(metilsulfonil)fen hl)espiro[2.4]hepta-4 6-d ieno;
5 4(6-(4-fIuorofeniI)espiro[2.4]hepta-4,6-dien-5-il) bencensulfonamida;
6 -(4 -flu orofen iI).2-metox i-5-(4-(m etils ulfon il)fen il) -pirid I n-.3-
carbonitrilo;
2-bromo-6-(4-fluorofenil)-5-(4-(metilsulfonil)fenil)-pi rid in-3-
carbonitrilo;
10 6-(4-fI u orofen I l)-5- (4(meti I su lion I I)feni I)-2 -fen i 1 -pi rid I n -3 -ca rbonitri lo;
4-(2-(4-metilpiridin-2-il)-4-(trifluorometi1)-1 H-imidazol - I -ii) bencensulfonamida;
4-(2-(5-metilpi rid in-3-il)-4-(trifluorometil)-1 H-imidazol-1 -ii) bencensulfonamida;
15 4-(2-(2-metilpi rid in-3-il)-4-(trifluorometil)-1 H-imidazol-1 -ii)
bencensulfonamida;
3-(I -(4-(metilsulfonil)fenil)-4-(trifluorometil)- 1 H-imidazol-2-iI) bencensulfonamida;
2-(I -(4-(metilsulfonil)fenil)-4-(trifluorometil)- I H-imidazol-2-il)
20 piridina;
2-metil-4-(l -(4-(metilsulfonhl)fenil)-4-(trifluorometil)-1 H-imidazol-2-
i I)piridi na
2-metil-6-(1 -(4-(metilsulfonil)fenil)-4-(trifluorometil)-1 H-imidazol-2-
ii) p1 rid in a;
25 4-(2-(6-metilpiridin-3-II)-4-(trifluorometil)- I H-imidazol-)-

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iI) ben censulfon amid a;
2-(3,4-difiuorofenil)-1 -(4-(metilsulfonil)fenil)-4-(trifluorometi1)-1 H-imidazol;
4-(2-(4-metilfenil)-4-(trifluorometil)-1 H-imidazol-1 -ii)
5 bencensulfonamida;
2-(4-clorofenil)-1 -(4-metilsulfonil)fenil)-4-metil-1 H-imidazol; 2-(4-clorofenil)-1 -(4-(metilsutfonil)fenil)-4-fenil-1 1-1-imidazol; 2-(4-clorofenil)-4-(4-ftuorofenil)-1 -(4-(metilsulfonil)fenil)-1 H-imidazol; 2-(3-fluoro-4-metoxifenil)- l -(4-(metilsulfonil)fenil)-4-(trifluorometil)-
10 1 H-imidazol;
1-(4-metilsulfonil)feriil)-2-feriil-4-trifluorometil-1 H-imidazol; 2-(4-metilfenil)-1 -(4-(metilsulfonil)fenil)-4-trifluorometil-1 H-imidazol; 4-(2-(3-cloro-4-metilfenil)-4-(trifluorometil-1 H-imidazol-1 -ii)
ben censulfonam Ida;
15 2-(3-fluoro-5-metilfenil)-1 -(4-metilsulfonhl)fenil)-4-(trifluorometil)-1 H-
imidazol;
4-(2-(3-fluoro-5-metilfenil)-4-(trifluorometil)-1 H-imidazol-1 -ii) bencensulfon am Ida;
2-(3-metilfenil)-1 -(4-(metilsulfonil)fenil)-4-(trifluorometil)-1 H-
20 imidazol;
4-(2-(3-metilfenil)-4-(trifluorometil)-1 H-imidazol-1-iI) bencensulforiam Ida;
I -(4-(metilsulfonil)fenil)-2-(3-clorofenhl)-4-(trifluorometil)-1 H-
I mid azol;
25 4-(2-(3-clorofenil)-4-(trifluorometil)-I H-imidazol-1 -ii)

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bencensulfonam ida;
4-(2-fenil-4-(trifluorometi-1 H-imidazol-1 -il)bencensulfonamida; 4-(2-(4-metoxi-3-clorofenil)-4-(trifluorometil)-1 H-imidazol- 1 -ii) bencensulfonamida;
5 1 -alil-4-(4-fluorofenil)-3-(4-(metilsulfonif)fenil)-5-(trifluorometil)-. 1 H-.
pirazol;
4-(1 -etil-4-(4-fluorofeniI)-5--(trifIuorometil).-1 H-pirazol-3-
) ben ce ri s u fo n a m ida;
N-len iI-(4-(4-fIuo rofen i f)-3-(4-(meti Is ulfon i l)fen i l)-5-(trifl u orometi
10 1 H-pirazol-1-il)acetamida;
(4-(4-fluorofenil)-3-(4-(metilsulfonil)fenil)-5-(trifluorometil)-1 H-pirazol-1-iI)acetato de etilo;
4-(4.fluorofenil)-3-(4-metiIsuIfonil)fenil)-1 -(2-feniletil)--1 H-pirazol; 4-(4-fluorofenil)-3-(4-(metilsulfonil)fenil)- 1 -(2-feniletil)-5-
15 (trifluorometil)pirazol;
I -etil-4-(4-fluorofenil)-3-(4-metilsulfonil)fenil)-5-(trifluorometil)- 1 H-pirazol;
5-(4-fluorofenil)-4-(4-metilsulfonil)fenil)-2-(trifluorometil)- 1 H-.
imidazol;
20 4-(4-metilsulfonil)fenil)-5-(2-tiofenil)-2-(trifluorometil)-1 H-imidazol;
5-(4-fluorofenil)--2-metodoxi-4-(metilsulfonil)fenil)--6-
(trifluorometil)pi rid ina;
2 -etoxi-5-(4-flu orofen i I)-4-(4-(meti Is u Ifon i I)fen I l)-6-
(trifluorometil)pt rid ina;
25 5-(4-fI u 010 len ii) -4- (4- (met its u If o n II) fe n ii) -2- (2 -prop i n I lox I) -6-

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(trifluorometil)pirid ma;
2-bromo-5-(4-f!uorofenU)-4-(4-metisulfon U) fen il)-6-(trifluorometil)pirid iria;
4-(2-(3-cIoro-4-metoxifenH)-4,5-difIuorofeni) bencensififonamida;
S I -(4-fIuorofeniI)-2-(4-metiIsuIfoni)fenH)benceno;
5-difluorometil-4-(4-meti(sufonil)fenil)-3-fenilisoxazol; 4-(3-etiI-5-fenilisoxazol-4-iI)bericensulfonam ida; 4-(5-difIuorometil-3-feni!isoxazo-4-iI)bencensutfonam ida; 4-(5-hidroximetil-3-fenilisoxazol-4-iI)bencensfflfonam ida;
10 4-(5-metil-3-fenihsoxazoI-4-iI)bencensufonamida;
I -(2-(4-fluorofeni)cicIopenten-1 -iI)-4-(metUsuIfonibenceno;
I -(2-(4-fluoro-2-metUfenil)ciclopenten-1-it)-4-(metilsulfonil) benceno;
I -(2-(4-c!orofeni)cicIopenten-1 -U)-4-(metilsulfonfl)benceno;
1 -(2-(2,4-difiuorofeniI)cicopenten-1 -il)-4-(metiIsuIfoni)bericeno;
15 1-(2-(4-trifluorometilfenil)ciclopenten-1-it)-4-(metilsulfonil) benceno;
1-(2-(4-metiltiofenil)ciclopenten-1-iI)-4-(metilsulfonil) benceno;
1 -(2-(4-fIuorofeni)-4,4-dimetiIcicopenten-1 -ii)4-(metiIsuIfoniI)
benceno;
4-(2-(4-fluorofenH)-4,4-dimetilciclopenten-1-ii) bencensulfonamida;
20 1 -(2-(4-cIorofeni)-4,4-dimeticicopenten-1 -iI)-4-(metilsulfoni)
benceno;
4-(2-(4-cIororofeniI)-44-dimetiIcicIopenten1 -U)bencensulfonamida; 4-(2-(4-fIuorofeni)ciclopenten1 -iI)bencens ulfonamida; 4.-(2-(4-clorofenhl)ciclopenten- I -il)bencensulfonam Ida;
25 1 -(2-(4-.metoxifenil)ciclopenten- I -iI)-4-(metilsulfonil)benceno;

1-(2-(2,3-d ifI uorofeni I) cic I openten- 1 -il)-4-(metilsulfonil) ben ceno; 4-(2-(3.-fluoro-4metodifenil)ciclopenten-1 -il) ben censulfon amid a; 1-(2(3cloro4-metoxifenil)ciclopenten-1-il)-4-(metilsulfonil) benceno; 4-(2-(3-cloro4-fluorofenH)cicIopenten-1 -il-bencensulfonamida;
5 4(2(2-metilp rid in-5-il)ciclopenten-1 -il)bencensulfonamda;
2-(4(4-fluorofenU).5--(4-metilsulfonil)fen il)oxazol-2-il)-2-.bencil-
acetato de etilo;
â cido 2-(4(4-fluorofenil)-5-(4-(metilsulfonil)fen)oxazol2-il)acØtco;
2-(ter-.butil)4--(4-fluorofen il)-5-(4-metilsulfonil)feni l)oxazol;
10 4-(4fluorofernl)-5-(4-(metilsulfonil)fen)-2-fenUoxazol;
4-(4-fluorofenit)-2-meti5(4-metiIsulfonil)fenU)oxazol; y 4-(5-(3tluoro-4-metoxfenil)-2-trifluorometil-.4oxazo Ill)
bence nsu If on am ida;
o una sal farm acØuticamente aceptable de los mismos.
15 Los N-bisfosfonatos preferiblemente se utihzan en la forma de
composiciones farmacØuticas que contienen una cantidad terapØuticamente efectiva del ingrediente activo opcionalmente junto con o en mezcla con vehIculos inorgÆnicos u orgÆnicos, sólidos o liquidos farmacØuticamente aceptables, los cuales son adecuados
20 para administraciOn.
Las composiciones farmacØuticas de N-bisfosfonato pueden
ser, por ejemplo, composiciones para administración enteral, tales
como oral, rectal inhalación de aerosol o administración nasal, composiciones para administraciOn parenteral, tal como intravenosa
25 o subcutÆnea, o composiciones para administraciôn transdØrmica

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(por ejemplo, pasiva o iontoforØtica).
Preferiblemerite, las composiciones farmacØuticas de N-bisfosfonato estÆn adaptadas para administración o parenteral (en especial intravenosa, intra-arterial o transdØrmica). Las
5 administraciones intravenosa y oral, primera y principal intravenosa,
se considera que es de importancia particular. Preferiblemente, el ingrediente activo de N-bisfosfonato estÆ en una forma parenteral, muy preferiblemente una forma intravenosa.
El modo particular de administración y la dosis se pueden
10 seleccionar a travØs del medico que atiende tomando en cuenta los
aspectos particulares del agente, especialmente en la edad, peso, estilo de vida, nivel de actividad, y estado de la enfermedad, segUn sea apropiado. Muy preferiblemente, sin embargo, el N-bisfosfonato
se administra intravenosamente.
15 La dosis del N-bisfosfonato para utilizarse en la invención depende de varios factores, tales como la efectividad y duración de acciôn del ingrediente activo, modo de administraciOn, especie de sangre caliente, y/o sexo, edad, peso y condición individual del animal de sangre caliente.
20 El taxol es el compuesto ester 6,12b-bis(acetiloxi)-12-(benzoiloxi)-2a,3,4,4a,5,6,9, 10,11,1 2,12a, 1 2b-dodecahidro-4, 11-dihidroxi-4a,8, I 3,13-tetrametil-5-oxo-7, I 1-metano-1 H-ciclodeca[3,4] benz[1,2-b)oxet-9-ilico de Æcido [2aR-[2aa, 4I, 4aR, 69, 9cL(aR*, IS*),1 I a,I 2(x,1 2aa, 1 2ba]]-(-(benzoilamino)-cL-
25 hidroxibencenpropanoico, alternativamente conocido como Paclitaxel,

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el cual es un agente anti-leucØmco y antitumoral, primero aislado como la forma I de la corteza del Ærbol del tejo del pacifico, Taxus brevifolia, Taxaceae, Los derivados adecuados de taxol para utilizarse en la presente invenciOn incluyen taxotere (es decir, el
5 compuesto ester 1 2b-(acetiloxi)-1 2-(benzoiloxi)-
2a,3 4,4a 5, 6, 9, 10,11 12,12a,12b-dodecahidro-4, 6, 11-trihidroxi-4a,8,13,13-tetrametit-5-oxo-7,1 1-metano-1 H-ciclodeca[3,4]benz[1 2-b]oxet-9-ilico de âcido [2aR-[2aa, 411, 4ccll, 611, 9a(aR*, 11S*),
I 2cr, I 2aa, I 2ba}]-l1-[[(dimetiletoxi)carbonil]-amino]-cL-
10 hidroxibencenpropanoico, alternativamente conocido como
docetaxel), taxanos, taxinas (por ejemplo, taxina I, taxina II, taxina A
o taxina B) o cualquier otro derivado de taxol adecuado. El taxol y sus derivados adecuados se pueden utilizar en combinación con un bisfosfonato y un inhibidor de COX-2 en la presente invención. El
15 taxotere es un derivado de taxol preferido para utilizarse en la
presente invenciôn. Las composiciones farmacØutcas de taxol o
derivados de taxol pueden ser, por ejemplo, composiciones para administración enteral, tal como oral, rectal, inhalación de aerosol, o
nasal, composiciones pare administraciôn parenteral, tales como

40 20 intravenosa a subcutÆnea, o composiciones para administración

transdØrmica (por ejemplo, pasiva o iontoforØtica).
Los agentes de la invenciOn (a. el inhibidor de COX-2 y el
bisfosfonato a b). El inhibidor de COX-2, el bisfosfonato y el taxol a
un derivado del mismo preferiblemente se utilize en la forma de
25 preparaciones farmacØuticas que contienen la cantidad

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en ser,

Las composiciones armaC6Uti0 de COX 2 pueden
cbon enteral, tat como oral,
ejemplO compOSiCi0S para admifliStra

15 rectal, /QJfl de aerosol compoSiCiofles para l o nasal,
administraciôfl parenteral, tal como intfaY° subcutÆnea, 0
composicbOneS para administraciôfl transdØrmica (por eernp1o, pasva

o iontoforØtica).

De preferencia, las compOSiciOneS farmacØuticas de COX-2

40 20 estÆn adaptadas para administraciófl oral o parenteral
(especbalmente oral). La admbnistración intravenosa y oral, la primera
y principal oral, se considera que es de importancia particular, preferiblemente, el ingredients activo del inhibidor de COX-2 estÆ en

forma oral.

25 El modo de administraciÔn particular y la dosis se pueden

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seleccionar por el medico que atiende tomando en cuenta los aspectos particulares del paciente, en especial la edad, peso, estilo de vida, nivel de actividad, etc.
La dosis de los agentes de la invenciôn depende de varios
5 factores, tales como la efectividad y duraciOn de acciOn del ingrediente activo, rnodo de administración, especie del animal de
sangre caliente y/o sexo, edad, peso y condiciôn individual del
animal de sangre caliente.
MÆs particularmente, las composiciones farmacØuticas
10 comprenden una cantidad efectiva inhibidora de ciclooxigenasa-2 del
46 inhibidor de COX-2 o compuesto de la fOrmula 1, que sustancialmente
estÆ libre de la actividad inhibidora de ciclooxigenasa-1 y de efectos
laterales atribuidos a esta.
Los compuestos farmacolOgicamente activos de la invención
15 son ütiles en la fabricaciOn de composiciones farmacØuticas que co
prende una caritidad efectiva de los mismos junto Con 0 en mezcla
con excipientes o vehiculos adecuados para aplicación ya sea enteral o parenteral. Se prefieren las tabletas y cÆpsulas de gelatina que comprenden el ingrediente activo junto con, a) diluyentes, por
20 ejemplo, lactosa, dextrosas, sacarosa, manitol, sorbitol, celulosa yb
lisina; b) lubricantes, por ejemplo, s(lice, talco, Æcido esteÆrico,su
sal de magnesio o de caiclo y/o glicol polietilØnico; para tabletas tambiØn c) aglutinantes, por ejemplo, silicato de magnesio-aluminio, pasta de almidón, gelatiria, tragacanto, metilcelulosa,
25 carboximetilcelulosa o polivinilpirrolidona; si se desea, d) agentes de

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desintegracion, por ejemplo aim idones, agar, âcido algInico 0 su sal
de sodio, o mezclas efervescentes; yb e) absorbentes, colorante, sabores

edulcorantes. Las composiciones inyectables de
preferencia son soluciones o suspensiones isotOnicas acuosas,

los
5 supositorios ventajosamente se preparari a partir de emuisiones o
suspensiones grasas. Dichas composiciones pueden ser esterilizadas
y/o contener auxiliares, tales como agerites conservadores, estabilizadores, humectantes o emulsificantes, promotores de solución, sales para regular la presión osmótica y/o regulares de pH.
10 AdemÆs, tambiØn pueden contener otras sustancias terapØuticamente
valiosas. Dichas composiciones se preparan de acuerdo con mØtodos convencionales de mezclado, granulación o revestimiento, respectivamente,

contienen de aproximadamente 0.1 a 75%, de
preferencia de aproximadamente I a 50% del ingrediente actvo.
15 Las tabletas pueden ser ya sea cubiertas con una pelIcula o cubiertas con capa entØrica, de acuerdo con los mØtodos conocidos
en la tØcnica.
Las formulaciones adecuadas para aplicación transdØrmica
incluyen una cantidad efectiva de un compuesto de la invenciOn con
20 un vehIculo. Los vehIculos ventajosos incluyen solventes farm acolOgicamente aceptables, que se pueden absorber para ayudar
a pasar a travØs de la pie[del huØsped. Por ejemplo, los dispositivos transdØrmicos estÆn en la forma de un vendaje que comprende un miembro de respaldo, un depôsito que coritiene el compuesto
25 opcionalmente con vehiculos, opcionalmente una barrera de control

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de velocidad para suministrar el compuesta de la piel del huØsped a una velocidad controlada y predeterminada durante un periodo prolongado de tiempo, y medios para asegurar el dispositivo a la pie!.
5 Las formulaciones adecuadas para aplicacióri tópica, por ejemplo, a la piel y ojos, incluyen solucianes acuosas, suspensiones, ungUentos, cremas, geles o formulaciones que se pueden rociar, par ejemplo, pars suministrarse a travØs de un aerosol, o simIares. Dichos sistemas de suministro tôpicos en particular serÆn apropiados
10 para aplicación dØrmica, por ejemplo, pars el tratamienta de cancer en la pie!, por ejemplo, para uso profilâctico en cremas, aspersiones
de lociones, y similares.
La dosis del inhibidor de COX-2 administrado depende de la
especie del animal de sangre caliente (mamifero), el peso del
15 cuerpo, edad y condiciôn individual, y la forma de administraciOn.
Una dosis unitaria para administraciOn oral a un mamIfero de aproximadamente 50 a 70 kg puede contener de entre aproximadamente 5 y 1000 mg, par ejemplo, de 100-800 mg, preferiblemente 200-400 mg del ingrediente activo.
20 Las formulaciones inhibidoras de COX -2 en forma de dosis unitaria individual contienen de preferencia de aproximadamente 1%
a aproximadamente 90%, y las formulaciones que no estân en una forma de dosis unitaria individual contienen de preferencia de aproximadamente 0.1% a aproximadamente 20% del ingrediente
25 activo, Las formas de dosis unitarias individuales tales como

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cÆpsutas, tabletas o grageas contienen, por ejemplo, de aproximadamente I mg a aproximadamente 1000 mg del ingrediente activo.
Las preparaciones farmacØuticas del inhibidor de COX -2 para
5 administración enteral y parenteral son, por ejemplo, aqueltas que estªn en formas de dosis unitarias, tales como grageas, tabletas o cÆpsutas y tambiØn ampolletas. Se preparan en una forma conocida per se, por ejemplo, a travØs de procedimientos convencionales de mezclado, granulacion, confecciôn, disolución o lipofilización. Por
10 ejemplo, se pueden obtener preparaciones farmacØuticas para administraciôn oral combinando el ingrediente activo con vehiculos sólidos, cuando es apropiado granular una mezcla resultante y procesar Is mezcla

grÆnulo si Se desea a es necesario despuØs de
la adición de auxitiares adecuados, a tabletas a nUcleos de grageas.
15 Otras preparaciones farmacØuticas aralmente administrables son capsules de relleno seco hechas de gelatina, y tambiØn cÆpsutas sellas suaves hechas de gelatina y un plastificante, tat como glicerof
o sorbitol. Las cÆpsulas de retleno seco pueden contener el ingrediente activo en la forma de un grÆnulo, par ejemplo, en mezcla
20 con Ilenadores tales como lactosa, aglutinantes, tales como almidones, y/o agentes de desliz, tale como talco a estearato de magnesio, y, cuando es apropiado, estabilizadores. En cÆpsulas suaves, el ingrediente activo de preferencia se disuelve a se suspende en lIquidos adecuados, tales coma aceites grasos, aceite
25 de parafina o glicoles polietilØnicos liquidos, siendo posible tambiØn

KIM
la adición de estabilizadores.
Las formulaciones parenterales especialmente son fluidos inyectables que son efectivos en varias formas, tales como intravenosa, intramuscular, intraperitoneal, intranasal, intradØrmica o
5 subcutÆneamente, Dichos fludos de preferencia son soluciones o
suspensiones acuosa isotônicas, las cuales pueden ser preparadas antes de uso, por ejemplo, a partir de preparaciones Iioflizadas que contienen el ingrediente activo solo o junto con un vehiculo farmacØuticamente aceptable. Las preparaciones farmacØuticas
10 pueden ser esterilizadas y/o contener auxiliares, por ejemplo, conservadores, estabilizadores, agentes humectantes yb emulsificantes, solubilizadores, sales para regular la presión osmótica y/o reguladores de pH.
Las formulacwnes adecuadas para aphcación transdØrmica
15 incluyen una cantidad efectiva del ingrediente activo con el vehculo.
Los vehiculos ventajosos incluyen solventes farmacolôgicamente aceptables que se pueden absorber para ayudar a pasar a travØs de
la piel del huØsped. Caracteristicamente, los dispostivos transdØrmicos estÆn en la forma de un vendaje que comprende un
20 miembro de respaldo, un depósito que contiene el compuesto opcionalmente con vehiculos, opcionalmente una barrera de control
de velocidad para suministrar el ingrediente activo a la piel de huØsped a una velocidad controlada y predeterminada durante un periodo prolongado de tiempo, y medios para asegurar el dispositivo
25 a la piel,

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Los siguientes ejemplos estân destinados a ilustrar la invención
y no deben ser coristruidos coma limitantes de la misma.

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A. Ejemplos de Formulación

ELemplo 1
Composiciôn de tableta granulada en hcimedo
10 Cantidad par tableta Ingredierite
25 mg Inhibidor de COX-2
79.7 mg Celulosa microcristalina
79.7 mg Monohidrato de lactosa
6 mg Hidroxipropilcelulosa
15 8 mg Croscarmelosa de sodio
0.6 mg Oxido de fierro
I mg Estearato de magnesio

Las resistericias de dosis de tabletas de entre 5 y 125 mg
20 pueden ser adaptadas variando el peso total, y la relaciOn de los primeras tres ingredientes. En general, se prefiere mantener una relaciÆn de 1:1 para celulosa microcristalina: monohidrato de lactosa.

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Elemplo 2
Composición de tableta granulada en hUmedo
Cantidad por tableta Ingrediente
12.5 mg Inhibidor de COX-2
5 86 mg Celulosa microcristalina
86 mg Monohidrato de lactosa
6 mg Hidroxipropilcelulosa
8 mg Croscarmelosa de sodio
0,6 mg Oxido de fierro
10 1 mg Estearato de magnesio

Elemplo 3
Corn posiciOn de tableta granulada en hümedo
Cantidad por tableta Ingrediente
15 10 mg Inhibidor de COX-2
87.2 mg Celulosa microcristalina
87.2 mg Monohidrato de lactosa
6 mg Hidroxipropilcelulosa
8 mg Croscarmelosa de sodio
20 0.6 mg Oxido de fierro
I mg Estearato de magnesio

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Eiemplo 4
ComposciOn de tableta granulada en hUmedo
Cantidad por tableta Ingrediente
5 mg Inhibidor de COX-2
5 89.7 mg Celulosa microcristalina
89.7 mg Monohidrato de lactosa
6 mg Hdroxipropilcelulosa
8 mg Croscarmelosa de sodio
0.6 mg Oxido de fierro
10 1 mg Estearato de magnesio

Elemplo S
ComposiciOn de tableta directamente comprmida
Cantidad par tableta lnqjediente
15 25 mg Inhibidor de COX-2
106.9 mg Celulosa microcristalina
106.9 mg Anhidrato de lactose
7.5 mg Croscarmelosa de sodlo
3.7 mg Estearato de magneslo
20

Las resistencias de dosis de tableta de entre 5 y 125 mg pueden ser adaptades variando el peso total de la tableta, y la relaciôn do los primeros 3 ingredientes. En general, se prefiere mantener una relación de 1:1 pare celulosa microcristalina:
25 monohidrato de lactosa.

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Elemplo 6
Composiciôn de tableta directamente comprimida
Cantidad por tableta Incirediente
12.5 mg Inhibidor de COX-2
5 113.2 mg Celulosa microcristalina
113.2 mg Anhidrato de lactosa
7.5 mg Croscarmelosa de sodio
3.7 mg Estearato de magnesw

10 Ejemplo 7
Composiciôn de tableta directamente comprimida
Cantidad por tableta Ingrediente
10 mg Inhibidor de COX-2
42.5 mg Celifiosa microcristalina
15 42.5 mg Anhidrato de lactosa
4 mg Croscarmelosa de sodio
1 mg Estearato de magnesia

Ejemplo 8
20 Composición de tableta directamente comprimida
Cantidad par tableta Inçirediente
5 mg Inhibidor de COX-2
45 mg Ceuosa microcristalina
45 mg Anhidrato de lactosa
25 4 mg Croscarmelosa de sodio

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Estearato de magneslO

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Composiciôn de câpsula de gelatina dura
5 Cantidad por tablej. Ingrediente
25 mg Inhibidor de COX-2
37 mg Celulosa microcristalina
37 mg Anhidrato de lactosa
I mg Estearato de magnesio
10 1 cÆpsula Câpsula de gelatina dura

Las resistencias de dosis de cÆpsula de entre 1 y 50 mg
pueden ser adaptadas variando el peso total del relleno, y la relacón de los primeros tres ingredierites. En general, se preftere mantener
15 una relación de 1:1 para celulosa microcristalina: monohidrato de
lactosa.

Ejemplo 10
Solución oral
20 Cantidad por 5 ml lnrediente
50 mg Inhibidor de COX-2
para 5 ml con óxido de polietileno 400

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Ejemplo 11
Suspension Oral
Cantidad par 5 ml de dosis
101 mg
150 mg

SusaensiOn Oral

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I ng red e n t e
Inhibidor de COX-2
Polivinilpirrolidona

Cantidad par 5 ml de dosis Ingrediente
2.5 mg Monolaurato de polioxietilensorbitÆn
10 mg Acido benzoico
para 5 ml con soluciOn de sorbitol (70%).
Las resistencias de dosis de suspension de entre 1 y 50 mg/5
ml pueden ser adaptadas variando la relaciOn de los primeros dos ingredientes.

Ejemplo 12
InfusiOn intravenosa
Cantidad par 200 ml
1mg
20 0.2 mg
1.8 mg
para 200 ml

25

Ingrediente
Inhibidor COX-2
Oxido de polietileno 400
Cloruro de sodlo
Agua purificada

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Ejemplo 13
PreparaciOn de Tableta de Combnaciôn
Se prepararon tabletas conteniendo 25.0, 50.0 y 100.0 mg, respectivamente, de un Taxol y 25 mg del inhibidor de COX-2, como
5 Se ilustra a continuaciOn:
Tableta para dosis conteniendo de 25-200 mg de Taxol y 25 mg
del inhibidor de COX-2.

Cantidad
10 Taxol 25.0 80.0 200.0
Inhibidor de COX-2 25.0 25.0 25.0
Celulosa microcristalina 37.25 100.0 175.0
Almidón de maiz alimenticio 37.25 4,25 8.5
modificado
15 Estearato de magnesio 0.50 0.75 15

Tanto los compuestos activos, celulosa como una porciOn del
almidôn de maiz se mezclaron y se granularon a una pasta de
almidóri de maiz a 10%. La granulaciOn resultante se tamizó, se secO
20 y se mezcló con el resto del almidón de maiz y el estearato de

40 magnesio. La granulación resultarite despuØs se comprimiO a tabletas

conteniendo 25.0, 50.0 y 100.0 mg, respectivamente, de taxol par
tableta, y 25 mg de inhibidor de COX-2 por tableta.

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Ejemplo 14
CUADRO I

Ingrediente Cantdad por 200 mg
de lote de tableta (kg)
5 NUcleo
G ran u I a ci
Sustancia de fÆrmaco de Æcido5-metil- 50**
2-(2 -cloro-6’-fluoroanhlino)fenilacetico
Celulosa microcristalina, NF (PH 101) 12.85
10 Monohidrato de lactosa, NF 11.65
Croscarmelosa de sodio, NF 1
Povidona, USP 4
Diôxido de titanio, USP 2
Agua purificada

USP 20.375
15 Fase extraganulada
Celulosa microcristalina, NF (PH 102) 13
Croscarmelosa de sodio, NF 3
Dióxido de titanio, USP 2
Estearato de magnesio, NF 0.5
20
Recubrimiento
Blanco "Opadry" 2.801
Amarillo "Opadry" 2.0
Rojo ’Opadry" 0.4
25 Negro ’Opadry" 0.0504
Agua purificada USP 29.758

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** El peso de la sustancia de fârmaco se toma con referencia a
la sustancia seca (100%) como base en el valor del ensayo (factorización). La diferencia en peso se ajusta a travØs de la cantidad de celulosa microcristalina utilizada.
5 Removida durante procesamiento.
lncluye un exceso del 50% para pØrdida durante el
procedimiento de recubrimiento.
El Cuadro 1 anterior, establece la fOrmula para un lote de aproximadamente 250,000 tabletas cubiertas con pelicula, de
10 liberaciOn inmediata de Æcido 5-metil-2-(2’-cloro-6’-fluoroanilino)-
fenilac6tico. Para hacer las tabletas, se dispersO el dióxido de titanio
en agua, seguido por la adiciOn de povidona y mezclado durante 20 minutos para hacer una suspension de povidona/dióxido de titanio.
La sustancia de IÆrmaco, lactosa, celulosa microcristalina y
15 croscarmelosa se mezclaron en un mezclador de alto esfuerzo
cortante (por ejemplo, un aparato de Collette Gral) durante 45 minutos pare formar una mezcla de fârmaco. La mezcla de fârmaco
se granulO en el mezclador de alto esfuerzo cortante con la suspensiOn de povidona/diôxido de titanio. La suspension se bombeó
20 a una velocidad de 3 kglminuto a la mezcla de fÆrmaco. La mezcla
resultante se mezclO 90 segundos mÆs despuØs de que se agregO toda la suspension. La granulaciOn hUmeda se secO un secador de lecho de fluido, utilizando una temperature de entrada de aire de 50°C. El objetivo de agua residual es de 3.5% (con una escala
25 permisible de 2.4-4.5%). La granulaciOn seca se hizo pasar a travØs

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de un tamiz utilizando un molino (oscilador) y un tamiz de 30 mallas. Los pasos previos se repitieron para hacer una segunda granulación.
El diOxido de titanio de la fase extra-granulada se hizo pasar a
travØs de un tamiz manual de 60 mallas. Las granulaciones secas se
5 mezclaron con la celulosa microcristalina de fase extra-granulada,
croscarmelosa de sodia y dioxide de titanio en un mezclador de coraza doble durante 300 revoluciones pars formar una mezcla penCiltima. Se hizo pasar estearato de magnesio a travØs de un tamiz manual de 60 mallas y Se secó con Is penUltima mezcla en un
10 mezclador de coraza doble durante 50 revoluciones para formar una
mezcla para la formación de tabletas. La mezcla para formación de tabletas se comprimiO a tabletas utilizando una prensa de tabletas y punzones ovalados.
Los polvos de recubrimiento (Opadry) se mezclaron con aqua
15 purificada pars hacer una suspensiOn de recubrimiento de 15% p/p.
Las peliculas Se cubrieron con pelicula con la suspension de recubrimiento en una charola de recubrimiento utilizando una temperatura de aire de entrada de 60 a 75°C.
El Cuadro 2 establece los contenidos de 200 mg de una tablets
20 cubierta con pelicula de àcido 5.metil-2-(2’-cloro-6’-
flu oroan ilino)fen ilacØtico.

25

49

CUADRO 2

Ingrediente Cantidad Función
teórica [mg]
NUcIeo
5 Sustancia de fÆrmaco do ªcido 5-metil- 200 Substanca activa
2-(2’-cloro-6’-fluoroanilino)fenac6tico
Celulosa microcristalina (PH 101) 51.4 Llenador
Lactosa 46.6 Llenador
Povidona 16 Aglutinante
10 DiÆxido de titariio 8 Color
Croscarmelosa de sodio 4 Desintegrarite
Agua purificada

Q. S. Uquido de granulaciOn

Fase extraganulada
15 Celulosa microcristahna (PH 102) 52 Llenador
Croscarmelosa de sodio 12 Desintegrante
Diôxido de titanio 8 Color
Estearato de magnesio 2 Lubricante
Peso do ncicteo 400
20
Recubrimiento

Blanco "Opadry" (OOFI 8296) 74676 Color
Amarillo "Opadry" (0012951) 5.3312 Color
Rojo "Opadry" (001715613) 10668 Color
25 Negro "Opadry" (00F17713) 0.1344 Color
Agua purificada" Q. S. Solvente de Recubrimiento
Peso Total 414

Removida durante el procesamiento
30

50

AdemÆs, las formulaciones de tableta pueden contener alcohol 5-metil-2-(2’-cloro-6’-fluoroanili no) ben cilico y/o ªcido 5-metil-2-(2’- cloro-6’-fluoroanilino)benzoico en una cantidad de entre aproximadamente 0.01 y 2% en peso, mâs especificamente de entre
5 aproximadamente 0.1 y 1.

Ejemplo 15
CÆpsulas conteniendo pellas cubiertas de ingrediente activo,
por ejemplo, pamidronato-pentahidrato disódico, como ingrediente
10 activo:

40 Pella de nUcleo:
Ingrediente activo (molido) 198.3 mg
Celulosa microcristalina 52.7 m
(Avicelfi PH 105) 250.0 mg
15
Recubrimiento interno +:
Celulosa HP -M 603 10.0 mg
Glicol polietilØnico 2.0 mg
Talco 8.0 mg
20 270.0 mg

Recubrimiento externo resistente a jugo gØstrico +:
Eudragitfi L 30 D (sôlido) 90.0 mg
Citrato de trietilo 21.0 mg
25 Antifoamfi AF 2.0 mg

51
Agua 7.0 n,
Talco 390.0 mg
Se humedeciO una mezcla de panidronato disódico con Avicelfi
PH 105 con agua

se amasó, se extruyó

se formó en esferas. Las
5 peflas secas despuØs se cubrieron sucesivamente en el lecho fluidizado con un recubrimiento interno, consistiendo de ceIuosa HP -
M 603, glicol polietilØnico (PEG) 8000

taco,

el recubrimiento

resistente a jugos gstricos acuosos, consistiendo de Eudragitfi L 30
D, citrato de trietito

Antifoamfi AF. Las peltas cubiertas se
10 espifivorearon con povo

se Henaron en cÆpsulas (tamaæo de
cØpsula 0) a travØs de una mâquina de reHeno de cÆpsulas comercial, por ejemplo, Hafliger

Karg.

Elemplo 16
15 Sistema transdØrmico adhesivo monoiltico, conteniendo como ingrediente activo, por ejempo, âcido 1-hidroxi-2-(imidazoLl-iI)- etan-2,2-difosf6nico,

Co mp Os i ci

n

20 Poliisobutileno (PIB) 300 5.0 g
(Oppanol B.1, BASF)
PIB 35000 3.0 g
(Oppanol BlO, BASF)
PIB 1200000 9.0 g
25 (Oppanol B100, BASF)

52

resina hidrogenada de hidrocarburo 43.0 g
Escorez 5320, Exxon)
1-dodecilazaciclopentan-2-ona 20.0 g
(Azone, Nelson Res., Irvine/CA)
S Ingredients actvo 20.0 q
Total 100.0 g

PreparaciOn:
Los componentes anteriores se disolvieron conjuntamente en
10 150 g de una fracciOn de petróleo de punto de ebulliciOn especial
100.125 enrollando en un lecho de engranaje de rodillo. La solución
se aplicô a una pelicula de pollØster (Hostaphan, Kalle) a travØs de
un dispositivo de extension utilizando un bisturl de 300 mm, proporcionando un recubrimiento de aproximadamente 75 g/m2.
15 DespuØs de secar (15 minutos a 600C), se aplicO una pelicula de
poliØster tratada con silicOn (espesor 75 mm, Laufenberg) como la pelicula desprendible. Los sistemas terminados se perforaron en
tamaæos en una forma deseada de 5 a 30 cm2 utilizando una
herramienta punzonadora. Los sistemas completos se sellaron

Is 20 individualmente en bolsas de papel aluminado.

Ejemplo 17
Frasco conteniendo 1.0 mg de Æcido 1-hidroxi-2-(imidazol-1-il)etan-1,1-difosf6nico liofilizado (sales de sodio mezcladas del
25 mismo). DespuØs de una dilución con 1 ml de agua, se obtuvo una

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solucOn (concentraciôn de I mg/ml) para infusOn intravenosa.

Composición
Ingredente activo (Æcdo dfosfónico libre) 1.0 mg
5 Manitol 46.0 mg
Citrato trisOdico x 2 H20 Ca. 3.0 mg
Agua I ml

Agua para inyeccion I ml
10

En 1 ml de agua, el ingrediente activo se titulô con citrato trisódico x 2 H20 a un pH de 6.0. DespuØs, el manitol se agregO y la solución se liofilizó y el liofilizato se colocó como relleno en un frasco.
15

Ejemplo 18
Ampolleta conteniendo ingrediente activo, por ejemplo, pamidronato-pentahidrato disódico disuelto en agua. La solución (concentraciôn 3 mg/ml) es para infusiOn intravenosa despuØs de
20 diluciôn.

Corn posición:
Ingrediente activo 19.73 mg
5.0 mg de ingrediente activo anhidro)
25 manitol 250 mg

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agua para iriyecciOn 5 ml

Ejemplo 19
lnhibiciôn de crecimiento de linea de cØlula cancerosa de
5 pecho humanas con la combinaciôn de Æcido zoledrónico y un
inhibidor de COX-2.

Propósito: La ciclo-oxigenasa (COX) es sintasa de prostaglandiria H,
la cual es la enzima principal para mediar la formación de
10 prostanoides (un tØrmino colectivo para prostaciclinas, prostaglandinas y tromboxanos). La COX-2 es sobre-regulada en un alto porcentaje de cÆnceres humanos comunes y estÆ asociada con comportamiento de tumor y pasivo y metastÆtico. Los inhibidores de COX-2 suprimen el crecimiento de cancer de colon in vitro
15 induciendo apoptosis. El Æcido zoledrónico, un bisfosfonato de nueva
generaciôn utilizado en el tratamiento de enfermedad ôsea inducida
01 cancer de pecho, sign ificativamente reduce el nümero de cØlula e induce apoptosis en cØlulas cancerosas de pecho humano. El propósito de este estudio fue determinar el efecto de combinar un
20 inhibidor de COX-2 con Æcido zoledrônico en el crecimiento de
cØlulas cancerosas de pecho.

MØtodos: el efecto de combinar el inhibidor de COX-2 (SC 236) y
â cido zoledrônico comparado con cualquier agente solo se probO en
25 una linea de cØlula de cancer de pecho humana transfectada HER-

5

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2/neu (MCF/18) y la linea transfectada de vector de control (MCF/neo). Se determinó el nümero de cØlulas despuØs de una incubaciôn de 3 dias utilizando el ensayo de tinciôn de tetrazollo de MPT.

Resultados: El tratamiento de las lineas de cØlula MCF/18 y MCF/neo de control transfectadas con HER-2/neu con el inhibidor de COX-2, SC236 (1-10 pM) dio como resultado una inhibición de crecimiento dependiente de la dosis (15-41% de inhibiciOn y 18-53%
10 de inhibiciôn, respectivamente). El tratamiento con Æcido zoledrónico
(1-10 pm) tambiØn proporcionO una inhibición de crecimiento de dosis. Sin embargo, el HER-2/neu que sobreexpresa cØlulas MCF/18 tue menos sensible ha Æcido zoledrónico (mediciôn del 9-53%) que
las cØlulas de MCF/neo (inhibiciôn del 8-67%). La combinación de
15 Æcido zoledrônico (5 pM) y SC 236 (5 pM) pareciô tener un efecto
inhibidor mejorado (menos que aditivo) en las cØlulas MCF/neo y un efecto aditivo en las cØlulas MCF/18.

Conclusion: el tratamiento con el inhibidor de COX-2, SC 236, solo
20 o Æcido zoledrônico sÆlo proporcionô una inhibiciôn de crecimiento
dependierite de dosis tanto en una linea de cØlula de cancer de pecho humana transfectada con HER-2/neu (MCF/18) y una linea transfectada de vector de control (MCF/neo). Sin embargo, la linea MCF/18 tue menos sensible al Æcido zoledrónico. La combinaciôn de
25 âcido zoledrônico con el inhibidor de COX-2, SC 236, proporcionó un

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efecto inhibidor mejorado en las cØlulas cancerosas de pecho de MCF/neo de control y un efecto aditivo en las cØlulas de MCF/18 transfectadas con HER-2/neu comparado con cualquier agente solo.

5 Ejemplo 20
lnhibición de crecimiento de lineas de cØlula cancerosa de
pecho humanas con la combinaciôn de un inhibidor de COX-2, Æcido zoledrónico y docetaxel.
El docetaxel es un agente antineoplÆstico que pertenece a la
10 familia de taxano. El docetaxel induce la fosforilaciôn bcl-2 y
subsecuente apoptosis y es efectivo en el tratamierito de pacientes
con cØncer de pecho o mama. El propOsito de este estudio the determinar el efecto de combinar un inhibidor de COX-2 con Æcido zoledrônico y/o taxotere en el crecimiento de cØlulas cancerosas de
15 pecho.

MØtodos: El efecto de combinar el inhibidor de COX-2 (SC 236) con
â cido zoledrónico y/o taxotere se probó en una linea de cØlulas
cancerosas de pecho humanas transfectadas con HER-2/neu
20 (MCF/18) y la linea transfectada del vector de control (MCF/neo) se
determiriO el nCimero de cØlulas despuØs de una incubaciOn de 3 dias utilizando un ensayo de tinte de tetrazolio de MTT.

Resultados: El tratamiento de las lineas de cØlulas de MCF/18
25 transfectadas con HER-2/rieu y de MCF/neo transfectadas de control

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con cada uno de los agentes do como resultado una inhibiciôn de crecimiento dependiente de dosis. Sin embargo, las cØlulas de MCF/18 transfectadas con HER-2/neu fueron menos sensibles at Æcido zoledrónico que las cØlutas de MCF/neo de control, inhibiciôn
5 del 9%-53% y 18%67%, respectivamente. El tratamiento con la
combinaciôn de CS 236 (5 pM) y taxotere (2 nM) proporcionó una
inhibición mejorada del crecimiento en lineas de MCF/18 y MCF/neo.
El tratamiento con Æcdo zotedrórnco (5 pM) y taxotere (2 nM)
tambiØn dio como resultado una inhibiciôn mejorada de crecimiento
10 en ambas lineas de cØlula. La combinación de CS 236 (5 pM) y âcido

40 zoledrónico (5 pM) tuvo un efecto inhibidor mejorado sobre las lineas
de MCF/neo y un efecto aditivo en las cØlulas de MCF/18. La triple
combinaciOn de los 3 agentes dio como resultado un pequeæo
incremento en la inhibicióri del crecimiento sobre

por arriba de
15 aquel visto con cualquiera de las dobles combinaciones.

Conclusion: Todas las posibles dobles combinaciones de un inhibidor de COX-2, Æcido zoledrOnico y/o un taxotere proporcionô
una inhibición mejorada de crecimiento comparado con cada agente
20 solo en las lineas de cØlula de cØncer de pecho transfectadas con
HER-2/neu de MCF/18 y transfectadas de vector de control de MCF/neo. La combinación del inhibidor de COX -2, SC 236, con Æcido zoledrónico fue aditiva en la Ilnea de cØlulas transfectadas con HER 2/neu. La triple combinaciôn dio como resultado un pequeæo
25 incremento en el la inhibición del crecimiento sobre y por aruba de

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aquel visto en cualquiera de las dobles combinaciofleS

Ejemplo2i

lnhibición de una linea de cØlula cancerosa de prostata humafla
5 con la combinaciÆn de un inhibidor de COX-2 y âcido zoledrófliCo.

Propósito: El propósito de este estudio fue determinar el efecto de combinar un inhibidor de COX-2 con Æcido zoledrónjco sobre el crecimiento de cØlulas cancerosas de próstata.

10

MØtodos: El efecto de combinar el inhibidor de COX-2 (SC 236) y Æcido zoledrônico comparado con cualquier agente solo se probó en
la linea de cØlula de carcinoma de próstata humano DU -145. Se determinO el nUmero de cØlulas despuØs de un tratamiento de 3 dIas
15 utilizando el ensayo de tinte de tetrazolicr de MTT.

Resultados: El tratamiento con el inhibidor de COX-2, SC 236, (1-25 pM) dio como resultado una inhibición de crecimiento dependiente de dosis (0-77%). El tratamiento con Æcido zoledrónico (1-10 pM)
20 tambiØn proporcionó una inhibición de crecimiento dependiente de
dosis 8-70%). La combinación de 3 pM de Æcido zoledrónico (inhibiciOn del 23%) y 5 pM de SC 236 (40% de inhibición) dio como resultado un efecto inhibidor aditivo (inhibición del 60%) en la linea
de cØlula de prOstata DU -145.
25

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Conclusion: El bsfosfonato, äcido zoledrôrnco y el inhibidor de
COX-2, SC 236 proporconaron la inhibición de crecimiento dependiente de doss como agentes individuales. El tratamiento de la
Ilnea de cØlula de carcinoma de prOstata huma DU -145 con la
5 combinaciÆn de estos dos agentes dio como resultado un efecto
inhibidor aditivo comparado con aquel visto con cualquier agente solo.

REIVINDICACIONES

1.- Una composición farmacØutica para el tratamiento de
malignidades, el cual comprende en combinaciOn un bisfosfonato y
5 Un inhibidor de COX-2 para uso simultâneo, secuencial o separado,
2.- El uso de Un inhibidor de COX-2 para la preparacOn de
un medicamento, para utilizarse en combinaciôn con un bisfosfonato pars el tratamiento de una enfermedad maligna.
3.- Un mØtodo pars tratar a un paciente que presenta una
10 enfermedad maligna, que comprende administrar al paciente una
cantidad efectiva de un bisfosfonato y una cantidad efectiva de un inhibidor de COX-2.

4.- Una composiciôn farmacØutica de acuerdo con la
reivindicaciOn 1, un USO de acuerdo con la reivindicaciôn 2, o Un
15 mØtodo de acuerdo con la reivindicación 3, para la inhibiciôn de
crecimiento de cØlula cancerosa a inducciOn de apoptosis de cØlula

cancerosa.

5.- Un mØtodo para tratar a un paciente que presenta una
enfermedad maligna, que comprende administrar al paciente una
20 cantidad efectiva de un bisfosfonato, una cantidad efectiva de un
inhibidor de COX-2 y una cantidad efectiva de un taxol o Un derivado
del mismo.
6.- Un mØtodo de acuerdo con la reivindicaciOn 3 o 5, en
donde el bisfosfonato es un N-bisfosfonato.
25 7.- Un mØtodo de acuerdo con la reivindicación 6, en donde

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el bisfosfonato es un compuesto de la formula I:

en donde:

X es hidrogeno, hidroxilo, amino, alcanoilo, o un grupo amino substituido por alquilo de 1 a 4 Ætomos de carbono, 0 alcanoilo;
10 R es hidrOgeno o alquilo de 1 a 4 Ætomos de carbono,
Rx es una cadena lateral que contiene un grupo amino opcionalmente substituido, 0 Ufl heterociclo que contiene nitrOgeno (incluyendo, heterociclos que contienen nitrOgeno aromÆtico), o una
sal farmacØuticamente aceptable del mismo o cualquier hidrato de
15 los mismos.
8.- Un mtodo de acuerdo con la reivindicaciOn 7, en donde
el bisfosfonato es Æcido 2-(imidazol-1 -il)-1-hidroxietan-1, 1-
difosfónico (âcido zoledrÆnico) o una sal farmacolOgicamente aceptable del mismo.
20 9.- Un mØtodo de acuerdo con la reivindicación 3, en donde
el inhibidor de COX-2 es un inhibidor de COX-2 que tiene una IC50 para la inhibición de COX-2 menor que aproximadamente 2 iM

una

IC50 para la inhibición de COX-1 mayor que aproximadamente 5 pM.
10,- Un mØtodo de acuerdo con la reivindicación 9, en donde
25 el inhibidor de COX-2 se selecciona del grupo que consiste de

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rofecoxib, etoricoxib, celecoxib, valdecoxib, parecoxib, 0 Ufl inhibidor
de COX -2 del derivado de Æcido 5-alquil-2-arilaminofenilac6tico, o una sal farmacØuticamente aceptable del mismo, 0 cualquier hidrato del mismo.
5 11.- Una composición de acuerdo con la reivindicación 1, que comprende una cantidad efectiva de un taxol, paclitaxel, taxotere, docetaxel, un taxano, una taxina, a cualquier otro derivado adecuado de taxol.

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International Filing Date

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Sheet No.,..3

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Xl CH

LI Switzerland and Liechtenstein Xl LC Saint Lucia
Xl CN China......................Xl LK Sri Lanka
Xi CO Colombia 0 LR Liberia
Xl CR Costa Rica...................0 LS Lesotho..................... Xl CU Cuba........................ Xl LT Lithuania
Xi

Czech Republic...............Xl LU Luxembourg
DE Germany....................Xl

Latvia

Xl

Denmark

Morocco

Xl

Dominica

MD Republic of Moldova
Algeria
Ecuador

MG Madagascar
Estonia

MK The former Yugoslav Republic
Xl

Spain.......................Macedonia
Xl

Finland

Mongolia
GB United Kingdom

MWMalawi

Grenada Xl

Mexico

Xi

Georgia

Mozambique
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Ghana

Norway

O SD Sudan

Xi SE Sweden
Xl SG Singapore
Xisi Slovenia....................

Xi SK Slovakia....................

o SL Sierra Leone.................
TJ Tajikistan...................
Xl TM Turkmenistan................
Xi TN Tunisia
XiTRlurkey......................

Xl Ti’ Trinidad and Tobago..........

o TI United Republic ofTanzania
Xl UA Ukraine...................
0 UG Uganda"...................
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Uzbekistan

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Viet Nam

Xl

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Zambia

Xl

Zimbabwe

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:
.i!li Yjct and the Grenadi e ....0.................................

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope ofthis statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration ofthat time limit. (Confirmation (includingfees) must reach the receiving Office within the 15-,nanthtime/imii.)

Form PCT/RO/101 (second sheet) (July 2002) See Notes to the requestform

Sheer No...4...

11

Supplemental Box Ifthe Supplemental Box is not used, this sheet should not be included in the request.

If in any ofthe Boxes, except Boxes Nos. VlII() to (v)for which Continuation of Box No. II

aspecialcontinuation box isprovided,thespaceisinsufficieni Novartis AG is applicant for all designated States tofurnishalltheinformation: in such case, write "Continuation ofBox No...," (indicate the number ofthe Box) ondfurnish the with the exception of: AT (Austria) and US (USA) information in the same manner as required according to the

captions of the Box in which the space was insufficient, in
particular:

(i)if more than two persons are to be indicated as applicants Continuation of Box No. Ill and/or inventors and no "continuation sheet" is available: in Novartis Pharma GmbH such case, write "Continuation ofBox No. I1l" andindicaiefor

each addirionalperson the same type ofinformation asrequired is applicant for AT (Austria) only.
in Box No. Iii. The country ofthe address indicatedin this Box
is the applicant’s State (that is, country) ofresidence i/no Stale
ofresidence is indicated below;
(ii) if in Box No. liar in any ofthe sub-boxes ofBox No. III, the
indication "the Stales indicated in the SupplementalBox" is

checked: in such case, write "Continuation ofBox Na. II" or "Continuation a/BoxNo. III- or "Continuation ofBoxes No. II
and No. ill" (as the case may be), indicate the name of the

applicant(s) involvedand, next to (each)such name, the Slate(s) (and/or, where applicable, ABJPO, Eurasian, European or OAPZpatent) for the purposes ofwhich the namedperson is

applicant;
(iii) if in Box No. liar in any ofthe sub-boxes ofBox No. Ill, the inventor or the inventor/applicant is not inventor for the purposes of all designated Stales or/or the purposes ofthe (lulledStales ofAmerica: in such case, write "Continuation of Box No. II" or "Continuation a/Box No. Iii "or "Continuation

ofBoxes No. II andNo III" (as the case may be), indicate the name of the invenior(s,) and, next to (each) such name,

the State(s) (and/or, where applicable, ARJPO, Eurasian, European or OAPI patent)for the purposes of which the namedperson is inventor,-
(iv)

nventor;(iv)

if in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, Write "Continuation of Box No. IV" and indicatefor eachfurther agent the same IJ.pe ofinformation as required in Box No. IV;

(v) if in Box No. I’, the name 0/any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of

addition, "or if in Box No. V, the name ofthe UnitedSiates of

America is accompanied by an indication "continuation" or "continuation-in-part ": in such case, write "Continuation of Box No. V’ and the name of each State involved (or OAPI), andafter the name a/each such Stale (or 0.4Ff), the number of

the parent title orparent application and the date ofgrant of
the parent title orfiling ofthe parent application;

(vi) if in Box No. Vi, there are more thanfive earlier applications whosepriority is claimed.’ in such case, write "Continuation

of Box No. Vi" and indicate for each additional earlier

application the same type of information as required in Box No, Vi.
2. if with regard to the precautionary designation statement

contained in Box No. V. the applicant wishes to exclude any State(s)from the scope ofthat statement: in such case, write
"Designation(s) excluded from precautionary designation statement" and indicate the name or Iwo-letter code of each

State so excluded

Form PCT/RO/10I (supplemental sheet) (March 2001; reprint July 2002) See Notes to the request form

Sheet No..,,...

Box No. VI PRIORITY CLAIM

The priority ofthe following earlier application(s) is hereby claimed:

Filing date Number Where earlier application is:
of earlier application
(day/,nont/i4’ear)

of earlier application al application:
i°n’j or Member regional application:* international application: of WTO regional Office receiving Office
item (1)
19 October 2001 60/345921 US

(19.10.01)
item (2)

item (3)

item (4)

item (5)

[] Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy ofthe earlier application(s) (only ifthe earlier application wasfiledwith the Office whichfor thepurposes ofthis international application is the receiving Office) identified

above as:

LIII all items J item (1) J item (2) U item (3) LII item (4) U item (5) LIother, see Supplemental Box
Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Conventionfor the Protection of Industrial Property or one Member of the World Trade Organizationfor which that earlier application wasfiled (Rule 4. lO(b)(I)):.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (iftwo or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen, the two-letter code may be used):

ISA!..

Request to use results of earlier search; reference to that search (fan earliersearch has been carried out by or requesredfrom the International Searching Authority):

Date (day/month/year) Number Country (Or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable Number of check-boxes below and indicate in the right column the number ofeach type ofdeclaration): declarations

[II Box No. VIII (i) Declaration as to the identity ofthe inventor

Box No. VIII (ii) Declaration as to the applicant’s entitlement, as at the international filing
date, to apply for and be granted a patent

Box No. VIII (iii) Declaration as to the applicant’s entitlement, as at the international filing
date, to claim the priority of the earlier application

[] Box No. VIII (iv) Declaration of inventorship (only for the purposes ofthe designation of the
United States of America)

Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty

Form PCT/RO/101 (third sheet) (July 2002) See Notes to the requestform

Sheet No,.....
Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains: This international application is accompanied by the following Number
(a) the following number of item(s) (mark the applicable check-boxes below and indicate in of items
sheets in paper form: right column the number ofeach item):
request (including 1. X fee calculation sheet
declaration sheets)

6 2. gg original separate power of attorney
description (excluding
sequence listing part)

44 3 0 original general power of attorney

claims

3 4.X copy ofgencral,power of attorney; reference number,
abstract

1 if any:.k’Y3’l................................
drawings

statement explaining lack of signature

Sub-total number ofsheets 54 6. 9 priority document(s) identified in Box No. Was
sequence listing part of
description (actual number 7.

translation of international application into

ofsheets iffiled in paper (lange)....................................... form, whether or not also 8. sate indications concerning deposited microorganism filed in computer readable

form; see (7) below)

0 or other biological material
Total number of sheets
9. 0 sequence listing in computer readable form (indicate also type and number ofearners (diskette, CD-ROM, CD-R or other))
(b) sequence listing part of description filed in (i) 0 copy submitted for the purposes ofinternational search
computer readable form under Rule I 31cr only (and not as part ofthe
(i) 0 only (under Section 801 (a)(i)) international application)
(ii) 0 in addition to being filed in paper (ii) 0 (only where check-box or (b’ii) is marked in left
form (under Section 801(a)(ii)) column) additional copies including, where applicable, the copy for the purposes ofinternational search under
Type and number of carriers (diskette, Rule 131cr

CD-ROM, CD-R or other) on which the (iii) 0 together with relevant statement as to the identity sequence listing part is contained (additional
copies to be indicated under item 9(u), in ofthe copy or copies with the sequence listing part
right column): mentioned in left column
.... 10. fJ other (specfy)....................................
Figure of the drawings which Language of filing of the
should accompany the abstract: international application:

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Nest to earh signature inacaie the nane oJthe p?isQnsigni,r amilhe capacity in which thepe-sson signs (fsuch capacity is not obviousfrom reading the request).

In the name of the applicants
The representative

16.10.2002 GROS,ntAV36671

ror receiving Jmnce use onmy

1. Date of actual receipt of the purported 2. Drawings: international application:
E 3 .

received:

Corrected date of actual receipt due to later but

timely received papers or drawings completing the purportedinternational application:
4. Date of timely receipt of the required E1 not received:
corrections under PCI Article 11(2):

5. International Searching Authority 6.Transmittal ofsearch copy delayed (iftwo or more are competent): ISA

until search fee is paid

For International Bureau use only

Date ofreceipt ofthe record copy by the International Bureau:

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(43) International Publication Date (10) International Publication Number

May 2003 (01.05.2003) PCT WO 03/035081 A I

(51) International Patent Ciassificatioti: A61 K 31/663. (72) Inventor; and
31/635. 3/444, 31/42, 31/365 31/337 31/)96. 45/00 (75) Inventor/Applicant (//u’ ’S on!)): GREEN,.Jouatlrait
A6 P 290). 35/tX) II (A61 K 3/663. 31:635) (AOl K I(iH/(’! I: Waldstrussc 12, C.11-11,14 Ar!cshcini (Cl
31/663, 31:635, 31:337) (A6 1K 31/66331:337)) A)) 1K

31/635, 31:337) (74) Agent: GROS, Florent; Novartis AG, Corporate Intellec
ma] properly. Patent & ’I radem:rrk I)epartmero. (.11 4002
(21) International Application Number: 11C’l’11iP021 1109)) Basel (CH).

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60/345,921 19 October 2001)) 9.10.200!) US

(71) Applicant for all designated States excel)/.4/. (/5): NO-VARTIS AG [CI 1/Cl lJ I.ichtsirasse 35, (’11-4056 Base]
(Cl 1).

(71) Applicant (for -IT on/C: NOVARTIS PIJARMA GMBH AT/A’I’[: Brunner Strasse 59, A - I 235 Vienna Al’).

(71) Applicants and
(72) Inventors: LIPTON, Allan [US/US I: Penn State College of’ Medicine, 5(X) University I)dvc. Hershey- PA 7033 ((IS). WITTERS, Lois, Mary JUS/US1, 25 Fisher Road. York Haven. PA 17370 (US).).

Designated States (national): Al). AG. Al- AM Al. Al). AZ, HA, B8, HG, BR, BY, BZ, CA, Cli, CN. CO. CR. CII.
(7., Dl), I)K, DM, 1)7,, I/C, 1/F, US, Fl, GB, (il), (il). (iI I.
HR 1116 11), 11.. IN, IS, JR KU, KG, KR KR. KZ. [C. l.K.
Li’. LU, IN, MA, Ml), MK, MN, MX, NO N7., CM, III I
P1.. 111, RO, RU, 51/, SU, Si. SK. ’1.1, TM. [N. ’IF. ’[I. LA.
US. U’/,, VC, VN. YU. 7.A. 7.W,

(84) Designated States fregionali: Furasian patent (A NI - AZ-BY. KU, KZ, MI), RU. ’II, TM). liuropean patent (,N11 FL. HG. Cli. CY, (7., DI!, DK I/I!, 1!S FL FR. 013. OR, II!,
U], MC, Ni- PT. SL SK. ’[R).

Published:

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IJ (54) Title: PHARMACFUTICAL COMPOSI’[’l()N FOR I SF FOR TI II! ’l’Rl./A’l’MIIN’F Ci" MAI.IGNANCII/S COMPRISING IN f4’) COMBINATION A BISPI-IOSI’I IONA’l’IIS, A COX -2- INI 1113110R AN]) A 1’AXOI_

(57) Abstract: A pharmaceutical composition [’or treatment of nialignancies, in particular a malignant disease which is associated with the development of hone metastases or excessive hone resorption, comprises in coiTthinallotl a his]Thc>Spltt>rliiteS. (.IOX-2 irthihito.r and/or a taxol or derivative thereof [’or simultaneous, sequential or separate Use. Also provided is a method of [reeling a patient suffering. [rot-fl a maligttant disease comprising administering to the patient an i.’l’l’ective amount of a hisphosphonates. an cli’ectivc amount o I a COX 2 inhibitor and/or and effective amount of a taxo I or derivative thereof,.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)
Applicant’s or agent’s tile reference

4-32199A/USN

FOR FURTHER see Nohfication of Transmittal of International Search Report

ACTION (Form PCT/ISN220) as well as, where applicable, item 5 below.
International application No. International filing date (day/month/year) [(Earliest) Priority Date (day/month/year)

PCT/EP 02/11696 1811012002 19/10/2001 Applicant

NOVARTIS AG

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of J.Q_ - sheets
It is also accompanied by a copy of each prior art document cited in this report.

1 basis of the report
a With regard to the language, the international search was carried out on the basis of the international application in the
language in which it was filed, unless otherwise indicated under this item.

Dthe international search was carried out on the basis of a translation of the international application furnished to this
Authority (Rule 23.1(b)).
b. With regard to any nucleotide and/or amino acid sequence disclosOd in the international application, the international search was carried out on the basis of the sequence listing

11 contained in the international application in written form.
El filed together with the international application in computer readable form.
Efurnished subsequently to this Authority in written form,
furnished subsequently to this Authority in computer readble form.
the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the
international application as filed has been furnished.
the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).
3. Unity of invention is lacking (see Box II).

4. With regard to the title,
the text is approved as submitted by the applicant
the text has been established by this Authority to read as follows:
PHARMACEUTICAL COMPOSITION FOR USE FOR THE TREATMENT OF MALIGNANCIES COMPRISING
IN COMBINATION A BIPHOSPHONATE, A COX -2 INHIBITOR AND A TAXOL

5. With regard to the abstract,
the text is approved as submitted by the applicant.
IIIthe text has been established, according to Rule 38.2(b), by this Authority as it appears in Box Ill. The applicant may,
within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No.

Fj as suggested by the applicant. None of the figures.
LII because the applicant tailed to suggest a figure.
because this figure better characterizes the invention.

Form PCT/ISN210 (first sheet) (July 1998)

INIttINAIIUNML btAHLorl twrt.nii International Application No

PCT/EP 02/11696

A CLASSIFICATION OFrJECT

MATTER

IPC 7 63 /635 A61K31/444 A61K31/42 A61K31/365
A61K31/337 A61K31/196 A61K45/06 A61P29/00 A61P35/00 //(A61K31/663,31:635),(A61K31/663,31:635,31:337)JA61K31/663,
Accordirtq In International Patent Classification (IPO) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system tolloweci by classification symbols)
IPC 7 A61K

Docutnentation searched other than tnilnimum documentation to the extent that such documents are included in the twirls searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, EMBASE, BIOSIS, PASCAL, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category Citation of document. with indication, where appropriate, of the relevant passages Relevant to claim No.

X WO 00 38730 A (MASFERRER JAIME L;GORDON 1-9,
GARY (US); SEARLE & CO (US); KOKI ALANE) 11-13
6 July 2000 (2000-07-06)
page 38, line 25 -page 62, line 11
page 68, line 12,15
page 79, line 23
page 97, line 27
page 103, line 24
page 104, line 10,11"
page 107, line 17 -page 108, line 21
page 142, line 25 - line 31
page 166 -page 170; table 19

- /--

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

Special categories of cited documents
1 later document published after the international filing date

or priority date and not in conflict with the application but A document defining the general state of the art which s not cited to understand the principle or theory underlying the considered to be of particular relevance invention
E earlier document but published on or after the international ’X document of particular relevance: the claimed invention filing date cannot be considered novel or cannot be considered to
document which may throw doubts on priority claim(s) or involve an inventive stop When the document is taken alone

which is cited to establish the publication date of snottier Y document of particular relevance: the claimed invention citation or other special reason (as specified) cannot be considered to involve all Inventive step when the

0’ document referring to an oral disctosure, use, exhibition or document is combined with one or more other such docu-
other means ments, such combination being obvious to a person skilled

P’ document published prior to the international filing date but in the art.
later than the priority dale claimed

document member of the same patent family
Date of the actual completion of the international search Dale of mailing of the international search report

27 February 2003 13/03/2003

Name and mailing address of the ISA Authorized officer
European Patent Office, P.R. 5818 Patenitaan 2
NL

2280 HV Rijswijk

Tel, (-431--70) 340-2040, lx. 31 651 ape nI, 4 0’ I Fax: (’-31 -70) 340-3016
Form PCT/!SA1210 (second sheet) (July 1992)

page 1 of 5

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International Application No

PCT/EP 02/11696

A. CLASSIFICATION OP SUBJECT MATTER

IPC 7 31:337),(A61K31/635.31:337)

Accordkig to International Patent Classitiction (IPG) or to bulb national classification ancHlIG
B. FIELDS SEARCHED

Minimum documentation, searched (classification system followed by classification symbols)

Documentation searched other tIler, minimum documentation to the eslent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms Used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.

P,X WITTERS, L. El AL.: "Inhibition of growth 1-4,6,8,
of human breast cancer cell lines with the 9,11
combination of zoledronic acid and a COX -2
Inhibitor"
EUROPEAN JOURNAL OF CANCER,
vol. 37, no. Suppi. 6,
22 October 2001 (2001-10-22), page 78
XP002232825
the whole document

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

Special categories of cited documents: T later document published after the international tiling date
or priority date and not in conflict with the application but
A document defining the general state of the art which is not cited to understand the principle or theory underlying the
considered to be of particular relevance invention

E earlier document but published on or after the international of particular relevance: the claimed invention tiling dale cannot be considered novel or cannot be considered to
L document which may throw doubts on priority claim(s) or invOlve an inventive step when the document is taken alone

which is cited to establish the publication date 01 another Y document of particular relevance: the claimed invention citation or other special reason (as specified) cannot be considered to involve an inventive step when the

0 document referring to an oral disclosure, use, exhibition or document is combined with one or more other such docu-
oilier means merits, such combination being obvious to a person skilled

 P document published prior to the international tiling date but in the art.
later than the priority date claimed

document member of the same patent family
Date of the actual completion of the international search Date of mailing of the international search report

27 February 2003

Name and mailing address of the ISA Authorized officer
European Patent Office, PB. 5818 Patenrisani 2
NL

2280 HV Rijswijk
Tel. (-i-31--70) 340-2040. Tx, 31 551 epO fll,
lLIt Fax (+31-70)340-3016

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page 2 of 5

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international Application No

PCT/EP 02/11696

C.(Contlnuatlon) DOCUMENTS CONSIDERED TO BE RELEVANT
Category Citation ot document, with indicalion,where appropriate. ot Ihe relevant passages Relevant to claim No.

P,X URBAN L ET AL: T’Antinociceptive effects 1-4,6,8,
of the bisphosphonate, zoledronate, in a 9,11
novel rat model of bone cancer pain."
SOCIETY FOR NEUROSCIENCE ABSTRACTS,
vol. 27, no. 1, 2001, page 1326
XP001145713

31st Annual Meeting of the Society for
Neuroscience;San Diego, California, USA; November 10-15, 2001
ISSN: 0190-5295
the whole document

A MCDONNELL F J ET AL: "Advances in cancer 1-13
pain management."
CURRENT ONCOLOGY REPORTS. UNITED STATES JUL 2000,
vol. 2, no. 4, July 2000 (2000-07), pages 351-357, XP001097289
ISSN: 1523-3790
abstract

p. 351: ’Nonsteroidal Anti-inflammatory Drugs’; p. 353: ’Biphosphonates’

A GLOTH, F. M.: "Pain Management in Older 1-13
Adults: Prevention and Treatment" JOURNAL OF THE AMERICAN GERIATRICS SOCIETY,
vol. 49, no. 3, February 2001 (2001-02), pages 188-199, XP002232826
page 190, right-hand column, paragraph 3
- page 191, left-hand column, paragraph 3

X WO 01 54688 A (MORRISON BRIGGS W;MERCK & 7,13
CO INC (US); WALDSTREICHER JOANNE (US)) 2 August 2001 (2001-08-02)
A page 2, line 6 - line 15 5,12
page 4, line 15

X SORIANO A F ET AL: "SYNERGISTIC EFFECTS 7,13
OF NEW CHEMOPREVENTIVE AGENTS AND CONVENTIONAL CYTOTOXIC AGENTS AGAINST HUMAN LUNG CANCER CELL LINES"
CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US,
vol. 59, 15 December 1999 (1999-12-15), pages 6178-6184, XP002923259
ISSN: 0008-5472
A abstract 5,12

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Form PCTIISA/210 (corltirrUatlon 01 second shoot) (July 1902)

page 3 of 5 -

INTERNATIONAL SEARCH REPORT International Application Na

I PCT/EP 02/11696

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C.(Contlnuatlofl) DOCUMENTS CONSIDERED TO BE RELEVANT
Category Citation of document, with indicationwhere appropriate, of the relevant passage, Relevant to claim No.

X DATABASE CANCERLIT ’Online! 7-9,13
OURA S ET AL: "Effective alendronate therapy against a bone metastasis
occurring during docetaxel therapy for breast cancer--a case report."
retrieved from STN
Database accession no. 1999430323 XP002232827
A abstract 5,6,12
& GAN TO KAGAKU RYOHO ’JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY!, (1999 SEP) 26
(10) 1469-73. JOURNAL CODE: 7810034, ISSN: 0385-0684.,

1st Dept. of Surgery, Wakayama Medical College.

X JAGDEV S P ET AL: "THE BISPHOSPHONATE, 7-9,13
ZOLEDRONIC ACID, INDUCES APOPTOSIS OF BREAST CANCER CELLS: EVIDENCE FOR SYNERGY WITH PACLITAXEL"
BRITISH JOURNAL OF CANCER, LONDON, GB, vol. 8, no. 84, 2001, pages 1126-1134, XP008001603
ISSN: 0007-0920
A abstract 5,6,12

X TORTORIELLO A (REPRINT) ET AL: "Docetaxel 7-9,13
plus letrozole pamidronate plus radiotherapy +1- goserelin in the treatjnent bone metastases by breast cancer. Preliminary data of phase II study."
ANNALS OF ONCOLOGY, (OCT 2000) VOL. 11,
SUPP. ’2!, PP. E64E64. PUBLISHER: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, P0 BOX 17, 3300 AA DORDRECHT, NETHERLANDS. ISSN: 0923-7534,
XP009006217
MED ONCOL CLIN VILIALBA, NAPLES, ITALY;ASL BA 1, MILAN, ITALY; SENOL UNIV NAPLES 2, NAPLES, ITALY; ASTONTERIA.UNIV FED NAPOLI 2, NAPLES, ITALY; ASL NA 1, NAPLES, ITALY; UNIV CANTAZARO, CLIN CHIR, CATANZARO, ITALY; UNIV CAGLIARI, 1-09124 CAGLIARI, ITALY

A abstract 5,6,12

Form PCTfA,210 cm5natoi-r of secorcf sheefl (July 1552)

page 4 of 5

IN I tHNA I IUPUkL t14rSt.,fl rn
nterr,ntk,riat Application No
PCT/EP 02/11696

C.(Contfnuatton) DOCUMENTS CONSIDERED TO BE RELEVANT
Cate)ory (anon of document. wtth indicaltonwhere appropnaie, of the relevant pasvages Relevant to clavo No

X MAGNETTO, S ET AL.: "Additive antitumor 7-9,13 activities of taxoids in combination with the bisphosphonate ibandronate against invasion and adhesion of human breast carcinoma cells to bone"
INTERNATIONAL JOURNAL OF CANCER,
vol. 83, 1999, pages 263-269, XF001146008 A abstract 5,6,12 page 263

Form PCTIISN21O (continuaFon 01 second sheet) (July 19iv2)

page 5 of 5

4P

International Application No, PCT,tP 02, 1696

[FURTHER INFORMATION CONTINUED FROM PCT/ISAI 210
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:
1. Claims: 1-6, 8 (part), 9 (part), 10-12
a composition comprising a bisphosphonate and a
COXinhibitor in combination (and a taxol) for the treatment
of malignancies

2. Claims: claims 7, 13 (all part)
a composition comprising a taxol and a COXinhibitor in combination for the treatment of malignancies

3. Claims: claims 7-9, 13 (all part)
a composition comprising a taxol and a bisphosphonate in combination for the treatment of malignancies

S

1_?

International Application No. PCTIP 02 I1696

FURTHER INFORMATION CONTINUED FROM PCT/ISAJ 210

Continuation of Box 1.2

Claims Nos.: 10

1) Present claim 10 relates to a compound defined by reference to the parameter ’IC 50 for COX-inhibition’.
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art.

2) The subject-matter of claims 1-6, 10, 11 and 12 - as far as relating to the definitions of the compounds mentioned below - relates

to * bisphosphonates

* COX-2 inhibitors
* taxols.

The definitions of the compounds relate to an extremely large number of possible drugs.
Support within the meaning of Article 6 PCT is to be found, however, for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the claimed scope is so broad that a meaningful search over the whole of the claimed scope is impossible. Furthermore, as ’COX-2 inhibitors’ represents a definition by means of a functional feature, it cannot.be guaranteed that the performed search is complete. It cannot be excluded that compounds fulfilling the requirements of the functional feature have not been identified as doing so in the prior art.

The search has been carried out for those parts relating to the compounds as defined in the following:
- bisphosphonates: in particular with respect to the compounds
identified by name on p. 5/6 and to the examples;
- COX -2 inhibitors: in particular with respect to the examples,
the compounds Identified by name in the descripition and the claims;
- taxols: in particular with respect to the examples, the
compounds identified by name in the descripition and the claims.

The applicant’s attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/11696

I Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3-6, 8-11 and 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged
effects of the composition.

2. T Claims Nos: 10

because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried Out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.

2. As all searchable claims Could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.

3. As only some of the required additional search tees were timely paid by the applicant, this International Search Report
covers only those claims for which tees were paid, specifically claims Nos.:

4. No required additional search tees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest The additional search fees were accompanied by the applicant’s protest.

LIINo protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

INTERNATIONAL SEARCH REPORT I International Application No
Information on patent family members
PCT/EP 02/11696

Patent document Publicaflon 1 Patent family Publication
cited in search report L date member(s) date
WO 0038730 A 06-07-2000 AU 2207000 A 31-07-2000
AU 2209800 A 31-07-2000
AU 2210400 A 31-07-2000
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HU 0104814 A2 29-04-2002
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JP 2002533387 T 08-10-2002
JP 2002533404 T 08-10-2002
JP 2002535249 T 22-10-2002
Jr 2002533405 T 08-10-2002
Jr 2002533406 T 08-10-2002
2002533407 1 08-10-2002
2002533416 T 08-10-2002
2002533422 T 08-10-2002

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Er 1253921 Al 06-11-2002
WO 0154688 Al 02-08-2001

Us 2001047022 Al 29-11-2001 ---

Form PCl/ISA/21 0 (Peflt family annex) (July 192)

0

The demand must be filed directly with the competent International Preliminary Examining Authority or, ([two or more Authoritire are competent, vdth the one chosen ly the applicant. The Jii/l name or two-letter code ofthat Authority may be indicated by the applicant on the line below: PEA/_

PCT rCHAPTERII I
DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of
international preliminary examination according to the Patent Cooperation Treaty and
hereby elects all eligible States (except where otherwise indicated)

jul ILIICIII4LIUAS4I -U L?A-IUIIMr, rUlllUl ity USC (JUly

Identification of IPEA] Date of receipt of DEMAND
Applicant’s or agent’s file reference

Box No I IDENTIFICATION OF THE INTERNATIONAL APPLICATION 4-32199A/USN
International application No, International filing date (day/month/year) (Earliest) Priority date (day/month/year)

18 October 2002 PCT/EP 02/11696 19 October 2001
(110.02) 1101
Title of invention

Pharmaceutical Composition for Use for the Treatment of Malignancies Comprising in Combination a Biphosphonate, a COX-2 Inhibitor and a Taxol

Box No. 11 APPLICANT(S)

Name and address: (Fatni,v name followed by given name; for a legal entity, full official designation. Telephone No,
The address must include postal code and name ofcountry.) +4161 324 11 11
Novartis AG Facsimile No.
Lichtstrasse35 +4161 322 75 32
4056 Basel T’eleprinter No.

CH Applicant’s registration No. with the Office

State (that is, country) of nationality: State that is, country) of residence:
OH OH

Name and address: (’Family name Jbllowed by given name; for a legal entity, full official designation. The address nuLct include postal code and name ofcountry)

Novartis Pharma GmbH
Brunner Strasse 59
1230 Vienna
AT

State (that is, country,) of nationality: State (that is, country) of residence,
AT AT

Name and address: (Family name jadowea’ by given name; fhr a legal entity, full official designation. The address must include postal code and name ofcaunoy)

GREEN, Jonathan
Waldstrasse 12
4144 Arlesheim
CH

State (that is, country) of nationality: State ’that is, country) of residence:
GB CH

Further applicants are indicated on a continuation sheet.

Form PCT/IPEA/401 (first sheet) (March 2001; reprint July 2002) See Notes to the demandform

Sheet No. .

2 International application No.
I PCT/EP 02/11696
Continuation of Box No. II APPLICANT(S)
Ifnone ofthefollowing sub-boxes is used, thissheet should not be included in the demand

Name and address: (Family namefollowed by given name; for a legal entity, full official designanoit The address must include postal code and name ofcounay) LIPTON, Allan
500 University Drive, Penn State College of Medicine
Hershey, PA 17033
Us

State (that is, country) of nationality: State (that is, counisy) ofresidence:
US US

Name and address: (Family namefollowed by given name; for a legal entity, full official designation. The address must include postal code and name ofcountly.)

WITTERS, Lois Mary
25 Fischer Road
York Haven, PA 17370
Us

State (that is, country) of nationality: State (that is, countn) of residence:

US jUS
Name and address: (Family namefollowed bygtven name; fur a legal entity, Ml official designation. The address must iclde postal code and name of country.)

State (that is, country) of national ity: State (that is, countr-?) of residence:

Name and address: (Family name followed by given name; for a legal ennty,full official designation. The address must include postal code and name ofcaunO)

State ’that is, country) of ionaIity 1State (that is, county) ofresidence:

Further applicants are indicated on another continuation sheet.

Form PCT/IPEA/401 (continuation sheet) (March 2001; reprint July 2002) See Notes to the demandform

International application No.

Sheet No,.3, PCT/EP 02/1 1696

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is common representative {] agent 11
and has been appointed earlier and represents the applicant(s) also for international preliminary examination.

is hereby appointed and any earlier appointment of(an) agent(s)/common representative is hereby revoked.
Elis hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address; (Family namefollowed by given name,’ for a legal entity,fuIl official designation. The address must include code and name of country.)

Telephone No.

postal +4161 324 11 11
GROS, Florent Facsimile No.

NovartisAG +4151 322 75 32 Corporate Intellectual Property Teleprinter No. Patent

Trademark Department
4002 Basel
CH Agent’s registration No. with the Office

ElAddress for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*
1. The applicant wishes the international preliminary examination to start on the basis of:
the international application as originally filed

the description El as originally filed
Elas amended under Article 34

the claims El as originally filed
Elas amended under Article 19 (together with any accompanying statement)

[III] as amended under Article 34
the drawings El as originally filed
Elas amended under Article 34

2, El The applicant wishes any amendment to the claims under Article 19 to he considered as reversed.

3. El The applicant wishes the start ofthe international preliminary examination to be postponed until the expiration of 20 months
from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made
under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1 (cl)). (This check-
box may he marked only where the time limit under Article 19 has not yet expired.)
Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy ofamendments to the claims under Article 19 and/or amendments ofthe international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination:.English.. I’ll............ Aj which is the language in which the international application was filed.
which is the language of a translation furnished for the purposes of international search.
which is the language of publication of the international application.
Elwhich is the language of the translation (to he) furnished for the purposes of international preliminary examination.

Box No, V ELECTION OF STATES

The applicant hereby elects all eligible States (that is. all.5tutes which have been designated and which are bound by Chapter 11 of the FCT)
excluding the following States which the applicant wishes not to elect:

Form PCT/IPEAI40I (second sheet) (March 2001; reprint July 2002) See Notes to the demandform

Sheet No.

International application No.
PCT/EP 02/11696

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in For International Preliminary
Box No. IV, for the purposes ofinternational preliminary examination: Examining Authority use only
received not received
1. translation ofinternational application

sheets LII D

2. amendments under Article 34

sheets IiIJ LIII
3. copy (or, where required, translation) of
amendments under Article 19

sheets

4. copy (or, where required, translation) of
statement under Article 19

sheets LI LI]
5. letter
sheets LI]
6. other (specy5’)

sheets LI] [II]

The demand is also accompanied by the item(s) marked below:
I, fee calculation sheet 5. J statement explaining lack ofsignature
2. original separate power of attorney 6. sequence listing in computer readable form

3. original general power of attorney 7. j other (pecifv): copy of general authorization 46171
4. LI copy of general power of attorney;
reference number, if any:
Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE
Ne.rtio each signature, indicate the name ofthe person signing and the capacity in which the person signs (:fsuch capacity is not obviousfrom reading the demand).

In the name of the applicants
The representative

18.03.2003 GS, brent AV 36671

46171

cur internauonai rreiiiniziary rammiiig itutnoruy use oniy I. Date of actual receipt of DEMAND:

2. Adjusted date ofreceipt of demand due
to CORRECTIONS under Rule 60.1(b):

3. The date ofreceipt ofthe demand is AFTER the expiration of 19 months The applicant has been
from the priority date and item 4 or 5, below, does not apply. informed accordingly.

[] The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of 4. Rule 80.5.

Although the date ofreceipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival
is EXCUSED pursuant to Rule 82.

For International Bureau use only
Demand received from IPEA on:

Form PCT/IPEAJ40 I (last sheet) (March 2001; reprint July 2002) See Notes to the

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant’s or agents file reference FOR FURTHER ACTION See Notification of Transmittal of International
4-321 99AAJSN Preliminary Examination Report (Form PCTAPEAJ416)

International application No. International filing date (dayAnont!i4’ear) Priority date (day,tnont4ear)
PCT,EP02/1 1696 18.10.2002 J9.10.2001

International Patent Classification (IPC) or both national classification and I PC
A61 K31 i663

Applicant
NOVARTIS AG et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining
Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

N This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have
been amended and are the basis for this report and/or sheets containing rectifications made before this Authority
(see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

I N Basis of the opinion
II 0 Priority
III N Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV 0 Lack of unity of invention
V N Reasoned statement under Rule 66.2(a)(4) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement
VI U Certain documents cited
VII 0 Certain defects in the international application
VIII 0 Certain observations on the international application

Date of submission of the demand Date of completion of this report

20.03.2003 18.12.2003

Name and mailing address of the international
preliminaryexamining authority:

Authorized Officer

)European Patent Office

D-80298 Munich
Tel. 89 2399

0 Tx: 523656 epmu d Hornich, E

+49
Fax: +49 89 2399

4465
Telephone No. +49 89 2399-8721

Form PCT1PEA/409 (Cover Sheet) (January 1994)

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT International application No. PCTiEP02/11696

I. Basis of the report
1. With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):

Description, Pages
1-44 as originally filed

Claims, Numbers
1-11 filed with telefax on 20.06.2003

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language:, which is:

C1 the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
El the language of publication of the international application (under Rule 48.3(b)).
Cl the language of a translation furnished for the purposes of international preliminary examination (under
Rule 55.2 and/or 55.3).
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
contained in the international application in written form.
El filed together with the international application in computer readable form.
L3 furnished subsequently to this Authority in written form.
O furnished subsequently to this Authority in computer readable form.
The statement that the subsequently furnished written sequence listing does not go beyond the disclosure
in the international application as filed has been furnished.
The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:

O the description, pages:
the claims, Nos.: 12,13
the drawings, sheets:

5. 0 This report has been established as if (some of) the amendments had not been made, since they have
been considered to go beyond the disclosure as filed (Rule 70.2(c)).
(Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.)
6. Additional observations, if necessary:

Form PCTAPEA’409 (July 1999)

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT International application No. PCTIEP02/1 1696

Ill. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
U the entire international application,
claims Nos. 3-10 (3-8, 10 with regard to industrial applicability only)
because:

the said international application, or the said claims Nos. 3-10 (with regard to industrial applicability) relate
to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
O the description, claims or drawings (Indicate particular elements below) or said claims Nos. are so unclear
that no meaningful opinion could be formed (specify):
L1 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion
could be formed.

no international search report has been established for the said claims Nos. 9
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative
Instructions:
O the written form has not been furnished or does not comply with the Standard.
O the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
1. Statement

Novelty (N) Yes: Claims 5, 8, 11
No: Claims 1-4, 6, 7, 10
Inventive step (IS) Yes: Claims
No: Claims 1-8, 10, 11
Industrial applicability (IA) Yes: Claims 1, 2, 11
No: Claims

2. Citations and explanations
see separate sheet

Form PCTAPEA/409 (July 1999)

INTERNATIONAL PRELIMINARY International application No. PCT/EP02/1 1696 EXAMINATION REPORT -SEPARATE SHEET

SECTION III

1. The IPEA will only formulate an assessment of novelty, inventive step and industrial
applicability for the parts of the present claims for which an International Search Report has been drawn up (R. 66.1(e) PCT)(cf. form PCT/ISA/210, Box I).

2. Claims 3-10 relate to subject-matter considered by this Authority to be covered by the
provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3. The subject-matter of claim 9 is unclear as relating to a result to be achieved
respectively the definition of the compound by means of a parameter. The claim thus does not fulfil R. 6.3 PCT defining that ’claims shall define the matter for which protection is sought in terms of the technical features of the invention’ (see also the PCT-Guidelines C-Ill. 4.7a).

SECTION V

4. References:

Dl: W00038730A

D2: WITTERS, L. ET AL.: ’Inhibition of growth of human breast cancer cell lines with the combination of zoledronic acid and a COX-2 Inhibitor’ EUROPEAN JOURNAL OF CANCER, vol. 37, no. Suppl. 6, 22 October 2001 (2001-10-22), page 78.
D3: URBAN L ET AL: ’Antinociceptive effects of the bisphosphonate, zoledronate,
in a novel rat model of bone cancer pain.’ SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 1, 2001, page 1326, 31st Annual Meeting of the Society for Neuroscience;San Diego, California, USA; November 10-15, 2001 ISSN: 0190-5295.
D4: MCDONNELL F J ET AL: ’Advances in cancer pain management.’ CURRENT
ONCOLOGY REPORTS. UNITED STATES JUL 2000, vol. 2, no. 4, July 2000

Form PCT/Separate SheetJ409 (Sheet 1) (EPO-April 1997)

INTERNATIONAL PRELIMINARY International application No. PCT/EP02/1 1696
EXAMINATION REPORT - SEPARATE SHEET

(2000-07), pages 351-357, ISSN: 1523-3790.
D5: GLOTH, F. M.: ’Pain Management in Older Adults: Prevention and Treatment’
JOURNAL OF THE AMERICAN GERIATRICS SOCIETY, vol. 49, no. 3, February 2001 (2001-02), pages 188-199.
D6: WO 01 54688 A
D7: SORIANO A F ET AL: ’SYNERGISTIC EFFECTS OF NEW
CHEMOPREVENTIVE AGENTS AND CONVENTIONAL CYTOTOXIC AGENTS AGAINST HUMAN LUNG CANCER CELL LINES’ CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 59,15 December 1999 (1999-12-15), pages 6178-6184, ISSN: 0008-5472.
D8: DATABASE CANCERLIT [Online] OURA S El AL: ’Effective alendronate
therapy against a bone metastasis occurring during docetaxel therapy for breast cancer--a case report’ retrieved from STN Database accession no. 1999430323

GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF
CANCER AND CHEMOTHERAPY], (1999 SEP) 26 (10) 1469-73. JOURNAL CODE: 7810034. ISSN: 0385-0684., 1st Dept. of Surgery, Wakayama Medical College.
D9: JAGDEV S P El AL: ’THE BISPHOSPHONATE, ZOLEDRONIC ACID,
INDUCES APOPTOSIS OF BREAST CANCER CELLS: EVIDENCE FOR
SYNERGY WITH PACLITAXEL’ BRITISH JOURNAL OF CANCER, LONDON,
GB, vol. 8, no. 84, 2001, pages 1126-1134, ISSN: 0007-0920.
D1 0: TORTORIELLO A (REPRINT) ET AL: ’Docetaxel plus letrozole
pamidronate plus radiotherapy +1- goserelin in the treatment bone
metastases by breast cancer. Preliminary data of phase II study.’ ANNALS

1 OF ONCOLOGY, (OCT 2000) VOL. 11, SUPP. [2], PP. E64-E64.

PUBLISHER: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, P0
BOX 17, 3300 AA DORDRECHT, NETHERLANDS. ISSN: 0923-7534.
MED ONCOL OLIN VILIALBA, NAPLES, ITALY;ASL BA 1, MILAN, ITALY;
SENOL UNIV NAPLES 2, NAPLES, ITALY; ASTONTERIA UNIV FED
NAPOLI 2, NAPLES, ITALY; ASL NA 1, NAPLES, ITALY; UNIV
CANTAZARO, OLIN CHR, CATANZARO, ITALY; UNIV CAGLIARI, I-
09124 CAGLIARI, ITALY.
D1 1: MAGNETTO, S. ET AL.: ’Additive antitumor activities of taxoids in
combination with the bisphosphonate ibandronate against invasion and adhesion of human breast carcinoma cells to bone’ INTERNATIONAL

Form PCT/Separate Sheet/409 (Sheet 2) (EPO-April 1997)

INTERNATIONAL PRELIMINARY International application No. PCT/EP02/1 1696 EXAMINATION REPORT - SEPARATE SHEET

JOURNAL OF CANCER, vol. 83, 1999, pages 263-269.

D2 and D3 were published between the priority date and the filing date of the present application.
On the assumption that the priority of the present application has been validly claimed, D2 and D3 are presently not considered prior art (R. 33.1 and 64.1 PCT).

5. Novelty, (Art. 33(2) PcT1 with regard to item 1.

5.1 Dl discloses combinations of COX-2 inhibitors (e.g. celecoxib, rofecoxib, JTE-522)
with antineoplastic agents, among them clodronate. pamLdronate and eticfronaie (p. 79,1.23; p. 103,1. 24, p.104,1.11).

Dl would thus anticipate the subject-matter of claims 1-4, 6. 7 and 1 Q.

5.2 The subject-matter of claims 5. 8 and 11 would appear to be novel with regard to the
available prior art.

6. Inventive Step (Art. 33(3) PCT with regard to item 1.

6.1 The problem underlying the present application is the provision of a pharmaceutical
composition for the treatment of malignancies.

The solution of the present application resides in the provision of a composition comprising a bisphosphonate and a COX-inhibitor in combination.
Such compositions are already known from Dl (see novelty).

6.2 Claims 5. 8 and 11 which would appear to be novel relate to the particular
bisphosphonate zoledronic acid respectively to the claimed compositions further comprising a taxol.

6.2.1 The particular effect of zoledronic acid in combination with COX-2 inhibitors, in comparison to combinations of related bisphosphonates with COX-2 inhibitors
which are already known (Dl), is not evident and would thus appear to be an

Form PCT/Separate Sheet/409 (Sheet 3) (EPO-April 1997)

INTERNATIONAL PRELIMINARY International application No. PCT/EP02/1 1696 EXAMINATION REPORT - SEPARATE SHEET

obvious modification of the state of the art.

6.2.2 Taxols in combination with COX-2 inhibitors respectively bisphosphonates useful for the treatment of malignancies are already known (see documents D6-
D1 1).

Furthermore, according to the available prior art, all three groups of compounds are known for their effect in treating malignancies, and the compositions defined within claims 5 and 11 would thus represent a mere combination of compounds.

Therefore, the further addition of a taxol to known compositions comprising a COX-2 inhibitor and a bisphosphonate would not be considered inventive.

6.3 An inventive step could thus at the moment not be acknowledged for the subject..
matter of claims 5. 8 and 11.

7. Industrial Applicability (Art. 33(4) PCT)

7.1 The requirements of industrial applicability would be fulfilled for the subject-matter of
claims 1 2 andt11 -

7.2 For the assessment of the present oiaims 3-10 on the question whether they are
industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims
to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound
for the manufacture of a medicament for a new medical treatment.

Form PCT/Separate Sheet/409 (Sheet 4) (EPO-April 1997)

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4-321 99A/USN

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1. A pharmaceutical composition for tre2ttnent of nilignanc lea which comprises in
combination a bisphósphonate and. a COX-2 inhibitorfor simultaneous, sequential or

separate use.

2. The use of a COX-2 inhibitor for the preparation of a medicarnent, for use in
combintjon with a bisphosphonate for treatment of a malignant disease.

3. A method of treating a patient suffering from a malignant disease comprising
administering to the patient an effective amount of a. bisphcsphonate and an effective amount of a COX-2 inhibitor.

4. A pharmaceutical composition according to claim 1, a use aecoding to claim 2, or a
method according to claim 3 for the inhibition of cancer cull growth or induction of cancer cell apoptosis.

5. A method of treating a patient suffering from a malignant disease comprising
administering to the patient an effective amount of a bispbosphonate, an effective
amount of a COX-2 inhibitor and an effect amount of a Taio1 or a derivative thereof:

6. A method according to claim 3 or S in which the bisphosphonate is an N.
bisphosphonate.

7. A method according to claim 6,, in which the bisphosplionate is a compound of formula I

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cp0:1603 18 31 F4.X +41 61,324 691 NOVARTIS FATEIT DEPT - CH

4-32199A/USN

wherein

X is hydrogeu,hydroxyL amino, alkanoyl,or an ami10 group substituted by C1-C11 alkyl,
or alkanoyl; -
R is hydrogen or C1-C4 alkyl and
Rx is a side chain which contains an optionally substituted amino group, or a nitrogen containing heterocycle (including aromatic nitrogen-containing beterocycles),
or a pharmaceutically acceptable salt thereof or any hydrate thereof.

. A method according to claim 7 in wtich the bisphosplionate is 2-(imiclazol-lyl)-1-
hythoxyethane-11--dipbo$phOflC acid (zoledrouic acid) or a pharmacologically
acceptable salt thereof.

9. A method according to claim 3, in which the COX-2 inhibitor is a COX-2 inhibitor
which has an ICo for COX-2 inhibition less than about 2LM and an IC5q for COX-1 inhibition greater than about 5pM

10.. A method according to claim 9, In Which the-COX-2 inhibitor Is selected from the group
consisting ofrofecoxib, etoricoxib, celecoxib, valdecoxib, parecoxib, or a 5-alkyl-.2-. irylaminopheny1acetic acid derivative COX-2 inhibitor, or a pharmaceutically
acceptable salt thereof, or any hydrate thereof.

11. A composition according to claim I comprising an effective amount of a laxol,
Paclitaxel, taxotere, docotaxel, a. texan-c, a taxina or any 0111cr suitable taxol derivative,

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NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year)
08 May 2003 (08.05.03)

Applicant’s or agents file reference
4-32199A/USN

International application No.
PCT/EP02/i 1696

From the INTERNATIONAL BUREAU To:

GROS, Florent
Nova rtis AG
Corporate Intellectual Property
Patent & Trademark Department
CH -4002 Basel
Switzerland

IMPORTANT NOTIFICATION

International filing date (day/rn onth/yea r)
18 October 2002 (18.10.02)

1. The following indications appeared on record concerning:

[1 the applicant the inventor the agent the common representative

State o.ttcn.l,t Ptn::f

NOVARTIS PHARMA GMBH AT AT
Brunner Strasse 59

A-1235 Vienna Telephone No.
Austria
Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person LI the name F x]the address the nationality the residence
Name and Address State of Nationality State of Residence
NOVARTIS PHARMA GMBH AT AT
Brunner Strasse 59

A-1230 Vienna Telephone No.
Au str a
Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

Elthe receiving Office the designated Offices concerned

the International Searching Authority rX1the elected Offices concerned

the International Preliminary Examining Authority other:

Authorized officer
The International Bureau of WIPO
34, chemin des Colombettes Chantal AUMAITRE
1211 Geneva 20. Switzerland

Facsimile No. (41-22) 740-1435 Telephone No. (41-22) 338 8669
Form PCT/lB/306 (March 1994) 005627777

fl

23.06.2003 M VT
4-32199A1USN PCT

Patrick E. Crawey EPO2/11696

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GROSS Florent
NOVARTIS AG

Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

Corporate Intellectual Property

EATY

25. Apr. 203 :

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PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing
(day/month/year) 23/04/2003

Applicant’s or agent’s file reference I REPLY DUE

within 2/00 months/days 4-32199A/USN from the above date of mailing International application No. International filing date (day/month/year) I

19/10/2001

Priority date (day/month/year)

PCT/EP 02/ 11696 18/10/2002
International Patent Classification (IPC) or both national classification and IPC

AG1K31/663
Applicant
NOVARTIS AG et al.

I. This written opinion is the first drawn up by this International Preliminary Examining Authority. I
2. This opinion contains indications relating to the following items:

I [fl Basis of the opinion
II Priority

III FXI Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

IV [] Lack of unity of invention

V [XI Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability;

citations and explanations supporting such statement

VI Certain documents cited

VII Certain defects n the international application
VIII Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.
When’ See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority
to grant an extension, see Rule 66.2(d).
How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3.
For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner’s obligation to consider amendments and/or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

I 4. The final date by which the international preliminary I

examination report must be established according to Rule 69.2 is: 19/02/2004 . I

Name and mailing address of the IPEA/ Authorized officer..

- I)European

Patent Office Examiner
Formalities officer D-80298 Munich
Tel. (+ 49-89) 2399-0, Tx: 523656 epmu d
Fax: (I 49-89) 2399-4465 (incl. extension of time limits)

Tel. (+ 49-89) 2399 2828
Form PCT/IPEA/408 (cover sheet) (march 20(J2)

WRITTEN OPINION International application N0PCT/EP 02/ 11696

I. Basis of the opinion

The basis of this written opinion is the application as originally filed.

Ill. Non-establishment of opinion with regard to novelty, inventive step and industrial
applicability

The question of whether the claimed invention appears to be novel, to involve an
inventive step, or to be industrially applicable has not been and will not be the subject
of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or
industrial applicability

1. To the extent that the international preliminary examination has been carried out (see item

It

Ill above), the following is pointed out:

2. In light of the documents cited in the international search report, it is considered that the
invention as defined in at least some of the claims, which have been the subject of an
international search report, does not appear to meet the criteria mentioned in Article 33(1)
POT, i.e. does not appear to be novel and/or to involve an inventive step (see international
search report, in particular the documents cited X and/or Y and corresponding claim references).

3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8
POT and indicate the basis of the amendments in the documents of the application as
originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken
into consideration for the establishment of the international preliminary examination report.
The attention of the applicant is drawn to the fact that if the application contains
an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an
international preliminary examination report will normally be established directly.
Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

Form PCT/408AE2 (EPO032002) P20725

6 NOVARTIS

International Bureau of WIPO
PCT Examination Section
34, chemin des Colombettes
1211 GenŁve20

Your Ref:

March 8, 2004

. Case: 432199AJUSN

International Application No. PCTJEP 02/11696

Ladies and Gentlemen

NovartisAG

Corporate Intellectual Property
CH4002 Basel
Switzerland
Tel: +41 61 32444 53
Fax: +41 61 322 75 32

Our Ref:
HA

Please be informed of a change of address of the following inventor and applicant (for the United States of America only):

LIPTON, Allan
new address: Division of Oncology, Room C6830, Hershey Medical Center, Hershey PA 17033, USA

Yours very truly

In the name of the applicant
The representative

GRUBB, Philip GA 36671

19

PC 04/03

Patrick E. Crawley Novartis AG .-/ CiZ
Patent Attorney, Group Head Corporate Intellectual Property I
Patent & Trademark Department CH
CH-4002 Basel
Switzerland

IT 0 \A R.T I S Tel: +41 61 324 47 96

Fax: -41 61 32469 12

International Preliminary Examining
Authority,
European Patent Office,
D80298 Munich,
Germany

2011 June 2003

Dear Sirs

By Fax
Confirmation copy by Mail
To: 0049 89 2399 4465
From:+41 61 324 6912
Pages:1 + 3 + 2

Your Ref:

re: International Patent Application No. PCT/EP 02/11696
Our Case 4-32199A1USN

Our Ret:

N1 77/11C

We refer to the first Written Opinion of the International Preliminary Examining
Authority dated 23 April 2003.

In view of the comments in paragraph V 2 of the Written Opinion, Applicants wish to
amend the claims of this application and enclose herewith (one copy by fax; three copies with confirmation) amended claims 1 to 11 on replacement pages 45 and 46. In addition we enclose
(one copy) of original filed pages 45 to 47, with the amendments which have been made
indicated by manuscript changes. The amended claims now relate to use of:
i) a bisphosphonate in combination with a COX-2 inhibitor, or
ii) a bisphosphonate in combination with a COX-2 inhibitor and a Taxol
for treatment of malignant diseases. None of the documents cited in the international search

40 report specifically disclose such combinations. The amended claims are novel over the

disclosures of the documents cited in the international search report,
In the name of Novartis AG

Patrick E. Crawley
Professional Representative GA No, 36671

Encs: amended claims (x3) + original pages 4547 with manuscript changes

4-32199A/USN

MUM

CLAIMS

A pharmaceutical composition for treatment of malignancies which comprises in combination a bisphosphonate and a COX-2 inhibitor for simultaneous, sequential or separate use.

2. The use of a COX-2 inhibitor for the preparation of a medicament, for use in
combination with a bisphosphonate for treatment of a malignant disease.

3. A method of treating a patient suffering froth a malignant disease comprising
administering to the patient an effective amount of a bisphosphonate and an effective

amount of a COX-2 inhibitor.

4. A pharmaceutical composition according to claim 1, a use accoding to claim 2. or a
method according to claim 3 for the inhibition of cancer cell growth or induction of cancer cell apoptosis.

5. - A method of treating a patient suffering from a malignant disease comprising
administering to the patient an effective amount of a bisphosphonate, an effective
amount of a COX-2 inhibitor and an effect amount of a Taxol or a derivative thereof

6. A method according to claim 3, or 5 in which the bisphosphonate is an N-
bispliosphonate.

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combination wia ffectarnount of a bisphosphonate or an effective amount of a

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method according to claim 6 9K, in which the hisphosphonate is a compound of
formula I
0

P(OR)2

Rx

(OR)2
0
wherein

X is hydrogen, hydroxyl, amino, alkanoyl,or an amino group substituted by C1 -C4 alkyl, or alkanoyl;

W R is hydrogen or C.C4 alkyl and

Rx is a side chain which contains an optionally substituted amino group, or a nitrogen containing heterocycle (including aromatic nitrogen-containing heterocycles),
or a pharmaceutically acceptable salt thereof or any hydrate thereof.

A method according to claim/,in which the bisphosphonate is 2-(imidazol-lyl)l hydroxyethane 1,1 -diphosphonic acid (zoledronic acid) or a pharmacologically
acceptable salt thereof.

7 "Ie A method according to claim 3, in which the COX-2 inhibitor is a COX-2 inhibitor
which has an IC0 for COX-2 inhibition less than about 2RM and an IC50 for COX-1
inhibition greater than about 5}IM.

/ A method according to claim)2 in which the COX-_2 inhibitor is selected from the
group consisting of rofecoxib, etoricoxib, celecoxib, valdecoxib, parecoxib, or a 5-alkyl-- 2-arylaminophenylacetic acid derivative COX-2 inhibitor, or a pharmaceutically
acceptable salt thereof, or any hydrate thereof.

4-32199A/USN

-47- 4

A composition according to claim I comprising an effective amount of a t.axol,
Paclitaxel, taxotei-e, docetaxel, a taxane, a taxine or any other suitable taxol derivative.
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CLAIMS

1 A pharmaceutical composition for treatment of malignancies which comprises in
combination a bisphosphonate and a COX-2 inhibitor for simultaneous, sequential of-
separate use. rseparate

2. The use of a COX-2 inhibitor for the preparation of a medicament, for use in
combination with a bisphosphonate for treatment of a malignant disease.

3. A method of treating a patient suffering from a malignant disease comprising
. administering to the patient an effective amount of a bisphosphonate and ail effective
amount of a COX-2 inhibitor.

4. A pharmaceutical composition according to claim 1, a use accoding to claim 2, or a
method according to claim 3 for the inhibition of cancer cell growth or induction of
cancer cell apoptosis.

5. A method of treating a patient suffering from a malignant disease comprising
administering to the patient an effective amount of a bisphosphonate, an effective
amount of a COX-2 inhibitor and an effect amount of a Taxol or a derivative thereof.

6. A method according to claim 3, or 5 in which the bisphosphonate is an N-
hisphosphonate. -

7. A method according to claim 6, in which the bisphosphonate is a compound of formula I

4-32199A/USN

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P(OR)2

Rx X

(OR)2
0
wherein

X is hydrogen, hydroxyl, amino, alkanoyl,or an amino group substituted by C1 -C4 alkyl,
or alkanoyl;
R is hydrogen or Cl-C4’ alkyl and
. Rx is a side chain which contains an optionally substituted amino group, or a nitrogen
containing heterocycle (including aromatic nitrogen-containing heterocycles),
or a pharmaceutically acceptable salt thereof or any hydrate thereof.

S. A method according to claim 7, in which the hisphosphonate is 2-(irnidazol-lyl)-1-
hydroxyethane- 1,1 -diphosphonic acid (zolecironic acid) or a pharmacologically
acceptable salt thereof.

9. A method according to claim 3, in which the COX-2 inhibitor is a COX-2 inhibitor
which has an IC0 for COX-2 inhibition less than about 2xM and an IC() for COX-1 inhibition greater than about 59M,

10. A method according to claim 9, in which the COX-2 inhibitor is selected from the group
consisting of rofecoxib, etoricoxib, celecoxib, valdecoxib, parecoxib, or a 5-alkyl-2-arylaminophenyl acetic acid derivative COX-2 inhibitor, or a pharmaceutically
acceptable salt thereof, or any hydrate thereof.

11. A composition according to claim I comprising an effective amount of a taxol,
Paclitaxel, taxotere, docetaxel, a taxane, a taxine or any other suitable taxol derivative.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date (10) International Publication Number
1 May 2003 (01.05.2003) PCT WO 03/035081 Al

(51) International Patent Classification7: A61 31/663,
31/635, 31/444, 31/42, 311365, 31/337, 31/196, 45/06,
A61P 29(00, 35/0011 (A61K 31/663, 31:635) (A61K
31/663, 31:635, 31:337) (A61K 31/663, 31:337) (A61K
31/635,31:337)

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60/345,921 19 October 2001 (19.10.2001) US

=_(71) Applicant (fo2411 designated States except AT US): NO-VARTIS AG [CH/CM; Lichtstrasse 35, CH-4056 Basel
(CH).

(71) Applicant (forATony): NOVARTIS PHARMA GMBH -_ [AT/AT]; Brunner Strasse 59, A-1235 Vienna (AT).

(71) Applicants and
(72) Inventors: LIPTON, Allan 4/us]; Penn State College
of Medicine, 500 University Drive, Hershey, PA 17033
(US). WITI’ERS, Lois, Mary [US/US]; 25 Fisher Road,
York Haven, PA 17370 (US).

(72) Inventor; and
(75) Inventor/Applicant (for US only): GREEN, Jonathan/[GB/Cl]; Waldstrnsse 12, CH-4144 Axiesheim (CH).

(74) Agent: GROS, Florent; Novartis AG, Corporate Intellec-tual Property, Patent & Trademark Department, C1-I-4002 Basel (CH).

(81) Designated States (national): AB, AG, AL AM, AT, AU, AZ, BA, BB, BO, BR, BY, BZ, CA, CH, CN, CO. CR, CU, CZ, DE, OK, DM, DZ, BC, EE, ES, Fl, GB, GD, GE, GB, HR, HU, ID, IL, IN, IS, JP, KE, KG, KPP, KR, KZ, LC, LK
LT, LU, LV, MA, MD, MK MN, MX, NO, NZ, OM, PH, FL, PT, RO, RU, SE, SG, SI, 5K, Ti, TM, TN, ’FR, TI’, UA, US, UZ, VC, VN, YU, ZA, ZW

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Published:

with international search report
- before the expiration of the time limitfor amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes andAbhrevlations"appearing at the begin-
ning ofeach regular Issue ofthe PCT Gazette.

If (54) Title: PHARMACEUTICAL COMPOSITION FOR USE FOR THE TREATMENT OF MALIGNANCIES COMPRISING IN ’) COMBINATION A BISPHOSPHONATES, A COX-2 INHIBITOR AND A TAXOL

(57) Abstract: A pharmaceutical composition for treatment of malignancies, in particular a malignant disease which is associated with the development ofbone metastases orexcessive bone resorption, comprises in combination a bisphosphonates, COX-2 inhibitor and/or a taxol or derivative thereof for simultaneous, sequential or separate use. Also provided is a method of treating a patient suffering from a malignant disease comprising administering to the patient an effective amount of a bisphosphonates, an effective amount of a COX-2 inhibitor and/or and effective amount of a taxol or derivative thereof.

REQUISITOS NECESARIOS PARA PRESENTACIONYAGILIZACION DEL
TRAMVTE

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tTäTos de identificaciôn de la la ((1 (del soticltante o persona quØ so presenta solicitud. - Descdpción do la invenciôn.
- Dibujos do serestos pertmnentes. () () - Comprobante de Paçjo de las tasas establecidas.

COMPLETA () INCOMPLETA
DlSEtlO INDUSTRIAL (
- tndicaciôn de que Se solicita el registro de Diseæo Industrial

- Datos de identlflcaciôn del solicltante o de la persona que presenta () () - la solicitud.
- Representaciôn grØfica o fotogràfic8 del DiseæoIndustrial o muestra dot

Material que Incorpora el dlseæo. () Comprobante de pago de las tasas establecidas () ()
COMPLETA () INCOMPLETA () ()

ESQUEMA DE TRAZADO
lndicaciôn de que solicita 91 registro de un Esquema de trazado.
- Datos de ldentlflcaclOn del solcltante o de la persona que presenta

La solicitud, () () Representaciôn gräfica del esquema de trazado () () Comprobante de pago de las tasas establecidas. () ()
COMPLETA

Firma ResponsablE

Fecha:

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Industria y Comercio
S U P E I? I NTEN DEN C 1 A

2020
Bogota, D.C.,

Doctor: Oficto NO L JIMENA ESCOBAR

Apoderado
NOVARTIS AG.

ASUNTO:
RadicaciOn NO 04-34537
Solicitud internacional PCT/EP02/1 1696
Fecha inicio fase nacional 19/05/2004
TrÆmite 011
Evento 379
ActuaciOn 430
Folios 001

Como resultado del examen de forma, realizado con fundamento el el articulo 38 do la DecisiOn 486 de la ComisiOn do la Comunidad Andina, articulo 27 del Tratado de CooperaciOn en Matena do Patentes (POT), regla 51 bis del Reglamento y Circular Unica de la Superintendencia de Industria y Comercio, so to comunica que:

La solicitud no contiene la copia del documento en que consta la cesiOn del derecho a la patente del inventor at solicitante o a su causante. (Art. 26-k) DecisiOn 486).

En cumplimiento do to dispuesto por el artIculo 39 de la DecisiOn 486, se le requiere para que dentro del tØrmino do dos meses siguientes a la fecha do notificaciOn del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar

cumplimiento at presente requerimiento, la solicitud se considerarÆ abandonada y perderÆsu prelaciOn.
NotifIquese el presente oficio conforme a to dispuesto en el numeral 5.2, literal e), del capItulo quinto del tItulo primero de la Circular Unica NO 10 de 2001.

ALIX CARMENA CESPEDES DE VERGEL
Jefe do la DivOn de Nuevas Creaciones.

El anterior requerimiento tue notificado por fijaciOn en lista do fecha,______________________

202060

Carrera 13 No. 27-00 Pisos 5, 7y 10 Conmutador: 382 0840
Fax: 382 2695

E-mail: info@sic.gov.co
www.sic.gov.co
Bogota, D.C., Colombia