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54. TÍTULO "TRATAMIENTO DE OSTEOPOROSIS RELACIONADO CON TERAPIA CON INHIBIDOR DE AROMATASA"

51. CLASIFICACIÓN INTERNACIONAL A61K 31/566

71. SOLICITANTE LUYETH

DOMICILIO NUEVA JERSEY, ESTADOS UNIDOS

74. APODERADO ALVARO CORREA ORDONEZ
T.P. 20.281

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Industria y Comercio
 SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1

SOLICITUD DE :

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Patente de Invención

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Patente de Modelo de Utilidad

☒

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE
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IDENTIFICACION

C.C.

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Otro

☐

Cual

Número

3

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Número 79.143.366 de

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TP 20.281

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7

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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

10

ANEXOS

000002

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arto final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Extracto publicación, propietario y temático; reporte de búsqueda internacional y opinión escrita

11

FIGURA CARACTERISTICA

~~SECRET~~

12

Solicita la concesión de la patente.

NOMBRE: ALVARO CORREA ORDÓÑEZ

FIRMA:

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CONCEPTO

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NOTIFICATION CONCERNING
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WYETH et al

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For an explanation as to the reason for this republication of the international application, reference is made to INID codes (13), (48) or (58) (or the case may be) on the front page of the attached document.

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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OF AROMATASE INHIBITOR THERAPY-RELATED OSTEOPOROSIS

(57) Abstract: This invention relates to the use bisphosphonate (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-yl) in the treatment or inhibition of osteoporosis and osteopenia related to aromatase inhibitor therapy.

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TREATMENT OF AROMATASE INHIBITOR THERAPY-RELATED OSTEOPOROSIS

BACKGROUND OF THE INVENTION

5 This invention relates to the use of bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol) in the treatment or inhibition of osteoporosis and osteopenia related to aromatase inhibitor therapy.

10 Aromatase inhibitors, such as anastrozole and letrozole, are frequently used for the adjuvant treatment of breast cancer and for the long term prevention of breast cancer following tamoxifen treatment. By their mechanism of action these drugs induce or amplify the estrogen deficiency that develops in post-menopausal women. The estrogen deficiency induced by aromatase inhibitors is necessary to combat estrogen-dependent breast cancer, but induces side effects in other tissues, notably
15 the bone. Aromatase inhibitors increase bone resorption, and ultimately induce osteopenia and osteoporosis. This has been demonstrated in clinical studies with an increase in biochemical markers of bone resorption, decrease in bone mineral density as measured by dual x-ray absorptiometry (DXA), and an increase incidence of fractures associated with aromatase inhibitors. Because aromatase inhibitors are
20 prescribed on a long-term basis over many years, treatment to prevent osteopenia and osteoporosis is necessary.

25 Bazedoxifene is a selective estrogen receptor modulator (SERM) that shows tissue-selective estrogen receptor agonist activity on the skeleton and lipid metabolism, while not stimulating uterine and breast tissues. In preclinical studies, bazedoxifene demonstrates improved compressive bone strength and a histomorphometric profile superior to that of raloxifene. This is supported by phase II clinical results, which reveal that bazedoxifene reduces biochemical markers of bone
30 resorption.

 These data show that bazedoxifene would potentially demonstrate: a) bone protection at a lower dose than currently marketed SERMs, b) no uterine agonist effect, c) a low potential to induce vasomotor flushes and d) improvement in the

serum lipid profile. In addition, data also demonstrate that bazedoxifene inhibits estradiol-stimulated proliferation of breast cancer cells, which suggests that bazedoxifene may also act like other SERMs that are able to reduce the risk of developing breast cancer.

5

DESCRIPTION OF THE INVENTION

This invention provides the use of bazedoxifene in a mammal receiving aromatase inhibitor therapy in the treatment or inhibition of osteoporosis and osteopenia, particularly related to the aromatase inhibitor therapy. This invention
10 also provides a combination of bazedoxifene and an aromatase inhibitor useful in the treatment of breast cancer, the inhibition of breast cancer in high risk women, and in inhibiting a recurrence of breast cancer, following an initial remission or cure. This invention also provides a product comprising a bazedoxifene and an aromatase inhibitor as a combined preparation useful in the treatment or inhibition of the
15 previously described conditions. This invention also provides a composition for use in treating or inhibiting the previously described conditions, comprising a bazedoxifene and an aromatase inhibitor wherein the composition is provided in an effective amount to a mammal in need thereof. This invention further provides the administration of bazedoxifene following completion of aromatase inhibitor treatment
20 to ameliorate symptoms or side effects of the aromatase inhibitor treatment.

In one aspect, the present invention provides methods for treating or inhibiting osteoporosis or osteopenia in a mammal receiving aromatase therapy, which comprises providing the mammal an effective amount of bazedoxifene. In
25 some such embodiments, the bazedoxifene is bazedoxifene acetate. In some such embodiments, the bazedoxifene is provided in combination with an aromatase inhibitor. In some such embodiments, the bazedoxifene or the aromatase inhibitor or both are provided in subtherapeutically effective amounts. In some embodiments, the aromatase inhibitor is selected from the group consisting of exemestane,
30 formestane, atamestane, fadrozole, letrozole, vorozole, and anastrozole. In some embodiments, the aromatase inhibitor is selected from the group consisting of letrozole and anastrozole.

In another aspect, the present invention provides methods for treating or inhibiting breast cancer in a mammal receiving aromatase therapy, which comprises providing the mammal an effective amount of bazedoxifene. In some such embodiments, the bazedoxifene is bazedoxifene acetate. In some such
5 embodiments, the bazedoxifene is provided in combination with an aromatase inhibitor. In some such embodiments, the bazedoxifene or the aromatase inhibitor or both are provided in subtherapeutically effective amounts. In some embodiments, the aromatase inhibitor is selected from the group consisting of exemestane, formestane, atamestane, fadrozole, letrozole, vorozole, and anastrozole. In some
10 embodiments, the aromatase inhibitor is selected from the group consisting of letrozole and anastrozole.

In a further aspect, this invention provides methods for treating or inhibiting recurrence of breast cancer in a mammal in need thereof, which comprises providing
15 the mammal an effective amount of bazedoxifene. In some such embodiments, the bazedoxifene is bazedoxifene acetate. In some such embodiments, the bazedoxifene is provided in combination with an aromatase inhibitor. In some such embodiment, the bazedoxifene or the aromatase inhibitor or both are provided in subtherapeutically effective amounts. In some embodiments, the aromatase
20 inhibitor is selected from the group consisting of exemestane, formestane, atamestane, fadrozole, letrozole, vorozole, and anastrozole. In some embodiments, the aromatase inhibitor is selected from the group consisting of letrozole and anastrozole.

25 Another aspect of the invention provides methods for treating or inhibiting breast cancer in a high risk woman, which comprises providing the woman an effective amount of bazedoxifene. In some such embodiments, the bazedoxifene is bazedoxifene acetate. In some such embodiments, the bazedoxifene is provided in combination with an aromatase inhibitor. In some such embodiments, the
30 bazedoxifene or the aromatase inhibitor or both are provided in subtherapeutically effective amounts. In some embodiments, the aromatase inhibitor is selected from the group consisting of exemestane, formestane, atamestane, fadrozole, letrozole,

vorozole, and anastrozole. In some embodiments, the aromatase inhibitor is selected from the group consisting of letrozole and anastrozole.

5 A further aspect of this invention is to provide methods for administering
bazedoxifene to a mammal who has completed aromatase inhibitor treatment to
ameliorate symptoms or side effects of the aromatase inhibitor treatment. In some
such embodiments, the symptom or side effects are osteopenia or osteoporosis. In
some such embodiments, the bazedoxifene is bazedoxifene acetate. In some such
embodiments, the bazedoxifene is provided in subtherapeutically effective amounts.

10

As used in accordance with this invention, the term "bazedoxifene" means
bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-
1H-indol-6-yl), or a pharmaceutically acceptable salt or prodrug thereof.

15

As used in accordance with this invention, the terms "treatment" or "treating"
mean curing, ameliorating or reversing the progress of a disease or disorder, or
ameliorating or reversing one or more symptoms or side effects of such disease or
disorder.

20

As used in accordance with this invention, the term "providing," with respect
to providing the bazedoxifene-aromatase inhibitor combination, means either directly
administering the combination, or administering a prodrug, derivative, or analog of
one or both of the components of the combination which will form an effective
amount of the combination within the body, and with respect to bazedoxifene, means
25 either directly administering bazedoxifene, or administering a prodrug, derivative, or
analog of bazedoxifene which will form an effective amount in the body.

30

As used in accordance with this invention, the term "high risk women" or "a
high risk woman" means a woman at least 35 years of age with a 5-year predicted
risk of breast cancer >1.67%, as calculated by the Gail Model [The Lancet, 355:18
(2000)].

As used in accordance with this invention, the term "subtherapeutically" means below the dosage levels used normally to treat a disease, i.e., a dosage less than the amount required for a therapeutic effect. When used for the combination therapy of bazedoxifene and an aromatase inhibitor, it may refer to a synergistic effect between the compounds.

Aromatase is an enzyme which converts androgens to estrone. Estrone can subsequently be converted to estradiol, which has been linked to increased growth or proliferation of estrogen receptor positive carcinoma. As used in accordance with this invention, the term "aromatase inhibitor" means compounds or substances which inhibit the activity of the enzyme aromatase. Thus, the goal of using aromatase inhibitors in chemotherapy is typically to reduce the levels of circulating estradiol, to ultimately inhibit the growth of neoplasms that are estrogen receptor positive or estrogen dependent. There are two types of aromatase inhibitors: steroidal (type I) and non-steroidal (type II) inhibitors. Examples of steroidal aromatase inhibitors include exemestane, formestane, atamestane, and the like. Examples of non-steroidal aromatase inhibitors include fadrozole, letrozole, vorozole, anastrozole, and the like.

The preparation of bazedoxifene and its pharmaceutically acceptable salts is described in US Patent 5,998,402, which is hereby incorporated by reference in its entirety. When administered for the treatment or inhibition of a particular disease state or disorder, it is understood that the effective dosage may vary depending upon, e.g., whether bazedoxifene is utilized with or without an aromatase inhibitor, the particular aromatase inhibitor utilized, if one is used, the mode of administration, the condition being treated, and severity thereof, as well as the various physical factors related to the individual being treated. Effective administration of the bazedoxifene of this invention may be in any of a variety of dosage regimes such as single dosage, multiple dosage, combination dosage and delay or time release dosage forms. Bazedoxifene acetate has been evaluated in clinical trials using dosages of 10, 20, and 40 mg/day. Based on the results of these trials, it is anticipated that doses between about 5 and about 80 mg/day of bazedoxifene will provide an effective amount within the methods of the invention. The projected daily

dosages are expected to vary with route of administration. The selection of the appropriate administration and dosage forms for an individual patient will be apparent to those skilled in the art. Such determinations are routine to one of ordinary skill in the art (see for example, *Harrison's Principles of Internal Medicine* 5 (1998), edited by Anthony Fauci et al., 14th edition, published by McGraw Hill).

10 In some embodiments, a combination of bazedoxifene and an aromatase inhibitor is administered in accordance with the invention wherein the aromatase inhibitor is letrozole, and wherein both are provided orally. In some such
15 embodiments, the initial oral dosage of bazedoxifene can be from about 5 to about 80 mg/day (on days that it is provided) and the initial oral dose of letrozole can be from about 1 to about 10 mg daily (on days that it is provided). In some such
20 embodiments, the initial oral dosage of bazedoxifene can be from about 10 to about 60 mg/day (on days that it is provided) and the initial oral dose of letrozole can be from about 1 to about 10 mg daily (on days that it is provided). In some such
25 embodiments, the initial oral dosage of bazedoxifene can be from about 10 to about 40 mg/day (on days that it is provided) and the initial oral dose of letrozole can be from about 1 to about 10 mg daily (on days that it is provided). Further, in some
30 such embodiments, the initial oral dosage of bazedoxifene can be from about 10 to about 30 mg/day (on days that it is provided) and the initial oral dose of letrozole can be from about 1 to about 10 mg daily (on days that it is provided). In some such
embodiments, the initial oral dosage of bazedoxifene can be from about 20 to about 40 mg/day (on days that it is provided) and the initial oral dose of letrozole can be from about 1 to about 10 mg daily (on days that it is provided).

25 In some embodiments, a combination of bazedoxifene and an aromatase inhibitor is administered in accordance with the invention wherein the aromatase inhibitor is anastrozole, and wherein both are provided orally. In some such
30 embodiments, the initial oral dosage of bazedoxifene can be from about 5 to about 80 mg/day (on days that it is provided) and the initial oral dose of anastrozole can be from about 1 to about 10 mg daily (on days that it is provided). In some such
embodiments, the initial oral dosage of bazedoxifene can be from about 10 to about 60 mg/day (on days that it is provided) and the initial oral dose of anastrozole can be

from about 1 to about 10 mg daily (on days that it is provided). In some such
embodiments, the initial oral dosage of bazedoxifene can be from about 10 to about
40 mg/day (on days that it is provided) and the initial oral dose of anastrozole can be
from about 1 to about 10 mg daily (on days that it is provided). In some such
5 embodiments, the initial oral dosage of bazedoxifene can be from about 10 to about
30 mg/day (on days that it is provided) and the initial oral dose of anastrozole can be
from about 1 to about 10 mg daily (on days that it is provided). In some such
embodiments, the initial oral dosage of bazedoxifene can be from about 20 to about
40 mg/day (on days that it is provided) and the initial oral dose of anastrozole can be
10 from about 1 to about 10 mg daily (on days that it is provided).

The aromatase inhibitors specifically named in this disclosure are
commercially available or can be made from known procedures in the literature. This
invention is not limited to the use of the specific aromatase inhibitors named herein;
15 the preparation of other aromatase inhibitors will be apparent to one skilled in the art
based on the literature.

As used in this invention, the combination regimen can be given
simultaneously or can be given in a staggered regimen, with bazedoxifene being
20 given at a different time than the aromatase inhibitor. This time differential may
range from several minutes, hours, days, weeks, or longer between administration of
the two agents. Therefore, the term "combination" does not necessarily mean
administered at the same time or as a unitary dose, but that each of the components
are administered during a desired treatment period. The agents may be
25 administered by the same or different routes. For example, one component may be
administered orally, while the other parenterally and these combinations can be
administered daily, weekly, or even once monthly.

Oral formulations containing the active compounds of this invention may
30 comprise any conventionally used oral forms, including tablets, capsules, buccal
forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may
contain mixtures of the active compound(s) with inert fillers and/or diluents such as
pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars,

artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface-modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Preferred surface-modifying agents include nonionic and anionic surface-modifying agents. Representative examples of surface-modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

The compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is nontoxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting

point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

For bazedoxifene, solid oral formulations, such as in the form of a film coated tablet or capsule, useful for this invention include the active pharmacological agents disclosed herein in combination with carrier or excipient systems having the components:

a) a filler and disintegrant component comprising from about 5% to about 82% by weight (wght) of the total formulation, preferably between about 30% and about 80% of the formulation, of which from about 4% to about 40% by weight of the total formulation comprises one or more pharmaceutically acceptable disintegrants;

b) optionally, a wetting agent comprising from about 0.2 to about 5% of the composition (wght), such as selected from the group of sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene castor oil derivatives, docosate sodium, quaternary ammonium compounds, sugar esters of fatty acids and glycerides of fatty acids;

c) a lubricant comprising from about 0.2% to about 10% of the composition (wght), such as selected from the group of magnesium stearate or other metallic stearates (e.g. calcium stearate or zinc stearate), fatty acid esters (e.g. sodium stearyl fumarate), fatty acids (e.g. stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, laurine, polyethylene glycols, metallic lauryl sulfates and sodium chloride; and

d) optionally, a glidant comprising from about 0.1% to about 10% (wght) of the composition, the glidant selected from those known in the art, including from the group of silicon dioxide, talc, metallic stearates, calcium silicate or metallic lauryl sulfates.

While the formulations described herein may be used in an uncoated or non-encapsulated solid form, in some embodiments the final compositions are coated or encapsulated. The pharmacological compositions may be optionally coated with a film coating, e.g., comprising from about 0.3% to about 8% by weight of the overall composition. Film coatings useful with the present formulations are known in the art and generally consist of a polymer (usually a cellulosic type of polymer), a colorant and a plasticizer. Additional ingredients such as wetting agents, sugars, flavors, oils and lubricants may be included in film coating formulations to impart certain characteristics to the film coat. The compositions and formulations herein may also be combined and processed as a solid, then placed in a capsule form, such as a gelatin capsule.

The filler component listed above may utilize the filler or binder components known in the art for solid oral formulations. Pharmaceutically acceptable fillers or binding agents can be selected from those known in the art such as, but not limited to, lactose, microcrystalline cellulose, sucrose, mannitol, calcium phosphate, calcium carbonate, powdered cellulose, maltodextrin, sorbitol, starch, or xylitol.

In conjunction with or in place of the materials listed above for the filler component, the present formulations utilize disintegrant agents. These disintegrants may be selected from those known in the art, including pregelatinized starch and sodium starch glycolate. Other useful disintegrants include croscarmellose sodium, croscopolone, starch, alginic acid, sodium alginate, clays (e.g. veegum or xanthan gum), cellulose hcc, ion exchange resins, or effervescent systems, such as those utilizing food acids (such as citric acid, tartaric acid, malic acid, fumaric acid, lactic acid, adipic acid, ascorbic acid, aspartic acid, erythorbic acid, glutamic acid, and succinic acid) and an alkaline carbonate component (such as sodium bicarbonate, calcium carbonate, magnesium carbonate, potassium carbonate, ammonium carbonate, etc.). The disintegrant(s) useful herein will comprise from about 4% to about 40% of the composition by weight, preferably from about 15% to about 35%, more preferably from about 20% to about 35%. Some components may have multiple functions in the formulations of this invention, acting e.g. as both a filler and a disintegrant. Such a component may be referred to as a filler disintegrant and its

function in a specific formulation may be singular even though its properties may allow multiple functionality.

The pharmaceutical formulations and carrier or excipient systems herein may also contain an antioxidant or a mixture of antioxidants, e.g., ascorbic acid. Other antioxidants which may be used include sodium ascorbate and ascorbyl palmitate, which may be used in conjunction with an amount of ascorbic acid. In some embodiments, the amount of antioxidant(s) is from about 0.5% to about 15% by weight. In some embodiments, the amount of antioxidants is from about 0.5% to about 5% by weight.

Among the formulations of this invention are pharmaceutical formulations containing a pharmaceutically effective amount of an active pharmacological agent and a carrier or excipient system comprising:

a) a filler and disintegrant component comprising between about 50% and about 87% of the formulation, with from about 4% to about 40% of the formulation comprising one or more disintegrant agents;

b) a wetting agent comprising between about 0.5% and about 2.7% of the formulation;

c) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and

d) a glidant comprising between about 0.1% and about 5.5% of the formulation.

The percentages listed in the formulations above indicate percentages by weight of the total weight of the components listed from a) to d). The formulations above may also contain an optional antioxidant component, e.g., ascorbic acid, at a concentration of from about 0.5% to about 5.5% by weight of the formulation. The formulations may be contained within a pharmaceutically acceptable capsule, such

as a gel capsule, or coated with a film coating comprising from about 0.3% to about 8% by weight of the formulation.

5 This invention also comprises a pharmaceutical carrier or excipient systems useful in pharmaceutical compositions utilizing as an active ingredient one or more of the compounds described herein, or a pharmaceutically acceptable salt thereof, as described herein. These pharmaceutical carrier or excipient systems comprise, by weight:

10 a) a filler and disintegrant component comprising between about 54% and about 80% of the formulation, with the disintegrant agent(s) therein comprising from about 4% to about 40% by weight of the overall formulation;

15 b) a wetting agent comprising between about 0.55% and about 2.5% of the formulation;

c) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and

20 d) a glidant comprising between about 0.1% and about 5.0% of the formulation.

25 In some embodiments the carrier or excipient systems above also optionally contain an antioxidant component, e.g., ascorbic acid, at a concentration of from about 0.1% to about 5.0% by weight.

Among the carrier or excipient systems of this invention are those comprising:

30 a) a filler and disintegrant component, as described above, comprising between about 50% and about 87% of the formulation, the disintegrant(s) therein comprising from about 25% to about 35% of the formulation, by weight;

- b) a wetting agent comprising between about 0.55% and about 2.7% of the formulation;
- c) a lubricant comprising between about 0.2% and about 5.5% of the formulation;
- d) a glidant comprising between about 0.1% and about 5.5% of the formulation; and
- e) an antioxidant component, e.g., ascorbic acid, at a concentration of from about 0.1% to about 5.5% by weight.

EXAMPLES

15

EXAMPLE 1

BAZEDOXIFENE ACETATE – RAPID DISSOLUTION FORMULATIONS

Ingredient	without Ascorbic Acid	with Ascorbic Acid
Bazedoxifene acetate, micronized*	10.00	10.00
Lactose NF fast flow	33.10	31.80
Microcrystalline Cellulose, NF (Avicel PH101)	25.00	25.00
Starch 1500	20.00	20.00
Sodium Lauryl Sulfate NF	1.50	1.50
Sodium Starch Glycolate	10.00	10.00
Ascorbic Acid USP	–	1.5
Sylold 244 FP	0.15	0.15
Magnesium Stearate	0.25	0.25

*Amount in formula is adjusted for actual potency of bazedoxifene as free base. Corresponding adjustment made with lactose.

The formulations given above in Table 1 were prepared by incorporating a portion of the excipients in the granulation and a portion is also added in the final blending steps as dry powders. A dissolution profile generated for the formulations demonstrated almost 90% release of the drug in 30 minutes. Thus, the unique combination of disintegrants and soluble diluents plus the incorporation of both granulated and powdered solids into the composition ensures the fastest release of drug.

Wet granulation of the formulations as described in Table 1 may be carried out by mixing the drug and ascorbic acid with a portion of the lactose, microcrystalline cellulose, pregelatinized starch and sodium starch glycolate. The sodium lauryl sulfate is dissolved in the water and used to granulate the mixture of powders in a high shear mixer. The granulation is dried in a fluid bed dryer to a moisture of 2-3%. The particle size of the dried granulation is controlled by passing through a mill equipped with knife-edged blades and using a 20- or 30-mesh screen. The silicon dioxide and remaining lactose, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate are mixed with the milled granulation in a tumble-type mixer. The final blend is prepared by adding magnesium stearate to the tumble-type mixer and mixing. Compression is carried out on a rotary tablet press using appropriate size tooling. Coating is performed in conventional coating pans and by applying the coating suspension to achieve a suitable film coat.

EXAMPLE 2
MODIFIED BAZEDOXIFENE ACETATE FORMULATION

%w/w

Ingredient	5% granulation
Bazedoxifene acetate, micronized ^a	5.00
Lactose NF	41.00
Microcrystalline Cellulose, NF	35.00
Pregelatinized Starch NF	10.00
Sodium Lauryl Sulfate NF	1.50
L-Ascorbic Acid USP	1.50
Sodium Starch Glycolate NF	5.50
Magnesium Stearate NF	0.50
Pur. Water USP ^b	qs

5 ^aAmount in formula is adjusted for actual potency of bazedoxifene acetate as free base. Corresponding adjustment made with lactose.

^bUsed in process but does not appear in the final product.

EXAMPLE 3
BAZEDOXIFENE ACETATE AT 5 % GRANULATION

10

 A preferred carrier or excipient system for formulating a granulation of from about 2 to about 8% by weight of one of the active pharmacological agents of this invention, e.g., about 5%, may be produced utilizing the carrier or excipient components on a weight percentage; lactose from about 32% to about 38%,
15 microcrystalline cellulose from about 32% to about 38%, pregelatinized starch from about 12% to about 16%, ascorbic acid from about 1% to about 2%, sodium lauryl sulfate from about 1% to about 2%, sodium starch glycolate from about 4% to about 8%, silicon dioxide from about 0.1% to about 0.2% and magnesium stearate from
20 about 0.3% to about 0.7%.

A formulation of this invention utilizing bazedoxifene as the active ingredient at a 5% granulation was prepared utilizing the components listed below in a granulation part and a dry part of components.

5	Item No.	Ingredients	Mg/Unit
Granulation Part:			
	1	Bazedoxifene acetate	5.00
	2	Lactose NF	20.60
10	3	Microcrystalline Cellulose NF	25.00
	4	Pregelatinized Starch NF	10.00
	5	Ascorbic Acid USP	1.50
	6	Sodium Lauryl Sulfate NF	1.50
	7	Sodium Starch Glycolate NF	4.00
15	8	Water, Purified USP	Q.S.
			73.60
Dry Part:			
20	9	Lactose NF (fast flo)	9.75
	10	Microcrystalline Cellulose NF	10.00
	11	Pregelatinized Starch NF	4.00
	12	Sodium Starch Glycolate NF	2.00
	13	Silicon Dioxide NF	0.15
25	14	Magnesium Stearate NF	0.60
			100.00

A film coat of White Opadry I (YS-1-18027-A) was applied to the tablets, which were compressed as follows:

30

	<u>Dose of Bazedoxifene</u>	<u>tablet weight, mg</u>	<u>mg of film coat applied/tablet</u>
	5 mg	100	6.0
	10 mg	200	8.0
5	20 mg	400	13.0

EXAMPLE 4

BAZEDOXIFENE IN THE TREATMENT OF OSTEOPENIA OR OSTEOPOROSIS

10 Mice, rats or monkeys may be treated daily with an aromatase inhibitor and bazedoxifene combination. Administration of both components of the combination may be by subcutaneous, intraperitoneal or oral routes for periods ranging from 2 weeks to one year. Bone mineral density may be measured by standard methods, a.g., dual-energy x-ray absorptiometry (Wickman, S. et al. *J. Clin. Endocrin. &*
15 *Metab.* 88(8):3785-3793 (2003); Vanderschueren, D. et al. *Endocrin.* 138(8):2310-2307 (1997)). Uterine weights may be measured as described by Schleweck, K. et al. in *J. Steroid Biochem. Mol. Biol.* 44(4-6):633-6 (1993). A decrease in uterine weight is a positive control, ensuring aromatase functional activity. An improvement in bone mass loss following co-treatment with bazedoxifene would demonstrate that
20 the bazedoxifene is effective in treating bone mass loss by maintaining bone mass without stimulating the uterus or breast tissues.

Those skilled in the art will recognize that various changes and/or modifications may be made to aspects or embodiments of this invention and that
25 such changes and/or modifications may be made without departing from the spirit of this invention. Therefore, it is intended that the appended claims cover all such equivalent variations as will fall within the spirit and scope of this invention. Each reference cited in the present application, including literature references, books, patents and patent applications, is incorporated herein by reference in its entirety.
30 This application claims priority benefit of U.S. Provisional Application Ser. No. 60/536,035 filed 01/13/04, which is incorporated by reference herein in its entirety.

What is claimed is:

1. A method of treating or inhibiting osteoporosis or osteopenia in a mammal receiving aromatase therapy, which comprises providing to said mammal an effective amount of bazedoxifene.
5
2. A method according to claim 1 wherein the bazedoxifene is provided in combination with an aromatase inhibitor.
- 10 3. A method according to claim 1 or claim 2, wherein the aromatase inhibitor is selected from the group consisting of exemestane, formestane, atamestane, fadrozole, letrozole, vorozole, and anastrozole.
- 15 4. A method according to claim 3, wherein the aromatase inhibitor is letrozole or anastrozole.
5. A method according to any one of claims 1 to 4, wherein the bazedoxifene or the aromatase inhibitor or both are provided in subtherapeutically effective amounts.
20
6. A method according to any one of claims 1 to 5, wherein the bazedoxifene is bazedoxifene acetate.
- 25 7. A method of treating or inhibiting breast cancer in a mammal in need thereof, which comprises providing to said mammal an effective amount of bazedoxifene and an aromatase inhibitor.
- 30 8. A method according to claim 7, wherein the aromatase inhibitor is selected from the group consisting of exemestane, formestane, atamestane, fadrozole, letrozole, vorozole, and anastrozole.
9. A method according to claim 8, wherein the aromatase inhibitor is letrozole or anastrozole.

10. A method according to any one of claims 7 to 9, wherein the bazedoxifene or the aromatase inhibitor or both are provided in subtherapeutically effective amounts.

5 11. A method according to any one of claims 7 to 10, wherein the bazedoxifene is bazedoxifene acetate.

12. A method of inhibiting the recurrence of breast cancer in a mammal in need thereof which comprises providing to said mammal an effective amount of
10 bazedoxifene and an aromatase inhibitor.

13. A method according to claim 12, wherein the aromatase inhibitor is selected from the group consisting of exemestane, formestane, atamestane, fadrozole, letrozole, vorozole, and anastrozole.

15 14. A method according to claim 13, wherein the aromatase inhibitor is letrozole or anastrozole.

15. A method according to any one of claims 12 to 14, wherein the
20 bazedoxifene or the aromatase inhibitor or both are provided in subtherapeutically effective amounts.

16. A method according to any one of claims 12 to 15, wherein the
25 bazedoxifene is bazedoxifene acetate.

17. A method of inhibiting breast cancer in a high risk woman, which comprises providing to said woman, an effective amount of bazedoxifene and an aromatase inhibitor.

30 18. A method according to claim 17, wherein the aromatase inhibitor is selected from the group consisting of exemestane, formestane, atamestane, fadrozole, letrozole, vorozole, and anastrozole.

18. A method according to claim 18, wherein the aromatase inhibitor is letrozole or anastrozole.

20. A method according to any one of claims 17 to 19, wherein the
5 basedoxifene or the aromatase inhibitor or both are provided in subtherapeutically effective amounts.

21. A method according to any one of claims 17 to 20, wherein the
basedoxifene is basedoxifene acetate.

10

22. A method according to any one of claims 1 to 21, wherein the effective amount of basedoxifene is from about 5 to about 80 mg/day.

23. A method according to claim 22, wherein the effective amount of
15 basedoxifene is from about 10 to about 80 mg/day.

24. A method according to claim 23, wherein the effective amount of basedoxifene is from about 10 to about 40 mg/day.

20 25. A method according to claim 24, wherein the effective amount of basedoxifene is from about 10 to about 30 mg/day.

26. A method according to claim 24, wherein the effective amount of basedoxifene is from about 20 to about 40 mg/day.

25

27. Use of a basedoxifene in the preparation of a medicament for use treating or inhibiting osteoporosis or osteopenia in a mammal aromatase therapy.

28. Use of a basedoxifene in the preparation of a medicament for use in
30 combination with an aromatase inhibitor for treating or inhibiting osteoporosis, osteopenia or breast cancer in a mammal.

28. Use of a bazedoxifene in the preparation of a medicament for use in combination with an aromatase inhibitor for inhibiting the recurrence of breast cancer in a mammal.

5 30. Use of a bazedoxifene in the preparation of a medicament for use in combination with an aromatase inhibitor for inhibiting breast cancer in a high risk woman.

10 31. A product comprising a bazedoxifene and an aromatase inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment or inhibition of osteoporosis, osteopenia or breast cancer in a mammal.

15 32. A product comprising a bazedoxifene and an aromatase inhibitor as a combined preparation for simultaneous, separate or sequential use in inhibiting breast cancer in a high risk woman, or in inhibiting the recurrence of breast cancer in a mammal.

20 33. A composition for use in a method of treating or inhibiting osteoporosis or osteopenia in a mammal, said composition comprising a bazedoxifene and an aromatase inhibitor and said method which comprises providing to said mammal an effective amount of said composition.

25 34. A composition for use in treating or inhibiting osteoporosis or osteopenia or breast cancer in a mammal comprising a bazedoxifene and an aromatase inhibitor.

35. A composition for use in inhibiting breast cancer in a high risk woman comprising a bazedoxifene and an aromatase inhibitor.

30 36. A composition for use in inhibiting the recurrence of breast cancer in a mammal comprising a bazedoxifene and an aromatase inhibitor.

TRATAMIENTO DE OSTEOPOROSIS RELACIONADO CON TERAPIA CON
INHIBIDOR DE AROMATASA

ANTECEDENTES DE LA INVENCION

5

Esta invención se refiere al uso de bazedoxifeno (1-[4-(2-azepan-1-il-etoxi)-bencil]-2-(4-hidroxi-fenil)-3-metil-1H-indol-5-ol) en el tratamiento o la inhibición de osteoporosis y osteopenia relacionado con la terapia con inhibidor de aromatasa.

10

Los inhibidores de aromatasa, tales como anastrozol y letrozol, se utilizan frecuentemente para el tratamiento adyuvante de cáncer de mama y para la prevención a largo plazo de cáncer de mama después del tratamiento con tamoxifeno. Por medio de su mecanismo de acción estos fármacos inducen o amplifican la deficiencia de estrógeno que se desarrolla en mujeres post-menopáusicas. La deficiencia de estrógeno inducida por inhibidores de aromatasa es necesaria para combatir el cáncer de mama dependiente del estrógeno, pero induce efectos secundarios en otros tejidos, notablemente, el hueso. Los inhibidores de aromatasa incrementan la resorción ósea, y por último inducen osteopenia y osteoporosis. Esto ha sido demostrado en estudios clínicos con un incremento en marcadores bioquímicos de resorción ósea, disminución en densidad mineral ósea según se mide mediante absorciometría de rayos X doble (DXA), y una incidencia incrementada de fracturas relacionadas con inhibidores de aromatasa. Ya que los inhibidores de aromatasa se prescriben en una base a largo plazo, durante varios años, el tratamiento para evitar osteopenia y osteoporosis es necesario.

25

El bazedoxifeno es un modulador selectivo del receptor de estrógeno (SERM) que muestra una actividad agonista del receptor selectivo de estrógeno-tejido en el esqueleto y metabolismo de lípidos, aunque no estimula los tejidos uterinos y de mama. En estudios preclínicos, el

bazedoxifeno demuestra resistencia ósea compresiva mejorada y un perfil histomorfométrico superior al de raloxifeno. Esto es apoyado por los resultados clínicos de la fase II, que revelan que bazedoxifeno reduce los marcadores bioquímicos de la resorción ósea.

5 Estos datos muestran que el bazedoxifeno puede demostrar potencialmente: a) protección ósea a una dosis inferior que el SERM en la actualidad comercializado, b) ningún efecto agonista uterino, c) un potencial bajo para inducir descargas vasomotoras y d) mejora en el perfil de lípidos en suero. Además, los datos también demuestran que el bazedoxifeno inhibe la
10 proliferación estimulada por estradiol de las células de cáncer de mama, que sugiere que el bazedoxifeno también pueda actuar como otros SERM que son capaces de reducir el riesgo de desarrollar cáncer de mama.

BREVE DESCRIPCION DE LA INVENCION

15

 Esta invención proporciona el uso de bazedoxifeno en un mamífero que recibe terapia con Inhibidor de aromatasa en el tratamiento o inhibición de osteoporosis y osteopenia, particularmente relacionado con la terapia con Inhibidor de aromatasa. Esta invención también proporciona una
20 combinación de bazedoxifeno y un inhibidor de aromatasa útil en el tratamiento de cáncer de mama, la inhibición de cáncer de mama en mujeres de alto riesgo, y para inhibir la reaparición de cáncer de mama, después de una remisión inicial o cura. Esta invención también proporciona un producto que comprende un bazedoxifeno y un inhibidor de aromatasa como una
25 preparación combinada útil en el tratamiento o inhibición de las condiciones previamente descritas. Esta invención también proporciona una composición para utilizarse en el tratamiento o inhibición de las condiciones anteriormente descritas, que comprende un bazedoxifeno y un inhibidor de aromatasa en donde la composición se proporciona en una cantidad efectiva a un mamífero

en necesidad de la misma. Esta invención además proporciona la administración de bazedoxifeno después de terminar un tratamiento con inhibidor de aromatasa para mejorar los síntomas o efectos secundarios del tratamiento con inhibidor de aromatasa.

5 En un aspecto, la presente invención proporciona métodos para tratar o inhibir osteoporosis u osteopenia en un mamífero que recibe terapia con aromatasa, que comprende proporcionar al mamífero una cantidad efectiva de bazedoxifeno. En dichas modalidades, el bazedoxifeno es acetato de bazedoxifeno. En dichas modalidades, el bazedoxifeno se proporciona en
10 combinación con un inhibidor de aromatasa. En algunas modalidades, el bazedoxifeno o el inhibidor de aromatasa o ambos se proporcionan en cantidades subterapéuticamente efectivas. En algunas modalidades, el inhibidor de aromatasa se selecciona del grupo que consiste en exemestano, formestano, alamestano, fadrozol, letrozol, vorozol y anastrozol. En algunas
15 modalidades, el inhibidor de aromatasa se selecciona del grupo que consiste en letrozol y anastrozol.

 En otro aspecto, la presente invención proporciona métodos para tratar o inhibir el cáncer de mama en un mamífero que recibe terapia con aromatasa, que comprende proporcionar al mamífero una cantidad efectiva de
20 bazedoxifeno. En dichas modalidades, el bazedoxifeno es acetato de bazedoxifeno. En dichas modalidades, el bazedoxifeno se proporciona en combinación con un inhibidor de aromatasa. En dichas modalidades, el bazedoxifeno o el inhibidor de aromatasa o ambos se proporcionan en cantidades subterapéuticamente efectivas. En algunas modalidades, el
25 inhibidor de aromatasa se selecciona del grupo que consiste en exemestano, formestano, alamestano, fadrozol, letrozol, vorozol y anastrozol. En algunas modalidades, el inhibidor de aromatasa se selecciona del grupo que consiste en letrozol y anastrozol.

En un aspecto adicional, esta invención proporciona métodos para tratar o inhibir la reaparición de cáncer de mama en un mamífero en necesidad del mismo, que comprende proporcionar al mamífero una cantidad efectiva de bazedoxifeno. En dichas modalidades, el bazedoxifeno es acetato de bazedoxifeno. En algunas modalidades, el bazedoxifeno se proporciona en combinación con un inhibidor de aromatasa. En dicha modalidad, el bazedoxifeno o el inhibidor de aromatasa o ambos se proporcionan en cantidades subterapéuticamente efectivas. En algunas modalidades, el inhibidor de aromatasa se selecciona del grupo que consiste en exemestano, formestano, atamestano, fadrozol, letrozol, vorozol y anastrozol. En algunas modalidades, el inhibidor de aromatasa se selecciona del grupo que consiste en letrozol y anastrozol.

Otro aspecto de la invención proporciona métodos para tratar o inhibir el cáncer de mama en una mujer de alto riesgo, que comprende proporcionar a la mujer una cantidad efectiva de bazedoxifeno. En algunas modalidades, el bazedoxifeno es acetato de bazedoxifeno. En dichas modalidades, el bazedoxifeno se proporciona en combinación con un inhibidor de aromatasa. En algunas modalidades, el bazedoxifeno o inhibidor de aromatasa o ambos se proporcionan en cantidades subterapéuticamente efectivas. En algunas modalidades, el inhibidor de aromatasa se selecciona del grupo que consiste en exemestano, formestano, atamestano, fadrozol, letrozol, vorozol, y anastrozol. En algunas modalidades, el inhibidor de aromatasa se selecciona del grupo que consiste en letrozol y anastrozol.

Un aspecto adicional de esta invención es proporcionar métodos para administrar bazedoxifeno a un mamífero que ha completado el tratamiento con inhibidor de aromatasa para mejorar los síntomas o efectos secundarios del tratamiento con inhibidor de aromatasa. En algunas modalidades, el síntoma o efectos secundarios son osteopenia u osteoporosis. En algunas modalidades, el bazedoxifeno es acetato de

bazedoxifeno. En dichas modalidades, el bazedoxifeno se proporciona en cantidades subterapéuticamente efectivas.

Como se utiliza de conformidad con esta invención, el término "bazedoxifeno" significa bazedoxifeno (1-[4-(2-azepan-1-il-etoxi)-bencil]-2-(4-
5 hidroxifenil)-3-metil-1H-indol-5-ol, o una sal o profármaco farmacéuticamente aceptable del mismo.

Como se utiliza de conformidad con esta invención, los términos "tratamiento" o "tratar" significa curar, mejorar, o invertir el progreso de una enfermedad o trastorno, o mejorar o invertir uno o más síntomas o efectos
10 secundarios de dicha enfermedad o trastorno.

Como se utiliza de conformidad con esta invención, el término "proporcionar" con respecto a proporcionar la combinación del inhibidor de aromatasa-bazedoxifeno, significa administrar directamente la combinación, o administrar un profármaco, derivado o análogo de uno o ambos de los
15 componentes de la combinación que formará una cantidad efectiva de la combinación dentro del cuerpo, y con respecto a bazedoxifeno, significa administrar directamente bazedoxifeno, o administrar un profármaco, derivado o análogo de bazedoxifeno que formará una cantidad efectiva en el cuerpo.

Como se utiliza de conformidad con esta invención, el término
20 "mujer de alto riesgo" o "una mujer de alto riesgo" significa una mujer de al menos 35 años con un riesgo predicho de 5 años de cáncer de mama $>1.67\%$ como se calcula mediante Gail Model [The Lancet, 355:18 (2000)].

Como se utiliza de conformidad con esta invención, el término "subterapéuticamente" significa por debajo de los niveles de dosis utilizados
25 normalmente para tratar una enfermedad, es decir, una dosis menor a la cantidad requerida para un efecto terapéutico. Cuando se utiliza para la terapia de combinación de bazedoxifeno y un inhibidor de aromatasa, puede referirse a un efecto sinérgico entre los compuestos.

La aromatasa es una enzima que convierte los andrógenos en estrona. La estrona puede convertirse subsecuentemente a estradiol, que se ha unido al crecimiento incrementado o proliferación del carcinoma del receptor de estrógeno positivo. Como se utiliza de conformidad con esta invención, el término "inhibidor de aromatasa" significa compuestos o sustancias que inhiben la actividad de la enzima aromatasa. De este modo, el objetivo de utilizar inhibidores de aromatasa en quimioterapia es típicamente para reducir los niveles de estradiol circulante, para inhibir finalmente el crecimiento de neoplasmas que son dependientes de estrógeno o del receptor de estrógeno positivo. Existen dos tipos de inhibidores de aromatasa: inhibidores esteroidales (tipo I) y no esteroideal (tipo II). Ejemplos de inhibidores de aromatasa esteroidales incluyen exemestano, formestano, atamestano, y similares. Ejemplos de inhibidores de aromatasa no esteroidales incluyen fadrozol, letrozol, vorozol, anastrozol y similares.

La preparación de bazedoxifeno y sus sales farmacéuticamente aceptables se describe en la patente de E.U.A. 5,998,402 que se incorpora en la presente por referencia en su totalidad. Cuando se administra para el tratamiento o inhibición de un estado de enfermedad particular o trastorno, se entiende que la dosis efectiva puede variar dependiendo de, por ejemplo, si el bazedoxifeno se utiliza con o sin un inhibidor de aromatasa, el inhibidor de aromatasa particular utilizado, si se utiliza uno, el modo de administración, la condición a tratar, y la severidad de la misma, como también varios factores físicos relacionados con los individuos a tratar. La administración efectiva de bazedoxifeno de esta invención puede estar en cualquier variedad de regímenes de dosificación tal como una dosis individual, dosis múltiple, dosis de combinación y formas de dosificación de liberación retardada y a tiempo. El acetato de bazedoxifeno ha sido evaluado en pruebas clínicas utilizando dosis de 10, 20 y 40 mg/día. Con base en los resultados de estas pruebas, se anticipa que las dosis entre alrededor de 5 y aproximadamente 80 mg/día de

bazedoxifeno proporcionarán una cantidad efectiva dentro de los métodos de la invención. Se espera que estas dosis diarias proyectadas varíen con la vía de administración. La selección de la administración apropiada y formas de dosificación para un paciente individual será evidente para los expertos en la técnica. Dichas determinaciones son rutina para un experto en la técnica (véase, por ejemplo *Harrison's Principles of Internal Medicine* (1998), editado por Anthony Fauci et al., 14^{ma} edición, publicada por McGraw Hill).

En algunas modalidades, una combinación de bazedoxifeno y un inhibidor de aromatasa se administran de conformidad con la invención en donde el inhibidor de aromatasa es letrozol, y en donde ambos se proporcionan oralmente. En dichas modalidades, la dosis oral inicial de bazedoxifeno puede ser de alrededor de 5 a aproximadamente 80 mg/día (en los días que se proporciona) y la dosis oral inicial de letrozol puede ser de alrededor de 1 a aproximadamente 10 mg diariamente (en los días que se proporciona). En algunas modalidades, la dosis oral inicial de bazedoxifeno puede ser de alrededor de 10 a aproximadamente 60 mg/día (en los días que se proporciona) y la dosis oral inicial de letrozol puede ser de alrededor de 1 a aproximadamente 10 mg diariamente (en los días que se proporciona). En dichas modalidades, la dosis oral inicial de bazedoxifeno puede ser de alrededor de 10 a aproximadamente 40 mg/día (en los días que se proporciona) y la dosis oral inicial de letrozol puede ser de alrededor de 1 a aproximadamente 10 mg diariamente (en los días que se proporciona). Además, en algunas modalidades, la dosis oral inicial de bazedoxifeno puede ser de alrededor de 10 a aproximadamente 30 mg/día (en los días que se proporciona) y la dosis oral inicial de letrozol puede ser de alrededor de 1 a aproximadamente 10 mg diariamente (en los días que se proporciona). En algunas modalidades, la dosis oral inicial de bazedoxifeno puede ser de alrededor de 20 a aproximadamente 40 mg/día (en los días que se

proporciona) y la dosis oral inicial de letrozol puede ser de alrededor de 1 a aproximadamente 10 mg diariamente (en los días que se proporciona).

En algunas modalidades, una combinación de bazedoxifeno y un inhibidor de aromatasa se administran de conformidad con la invención en donde el inhibidor de aromatasa es anastrozol, y en donde ambos se proporcionan oralmente. En dichas modalidades, la dosis oral inicial de bazedoxifeno puede ser de alrededor de 5 a aproximadamente 80 mg/día (en los días que se proporciona) y la dosis oral inicial de anastrozol puede ser de alrededor de 1 a aproximadamente 10 mg diariamente (en los días que se proporciona). En dichas modalidades, la dosis oral inicial de bazedoxifeno puede ser de alrededor de 10 a aproximadamente 60 mg/día (en los días que se proporciona) y la dosis oral inicial de anastrozol puede ser de alrededor de 1 a aproximadamente 10 mg diariamente (en los días que se proporciona). En algunas modalidades, la dosis oral inicial de bazedoxifeno puede ser de alrededor de 10 a aproximadamente 40 mg/día (en los días que se proporciona) y la dosis oral inicial de anastrozol puede ser de alrededor de 1 a aproximadamente 10 mg diariamente (en los días que se proporciona). En algunas modalidades, la dosis oral inicial de bazedoxifeno puede ser de alrededor de 10 a aproximadamente 30 mg/día (en los días que se proporciona) y la dosis oral inicial de anastrozol puede ser de alrededor de 1 a aproximadamente 10 mg diariamente (en los días que se proporciona). En algunas modalidades, la dosis oral inicial de bazedoxifeno puede ser de alrededor de 20 a aproximadamente 40 mg/día (en los días que se proporciona) y la dosis oral inicial de anastrozol puede ser de alrededor de 1 a aproximadamente 10 mg diariamente (en los días que se proporciona).

Los inhibidores de aromatasa específicamente nombrados en esta descripción se encuentran comercialmente disponibles o pueden elaborarse de procedimientos conocidos en la literatura. Esta invención no se limita al uso de los inhibidores de aromatasa específicos nombrados en la

presente; la preparación de otros inhibidores de aromatasa será evidente para un experto en la técnica con base en la literatura.

Como se utiliza en esta invención, el régimen de combinación puede darse simultáneamente o puede darse en un régimen espaciado, el
5 bazedoxifeno dándose en un momento diferente al inhibidor de aromatasa. Esta diferencia de tiempo puede oscilar de varios minutos, horas, días, semanas o mayor entre la administración de los dos agentes. Por lo tanto, el término "combinación" no necesariamente significa administrado al mismo
10 tiempo o como una dosis unitaria, sino que cada uno de los componentes se administra durante un periodo de tratamiento deseado. Los agentes pueden administrarse mediante las mismas vías o diferentes vías. Por ejemplo, un componente puede administrarse oralmente, mientras el otro parenteralmente y estas combinaciones pueden administrarse diariamente, semanalmente, o incluso una vez al mes.

15 Las formulaciones orales que contienen los compuestos activos de esta invención pueden comprender cualquier forma oral convencionalmente utilizada, incluyendo tabletas, cápsulas, formas bucales, pastillas, trociscos, y suspensiones o soluciones líquidas orales. Las cápsulas pueden contener mezclas del(de los) compuesto(s) con llenadores inertes y/o
20 diluyentes tal como almidones farmacéuticamente aceptables (por ejemplo, malz, papa o almidón de tapioca), azúcares, agentes edulcorantes artificiales, celulosas en polvo, tal como celulosa cristalina y microcristalina, harinas, gelatinas, gomas, etcétera. Las formulaciones en tableta útiles pueden elaborarse mediante compresión convencional, granulación en húmedo o
25 mediante métodos de granulación en seco y utilizar diluyentes farmacéuticamente aceptables, agentes aglutinantes, lubricantes, desintegrantes, agentes modificadores de superficie (incluyendo, agentes tensioactivos), agentes de suspensión o estabilizadores, incluyendo, más no limitándose a, estearato de magnesio, ácido esteárico, talco, laurilsulfato de

sodio, celulosa microcristalina, carboximetilcelulosa cálcica, polivinilpirrolidona, gelatina, ácido alginico, goma de acacia, goma de xantano, citrato de sodio, silcatos complejos, carbonato de calcio, glicina, dextrina, sacarosa, sorbitol, fosfato dicálcico, sulfato de calcio, lactosa, caolín, manitol, 5 cloruro de sodio, talco, almidones secos y azúcar en polvo. Los agentes modificadores de superficie preferidos incluyen agentes modificadores de superficie no iónicos y aniónicos. Ejemplos representativos de agentes modificadores de superficie incluyen, pero no se limitan a, poloxámero 188, cloruro de benzalconio, estearato de calcio, alcohol cetosteárilico, cera 10 cetomacrogol emulsificante, ésteres de sorbitán, dióxido de silicio coloidal, fosfatos, dodecilsulfato de sodio, aluminosilicato de magnesio y trietanolamina. Las formulaciones orales en la presente pueden utilizar formulaciones de liberación a tiempo o retardadas estándar para alterar la absorción del(de los) compuesto(s) activo(s). La formulación oral también puede consistir en 15 administrar el ingrediente activo en agua o un jugo de frutas, que contiene solubilizantes o emulsificantes apropiados según sea necesario.

En algunos casos puede ser conveniente administrar los compuestos directamente a las vías aéreas en forma de un aerosol.

Los compuestos también pueden administrarse parenteralmente 20 o intraperitonealmente. Las soluciones o suspensiones de estos compuestos activos como una base libre o una sal farmacológicamente aceptable pueden prepararse en agua mezclada adecuadamente con un agente tensioactivo tal como hidroxipropilcelulosa. Las dispersiones también pueden prepararse en glicerol, polietilenglicoles líquidos y mezclas de los mismos en aceites. Bajo 25 condiciones ordinarias de almacenamiento y uso, estas preparaciones contienen un conservador para evitar el crecimiento de microorganismos.

Las formas farmacéuticas adecuadas para uso inyectable incluyen soluciones o dispersiones acuosas estériles y polvos estériles para la preparación extemporánea de soluciones o dispersiones inyectables estériles.

En todos los casos, la forma debe ser estéril y debe ser fluida al grado que exista una fácil capacidad de inyección. Debe ser estable bajo las condiciones de fabricación y almacenamiento y debe conservarse contra la acción contaminante de microorganismos tales como bacterias y hongos. El portador
5 puede ser un solvente o un medio de dispersión que contiene, por ejemplo, agua, etanol, poliol (por ejemplo, glicerol, propilenglicol y polietilenglicol líquido), mezclas adecuadas de los mismos, y aceites vegetales.

Para los propósitos de esta descripción, se entiende que las administraciones transdérmicas incluyen todas las administraciones a través
10 de la superficie del cuerpo y los revestimientos interiores de los pasajes corporales que incluyen tejidos epiteliales y mucosos. Dichas administraciones pueden llevarse a cabo utilizando los compuestos de la presente, o sales farmacéuticamente aceptables de los mismos, en lociones, cremas, espumas, parches, suspensiones, soluciones, y supositorios (rectal y vaginal).

15 La administración transdérmica puede lograrse a través del uso de un parche transdérmico que contiene el compuesto activo y un portador que es inerte al compuesto activo, es no tóxico a la piel, y permite el suministro del agente para absorción sistémica en la corriente sanguínea por medio de la piel. El portador puede tomar cualquier número de formas tal
20 como cremas y ungüentos, pastas, geles y dispositivos oclusivos. Las cremas y ungüentos pueden ser un líquido viscoso o emulsiones semisólidas o ser del tipo aceite en agua o agua en aceite. Las pastas comprendidas por polvos absorbentes dispersas en petróleo o petróleo hidrófilo que contiene el ingrediente activo también pueden ser adecuados. Una variedad de
25 dispositivos oclusivos puede utilizarse para liberar el ingrediente activo en la corriente sanguínea tal como una membrana semi-permeable que cubre un depósito que contiene el ingrediente activo con o sin un portador, o una matriz que contiene el ingrediente activo. Otros dispositivos oclusivos son conocidos en la literatura.

Las formulaciones en supositorio pueden elaborarse de materiales tradicionales, incluyendo manteca de cacao, con o sin la adición de ceras para alterar el punto de fusión del supositorio y glicerina. Las bases del supositorio solubles en agua, tal como polietilenglicoles de varios pesos
5 moleculares también pueden utilizarse.

Para bazedoxifeno, las formulaciones orales sólidas, tales como en forma de una tableta o cápsula revestida con película, útil para esta invención incluyen los agentes farmacológicos activos descritos en la presente en combinación con un portador o sistemas excipientes que tienen los
10 componentes:

a) un llenador y componente desintegrante que comprende de alrededor de 5% a aproximadamente 82% en peso de la formulación total, preferiblemente entre alrededor de 30% y aproximadamente 80% de la formulación, de la cual de alrededor de 4% a aproximadamente 40% en peso
15 de la formulación total comprende uno o más desintegrantes farmacéuticamente aceptables.

b) opcionalmente, un agente humectante que comprende de alrededor de 0.2 a aproximadamente 5% de la composición (en peso), tal como la seleccionada del grupo de laurilsulfato de sodio, ésteres de ácido
20 graso de polioxietileno sorbitán, éteres alquílicos de polioxietileno, ésteres de ácido graso de sorbitán, polietilenglicoles, derivados de aceite de ricino de polioxietileno, docusato de sodio, compuestos de amonio cuaternario, ésteres de azúcar de ácidos grasos y glicéridos de ácidos grasos;

c) un lubricante que comprende de alrededor de 0.2% a
25 aproximadamente 10% de la composición (en peso) tal como se selecciona del grupo de estearato de magnesio u otros estearatos metálicos (por ejemplo, estearato de calcio o estearato de zinc), ésteres de ácido graso (por ejemplo estearil fumarato de sodio), ácidos grasos, (por ejemplo, ácido esteárico), alcoholes grasos, behenato de glicerilo, aceite mineral, parafinas, aceites

vegetales hidrogenados, leucina, polietilenglicoles, laurilsulfatos metálicos y cloruro de sodio; y

d) opcionalmente, un deslizante que comprende de alrededor de 0.1% a aproximadamente 10% (en peso) de la composición, el deslizante seleccionado de aquellos conocidos en la técnica, incluyendo del grupo de dióxido de silicio, talco, estearatos metálicos, silicato de calcio o lauril sulfatos metálicos.

Aunque las formulaciones descritas en la presente pueden utilizarse en una forma sólida no revestida o no encapsulada, en algunas modalidades las composiciones finales son revestidas o encapsuladas. Las composiciones farmacológicas pueden revestirse opcionalmente con un revestimiento de película, por ejemplo, que comprende de alrededor de 0.3% a aproximadamente 8% en peso de la composición total. Los revestimientos de película útiles con las formulaciones de la presente son conocidos en la técnica y generalmente consisten en un polímero (usualmente un tipo celulósico de polímero), un colorante y un plastificante. Ingredientes adicionales tales como agentes humectantes, azúcares, sabores, aceites y lubricantes pueden incluirse en las formulaciones de revestimiento de película para impartir ciertas características al revestimiento de película. Las composiciones y formulaciones en la presente también pueden combinarse y procesarse como un sólido, posteriormente colocarse en una forma de cápsula, tal como una cápsula de gelatina.

El componente llenador listado anteriormente puede utilizar el llenador o componentes aglutinantes conocidos en la técnica para formulaciones orales sólidas. Los llenadores o agentes aglutinantes farmacéuticamente aceptables pueden seleccionarse de aquellos conocidos en la técnica tal como, pero sin limitación, lactosa, celulosa microcristalina, sacarosa, manitol, fosfato de calcio, carbonato de calcio, celulosa en polvo, maltodextrina, sorbitol, almidón, o xilitol.

En conjunto con o en lugar de los materiales listados anteriormente para el componente llenador, las formulaciones de la presente utilizan agentes desintegrantes. Estos desintegrantes pueden seleccionarse de los conocidos en la técnica, incluyendo almidón pregelatinizado y glicolato de almidón sódico. Otros desintegrantes útiles incluyen sodio de croscarmelosa, crospovidona, almidón, ácido algínico, alginato de sodio, arcillas (por ejemplo, goma de veegum o xantano), flóculo de celulosa, resina de intercambio iónico o sistemas efervescentes, tal como los que utilizan ácidos alimenticios (tal como ácido cítrico, ácido tartárico, ácido málico, ácido fumárico, ácido láctico, ácido adipico, ácido ascórbico, ácido aspártico, ácido eritróico, ácido glutámico y ácido succínico) y un componente de carbonato alcalino (tal como bicarbonato de sodio, carbonato de calcio, carbonato de magnesio, carbonato de potasio, carbonato de amonio, etc). El(los) desintegrante(s) útil(es) en la presente comprenderá(n) de alrededor de 4% a aproximadamente 40% de la composición en peso, preferiblemente de alrededor de 15% a aproximadamente 35%, más preferiblemente de alrededor de 20% a aproximadamente 35%. Algunos componentes pueden tener funciones múltiples en las formulaciones de esta invención, actuando por ejemplo, como un llenador y un desintegrante. Dicho componente puede mencionarse como un desintegrante del llenador y su función en una formulación específica puede ser singular aún cuando sus propiedades puedan permitir funcionalidad múltiple.

Las formulaciones farmacéuticas y portador o sistemas excipientes en la presente pueden también contener un antioxidante o una mezcla de antioxidantes, por ejemplo, ácido ascórbico. Otros antioxidantes que pueden utilizarse incluyen ascorbato de sodio y palmitato de ascorbilo, que pueden utilizarse en conjunto con una cantidad de ácido ascórbico. En algunas modalidades, la cantidad de antioxidante(es) es de alrededor de 0.5%

a aproximadamente 15% en peso. En algunas modalidades, la cantidad de antioxidantes es de alrededor de 0.5% a aproximadamente 5% en peso.

Entre las formulaciones de esta invención se encuentran las formulaciones farmacéuticas que contienen una cantidad farmacéuticamente efectiva de un agente farmacológico activo y un portador o sistema excipiente
5 que comprende:

a) un llenador y un componente desintegrante que comprende entre alrededor de 50% y aproximadamente 87% de la formulación, con de alrededor de 4% a aproximadamente 40% de la formulación comprendiendo
10 uno o más agentes desintegrantes;

b) un agente humectante que comprende entre alrededor de 0.5% y aproximadamente 2.7% de la formulación;

c) un lubricante que comprende entre alrededor de 0.2% y aproximadamente 5.5% de la formulación; y

15 d) un deslizante que comprende entre alrededor de 0.1% y aproximadamente 5.5% de la formulación.

Los porcentajes listados en las formulaciones anteriores indican porcentajes en peso del peso total de los componentes listados de a) a d). Las formulaciones anteriores también pueden contener un componente
20 antioxidante opcional, por ejemplo, ácido ascórbico, en una concentración de alrededor de 0.5% a aproximadamente 5.5% en peso de la formulación. Las formulaciones pueden contenerse dentro de una cápsula farmacéuticamente aceptable, tal como una cápsula en gel o revestirse con un revestimiento de película que comprende de alrededor de 0.3% a aproximadamente 8% en
25 peso de la formulación.

Esta invención también comprende sistemas de portador y excipientes farmacéuticos útiles en composiciones farmacéuticas que utilizan como un ingrediente activo uno o más de los compuestos descritos aquí, o una sal farmacéuticamente aceptable del mismo, como se describe en la

presente. Estos sistemas de portador o excipiente farmacéuticos comprenden, en peso:

a) un llenador y componente desintegrante que comprende entre alrededor de 54% y aproximadamente 80% de la formulación, con el agente(s) desintegrante(s) en el mismo comprendiendo de alrededor de 4% a aproximadamente 40% en peso de la formulación total;

b) un agente humectante que comprende entre alrededor de 0.55% y aproximadamente 2.5% de la formulación;

c) un lubricante que comprende entre alrededor de 0.2% y aproximadamente 5.5% de la formulación, y

d) un deslizante que comprende entre alrededor de 0.1% y aproximadamente 5.0% de la formulación.

En algunas modalidades los sistemas de portador o excipientes anteriores también pueden contener opcionalmente un componente anti-oxidante, por ejemplo, ácido ascórbico, a una concentración de alrededor de 0.1% a aproximadamente 5.0% en peso.

Entre los sistemas de portador o excipientes de la invención están aquellos que comprenden:

a) un llenador y componente desintegrante, como se describió anteriormente, que comprende entre alrededor de 50% y aproximadamente 87% de la formulación, el desintegrante(s) el mismo comprende de alrededor de 25% a aproximadamente 35% de la formulación, en peso

b) un agente humectante que comprende entre alrededor de 0.55% y aproximadamente 2.7% de la formulación;

c) un lubricante que comprende entre alrededor de 0.2% y aproximadamente 5.5% de la formulación;

d) un deslizante que comprende entre alrededor de 0.1% y aproximadamente 5.5% de la formulación; y

e) un componente anti-oxidante, por ejemplo, ácido ascórbico, a una concentración de alrededor de 0.1% a aproximadamente 5.5% en peso.

EJEMPLOS

EJEMPLO 1

Acetato de bazedoxifeno-formulación de disolución rápida

Ingrediente	Sin ácido ascórbico	Con ácido ascórbico
Acetato de bazedoxifeno micronizado*	10.00	10.00
Flujo rápido de lactosa NF	33.10	31.60
Celulosa microcristalina, NF (Avicel PH101)	25.00	25.00
Almidón 1500	20.00	20.00
Laurilsulfato de sodio NF	1.50	1.50
Glicolato de almidón sódico	10.00	10.00
Ácido ascórbico USP	—	1.5
Sylolid 244 FP	0.15	0.15
Estearato de magnesio	0.25	0.25

* La cantidad en la fórmula se ajusta para potencia real de bazedoxifeno como base libre. El ajuste correspondiente elaborado con lactosa.

Las formulaciones dadas anteriormente en el cuadro 1 se prepararon al incorporar una porción de los excipientes en la granulación y una porción también se añade en los pasos de combinación finales como polvos secos. Un perfil de disolución generado para las formulaciones demostró casi 90% de liberación del fármaco en 30 minutos. De este modo, la combinación única de desintegrantes y diluyentes solubles más la incorporación de sólidos granulados y en polvo en la composición asegura la liberación más rápida del fármaco.

La granulación en húmedo de las formulaciones como se describe en el cuadro 1 puede llevarse a cabo al mezclar el fármaco y ácido ascórbico con una porción de lactosa, celulosa microcristalina, almidón pregelatinizado y glicolato de almidón sódico. El laurilsulfato de sodio se disuelve en agua y se utiliza para granular la mezcla de polvos en un mezclador de alto esfuerzo cortante. La granulación se seca en un secador de lecho fluidizado a una humedad de 2-3%. El tamaño de particular de la

granulación seca se controla al pasar a través de un laminador equipado con
hojas de cuchilla y utilizando un tamiz de malla 20- ó 30-. El dióxido de silicio y
lactosa restante, celulosa microcristalina, almidón pregelatinizado, y glicolato
de almidón de sódico se mezclan con la granulación laminada en un
5 mezclador tipo tambor. La mezcla final se prepara al agregar estearato de
magnesio al mezclador tipo tambor y mezclando. La compresión se lleva a
cabo en una prensa de tabletas giratoria utilizando un maquinado de tamaño
apropiado. El revestimiento se realiza en charolas de revestimiento
convencionales y al aplicar la suspensión de revestimiento para lograr un
10 revestimiento de película adecuado.

EJEMPLO 2**Formulación de acetato de bazedoxifeno modificada****% P/P**

5

Ingrediente	Granulación al 5%
Acetato de bazedoxifeno, micronizado ^a	5.00
Lactosa NF	41.00
Celulosa microcristalina, NF	35.00
Almidón pregelatinizado NF	10.00
Lauril sulfato de sodio NF	1.50
Ácido L-ascórbico USP	1.50
Glicolato de almidón sódico NF	5.50
Estearato de magnesio NF	0.50
Agua purificada USP ^b	q.n.

^a La cantidad en la fórmula se ajusta para potencia real del acetato de bazedoxifeno como base libre. El ajuste correspondiente elaborado con lactosa

10

^b Utilizada en un procedimiento pero no aparece en el producto final.

EJEMPLO 3**Acetato de bazedoxifeno a una granulación al 5%**

15

Un sistema de portador o excipiente preferido para formular una granulación de alrededor de 2 a aproximadamente 8% en peso de uno de los agentes farmacológicos activos de esta invención, por ejemplo, de alrededor de 5%, puede producirse utilizando los componentes de portador o excipientes en un porcentaje en peso; la lactosa de alrededor de 32% a aproximadamente 38%, celulosa microcristalina de alrededor de 32% a aproximadamente 38%, almidón pregelatinizado de alrededor de 12% a aproximadamente 16%, ácido ascórbico de alrededor de 1% a aproximadamente 2%, lauril sulfato de sodio de alrededor de 1% a aproximadamente 2%, glicolato de almidón sódico de alrededor de 4% a aproximadamente 8%, dióxido de silicio de alrededor de 0.1% a aproximadamente 0.2% y estearato de magnesio de alrededor de 0.3% a aproximadamente 0.7%.

20

25

Una formulación de esta invención que utiliza bazedoxifeno como el ingrediente activo a una granulación al 5% se prepara utilizando los

componentes listados a continuación en una parte de granulación y en una parte seca de los componentes.

	No. de artículo	Ingredientes	Mg/Unidad
5	Parte de granulación		
	1	Acetato de bazedoxifeno	5.00
	2	Lactosa NF	26.60
	3	Celulosa microcristalina NF	25.00
	4	Almidón pregelatinizado NF	10.00
	5	Ácido ascórbico USP	1.50
	6	Lauril sulfato de sodio	1.50
	7	Glicolato de almidón sódico NF	4.00
	8	Agua purificada USP	C.N.
			73.60
10	Parte Seca:		
	9	Lactosa NF (Flujo rápido)	9.75
	10	Celulosa microcristalina NF	10.00
	11	Almidón pregelatinizado NF	4.00
	12	Glicolato de almidón sódico	0.15
	13	Dióxido de silicio NF	0.15
	14	Estearato de Magnesio	0.50
			100.00

Un revestimiento de película de White Opadry I (YS-1-18027-A)

se aplicó a las tabletas, que se comprimieron de la siguiente manera:

<u>Dosis de bazedoxifeno</u>	<u>Peso de la tableta</u> mg	<u>mg del revestimiento de película</u> <u>aplicación/tableta</u>
5 mg	100	6.0
10 mg	200	8.0
20 mg	400	13.0

5

EJEMPLO 4**Bazedoxifeno en el tratamiento de osteopenia u osteoporosis**

Ratones, ratas o chongos pueden tratarse diariamente con un

10 inhibidor de aromatasa y combinación de bazedoxifeno. La administración de ambos componentes de la combinación puede ser por vía subcutánea, intraperitoneal u oral durante periodos que oscilan de 2 semanas a 1 año. La densidad mineral ósea puede medirse mediante métodos estándar, por ejemplo, absorciometría de rayos X de doble energía (Wickman, S. et al. *J. Clin. Endocrin. & Metab.* 88(8): 3785-3793 (2003); Vanderschueren, D. et al. *Endocrin.* 138(8):2310-2307(1997)). Los pesos uterinos pueden medirse como se describe por Schiewack, K. et al en *J. Steroid Biochem. Mol Biol.* 44(4-6):833-8 (1993). Una disminución en el peso uterino es un control positivo, asegurando actividad funcional de aromatasa. Una mejora en la pérdida de

15 masa ósea después del co-tratamiento con bazedoxifeno puede demostrar que el bazedoxifeno es efectivo para tratar pérdida de masa ósea al mantener la masa ósea sin estimular el útero o tejidos de mama.

20

Los expertos en la técnica reconocerán que varios cambios y/o modificaciones pueden elaborarse a aspectos o modalidades de la invención y

25 que dichos cambios y/o modificaciones pueden elaborarse sin apartarse del espíritu de esta invención. Por lo tanto, se pretende que las reivindicaciones anexas cubran dicha variaciones equivalentes que entren dentro del espíritu y alcance de esta invención. Cada referencia citada, en la presente solicitud, incluyendo referencias de literature, libros, patentes y solicitudes de patente

se incorporan por referencia en la presente en su totalidad. Esta solicitud reclama el beneficio de prioridad de la solicitud provisional de E.U.A. No. de serie 60/538,035 presentada 01/13/04, que se incorpora por referencia en la presente en su totalidad.

NOVEDAD DE LA INVENCION

REIVINDICACIONES

5 1.- Un método para tratar o inhibir osteoporosis u osteopenia en un mamífero que recibe terapia con aromatasa, que comprende proporcionar a dicho mamífero una cantidad efectiva de bazedoxifeno.

 2.- El método de conformidad con la reivindicación 1, caracterizado además porque el bazedoxifeno se proporciona en combinación
10 con un inhibidor de aromatasa.

 3.- El método de conformidad con la reivindicación 1 ó 2, caracterizado además porque el inhibidor de aromatasa se selecciona del grupo que consiste en exemestano, formestano, atamestano, fadrozol, letrozol, vorozol, y anastrozol.

15 4.- El método de conformidad con la reivindicación 3, caracterizado además porque el inhibidor de aromatasa es letrozol o anastrozol.

 5.- El método de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque el bazedoxifeno o el
20 inhibidor de aromatasa o ambos se proporcionan en cantidades sub-terapéuticamente efectivas.

 6.- El método de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado además porque el bazedoxifeno es acetato de bazedoxifeno.

25 7.- El método para tratar o inhibir cáncer de mama en un mamífero en necesidad del mismo, que comprende proporcionar a dicho mamífero una cantidad efectiva de bazedoxifeno y un inhibidor de aromatasa.

 8.- El método de conformidad con la reivindicación 7, caracterizado además porque el inhibidor de aromatasa se selecciona del

grupo que consiste en exemestano, formestano, atamestano, fadrozol, letrozol, vorozol, y anastrozol.

9.- El método de conformidad con la reivindicación 8, caracterizado además porque el inhibidor de aromatasa es letrozol o
6 anastrozol.

10.- El método de conformidad con cualquiera de las reivindicaciones 7 a 9, caracterizado además porque el bazedoxifeno o el inhibidor de aromatasa o ambos se proporcionan en cantidades sub-terapéuticamente efectivas.

10 11.- El método de conformidad con cualquiera de las reivindicaciones 7 a 10, caracterizado además porque el bazedoxifeno es acetato de bazedoxifeno.

12.- Un método para inhibir la reaparición de cáncer de mama en un mamífero en necesidad del mismo, que comprende proporcionar a dicho
15 mamífero una cantidad efectiva de bazedoxifeno y un inhibidor de aromatasa.

13.- El método de conformidad con la reivindicación 12, caracterizado además porque el inhibidor de aromatasa se selecciona del grupo que consiste en exemestano, formestano, atamestano, fadrozol, letrozol, vorozol, y anastrozol.

20 14.- El método de conformidad con la reivindicación 13, caracterizado además porque el inhibidor de aromatasa es letrozol o anastrozol.

15.- El método de conformidad con cualquiera de las reivindicaciones 12 a 14, caracterizado además porque el bazedoxifeno o el
25 inhibidor de aromatasa o ambos se proporcionan en cantidades sub-terapéuticamente efectivas.

16.- El método de conformidad con cualquiera de las reivindicaciones 12 a 15, caracterizado además porque el bazedoxifeno es acetato de bazedoxifeno.

17.- Un método para inhibir cáncer de mama en una mujer de alto riesgo, que comprende proporcionar a dicha mujer, una cantidad efectiva de bazedoxifeno y un inhibidor de aromatasa.

18.- El método de conformidad con la reivindicación 17,
5 caracterizado además porque el inhibidor de aromatasa se selecciona del grupo que consiste en exemestano, formestano, atamestano, fadrozol, letrozol, vorozol, y anastrozol.

19.- El método de conformidad con la reivindicación 18,
10 caracterizado además porque el inhibidor de aromatasa es letrozol o anastrozol.

20.- El método de conformidad con cualquiera de las reivindicaciones 17 a 19, caracterizado además porque el bazedoxifeno o el inhibidor de aromatasa o ambos se proporcionan en cantidades sub-terapéuticamente efectivas.

15 21.- El método de conformidad con cualquiera de las reivindicaciones 17 a 20, caracterizado además porque el bazedoxifeno es acetato de bazedoxifeno

22.- El método de conformidad con cualquiera de las reivindicaciones 1 a 21, caracterizado además porque la cantidad efectiva de
20 bazedoxifeno es de alrededor de 5 a aproximadamente 80 mg/día.

23.- El método de conformidad con la reivindicación 22, caracterizado además porque la cantidad efectiva de bazedoxifeno es de alrededor de 10 a aproximadamente 60 mg/día.

24.- El método de conformidad con la reivindicación 23,
25 caracterizado además porque la cantidad efectiva de bazedoxifeno es de alrededor de 10 a aproximadamente 40 mg/día.

25.- El método de conformidad con la reivindicación 24, caracterizado además porque la cantidad efectiva de bazedoxifeno es de alrededor de 10 a aproximadamente 30 mg/día.

26.- El método de conformidad con la reivindicación 24, caracterizado además porque la cantidad efectiva de bazedoxifeno es de alrededor de 20 a aproximadamente 40 mg/día.

5 27.- Uso de bazedoxifeno en la preparación de un medicamento para utilizarse en el tratamiento o inhibición de osteoporosis u osteopenia en una terapia de aromatasa para mamífero.

28.- Uso de bazedoxifeno en la preparación de un medicamento para uso en combinación con un inhibidor de aromatasa para tratar o inhibir osteoporosis, osteopenia o cáncer de mama en un mamífero.

10 29.- Uso de bazedoxifeno en la preparación de un medicamento para uso en combinación con un inhibidor de aromatasa para inhibir la reaparición de cáncer de mama en un mamífero.

30.- Uso de bazedoxifeno en la preparación de un medicamento para uso en combinación con un inhibidor de aromatasa para inhibir el cáncer
15 de mama en una mujer de alto riesgo.

31.- Un producto que comprende un bazedoxifeno y un inhibidor de aromatasa como una preparación combinada para uso simultáneo separado o secuencial en el tratamiento o inhibición de osteoporosis, osteopenia o cáncer de mama en un mamífero.

20 32.- Un producto que comprende un bazedoxifeno y un inhibidor de aromatasa como una preparación combinada para uso simultáneo separado o secuencial para inhibición del cáncer de mama en una mujer de alto riesgo o inhibición de la reaparición de cáncer de mama en un mamífero.

33.- Una composición para utilizarse en un método para tratar o
25 Inhibir osteoporosis u osteopenia en un mamífero, dicha composición comprende un bazedoxifeno y un inhibidor de aromatasa y dicho método que comprende proporcionar a dicho mamífero una cantidad efectiva de dicha composición.

34.- Una composición para utilizarse en el tratamiento o inhibición de osteoporosis u osteopenia o cáncer de mama en un mamífero que comprende un bazedoxifeno y un inhibidor de aromatasa.

5 35.- Una composición para utilizarse en la inhibición de cáncer de mama en una mujer de alto riesgo que comprende un bazedoxifeno y un inhibidor de aromatasa.

36.- Una composición para utilizarse en la inhibición de la reaparición de cáncer de mama en un mamífero que comprende un bazedoxifeno y un inhibidor de aromatasa.

RESUMEN DE LA INVENCION

Esta invención se refiere al uso de bazedoxifeno (1-[4-(2-azepan-
1-il-etoxi)-bencil]-2-(4-hidroxi-fenil)-3-metil-1H-indol-5-ol) en el tratamiento o
5 inhibición de osteoporosis y osteopenia relacionada con la terapia con
inhibidor de aromatasa.

10

15

20

PM/kra*nsh*aom*gcg*aom*

P06-1091F

From the INTERNATIONAL SEARCHING AUTHORITY

PCT 000056
45

To:

COZEN O'CONNOR
Attn: Buck, Margaret M.
1900 Market Street
Philadelphia, Pennsylvania 19103
UNITED STATES OF AMERICA

RECEIVED
COZEN IP DEPT.

FEB 15 2006

DUE DATE 3-14-06 idS

MAX DATE 4-14-06 idS

DOCKETED BY 3-14-06 idS

(PCT Rule 44.1)

4/02/2006

Applicant's or agent's file reference

AM101514 PCT WUTHOCP1-SOG

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2005/000803

International filing date
(day/month/year)

11/01/2005

Applicant

WYETH

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the international Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.. (41-22) 338.82 70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Sylvia Hermier

AS M WUTHOCP1
212806
Copy sent to Client

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
AM101514 PCT		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US2005/000803	11/01/2005	13/01/2004
Applicant		
WYETH		

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 5 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.
- ☐ The 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** disclosed in the international application, see Box No. I.
2. ☒ **Certain claims were found unsearchable** (See Box II)
3. ☐ **Unity of invention is lacking** (see Box III)
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:
5. With regard to the **abstract**,
- ☒ the text is approved as submitted by the applicant
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the **drawings**,
- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
- ☐ as suggested by the applicant
- ☐ as selected by this Authority, because the applicant failed to suggest a figure.
- ☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/000803 -- 000059

A. CLASSIFICATION OF SUBJECT MATTER

A61K31/566 A61K31/565 A61K31/55 A61K31/4196 A61K31/4184
A61P19/00

48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent 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)

EPO-Internal, EMBASE, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	WO 02/30355 A (KRAGIE, LAURA) 18 April 2002 (2002-04-18) page 1, line 9 - line 22 page 4, line 8 - line 12 page 5, line 19 - line 32 page 7, paragraph 3 page 8, paragraph 3 - page 9, paragraph 1 ----- -/--	1-36

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

° Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

* & * document member of the same patent family

Date of the actual completion of the international search

6 February 2006

Date of mailing of the international search report

14/02/2006

Name and mailing address of the ISA

European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Leherte, C

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US2005/000803

0000803

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GRUBBS C J ET AL: "Efficacy of an aromatase inhibitor and an estrogen receptor modulator either alone or in combination in the prevention of mammary cancer" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 40, March 1999 (1999-03), page 651, XP001155114 & 90TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH; PHILADELPHIA, PENNSYLVANIA, USA; APRIL 10-14, 1999 ISSN: 0197-016X the whole document	1-36
Y	WO 03/105834 A (WYETH; KOWM, BARRY, S; JENKINS, SIMON, N; ERNER, JAMES, C; COLLINS, MA) 24 December 2003 (2003-12-24) page 1, line 13 - line 15	1-36
Y	US 5 998 402 A (MILLER ET AL) 7 December 1999 (1999-12-07) cited in the application column 19, paragraph 1 - paragraph 2	1-36

* see PCT-ARTICLE 17(2)(b) for definition of "relevant passages"; see also PCT-ARTICLE 17(2)(b)

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US2005/000803

000061

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-26 and 33 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 compound/composition.
2. ☐ Claims Nos.:
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:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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 fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees 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.
- ☐ No protest accompanies the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No. PCT/US2005/000803

000062

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0230355	A	18-04-2002	AU 1319802 A
		CA 2462081 A1	22-04-2002
			18-04-2002
WO 03105834	A	24-12-2003	AU 2003248707 A1
			31-12-2003
		CA 2489098 A1	24-12-2003
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PATENT COOPERATION TREATY

000063

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

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To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION See paragraph 2 below

International application No
PCT/US2005/000803

International filing date (day/month/year)
11.01.2005

Priority date (day/month/year)
13.01.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31568, A61K31565, A61K3155, A61K314186, A61K314184, A61P1900

Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA.



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/000803

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently in this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

54 -- 080065
International application No.
PCT/US2005/000803

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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:

- ☐ the entire international application,
- ☒ claims Nos. 1, 2, 5-7, 10-12, 15-17 and 20-36 (all partially) and 1-26, 33 (with regard to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 1-26, 33 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

- ☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
- ☐ 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 whole application or for said claims Nos. 1, 2, 5-7, 10-12, 15-17 and 20-36 (all partially)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

55-000006
International application No.
PCT/US2005/000803

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-36
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-36
Industrial applicability (IA)	Yes: Claims	see separate sheet
	No: Claims	

2 Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/000803

Re Item III

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

1) Claims 1-26 and 33 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).

2) Claims 1, 2, 5-7, 10-12, 15-17 and 20-36 encompass a genus of compounds defined only by their function ("aromatase inhibitor"), wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

The claims cover all combinations of aromatase inhibitor with bazedoxifene, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such combinations.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the pharmaceutical compositions, containing an aromatase inhibitor, selected from exemestane, formestane, atamestane, fadrozole, letrozole, vorozole or anastrozole, combined with bazedoxifene.

3.) No opinion of the present Authority will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Attention is drawn to the fact that the present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an International Search Report has been drawn up (i.e. only for pharmaceutical compositions, containing compounds explicitly disclosed in the claims).

1) DOCUMENTS USED IN EXAMINATION

The following documents are referred to in this communication:

D1: WO 02/30355 A (KRAGIE, LAURA) 18 April 2002 (2002-04-18)

D2: US-A-5 998 402 (MILLER ET AL) 7 December 1999 (1999-12-07)

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

2) INVENTIVE STEP

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-36 does not involve an inventive step.

The problem to be solved by the present application is the provision of a medicament useful in the treatment or inhibition of osteoporosis and osteopenia related to aromatase inhibitor therapy.

The solution proposed by the applicant is a medicament containing an aromatase inhibitor, selected from exemestane, formestane, alamestane, fadrozole, letrozole, vorozole or anastrozole, combined with bazedoxifene.

Document D1 and D2 describe the use of selective-estrogen receptor modulators (SERM) agents as adjuvant therapies to combine with aromatase inhibition.

Document D3 and D4 disclose bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol), a selective-estrogen receptor modulator.

Therefore the features disclosed in D1 (or D2) and D3 (or D4) would be combined by the skilled person, without exercise of any inventive skills in order to solve the problem posed, and the proposed solution thus cannot be considered inventive (Article 33(3) PCT).

Even more the use of a combination of two or more active ingredients with known identical therapeutic use can only be considered as inventive when a surprising effect, an unexpected high synergistic effect or reduced side effects for example, can be assigned in relation to the claimed therapeutic use. In this respect, the present application lacks supportive evidence.

3) INDUSTRIAL APPLICABILITY

Present claims 1-26 and 33 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims 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.

Retiro folios 70, 71 y 72
- Extracto y Tablas

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Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL
TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION (4) MODELO DE UTILIDAD ()	()	()
-Indicación de que se solicita la concesión de una patente.	(✓)	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	(✓)	()
-Descripción de la invención.	(✓)	()
-Dibujos de ser estos pertinentes.	(✓)	()
-Comprobante de Pago de las tasas establecidas.	(✓)	()
COMPLETA (✓) INCOMPLETA ()	()	()
DISEÑO INDUSTRIAL ()		
-Indicación de que se solicita el registro de Diseño Industrial.	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
-Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA () INCOMPLETA ()	()	()
ESQUEMA DE TRAZADO ()		
-Indicación de que se solicita el registro de Diseño Industrial.	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
-Representación gráfica del Esquema Trazado.	()	()
-Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA () INCOMPLETA ()	()	()

Firma Responsable:

Fdo B

Fecha:

Julio 12, 2006