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54. TÍTULO ' ANCORATO DE BAZEDOFENO COMO  
MODULADOR DEL RECEPTOR DE ESTROGENO  
SELECTIVO "

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71. SOLICITANTE WYETH

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Capítulo II.

2

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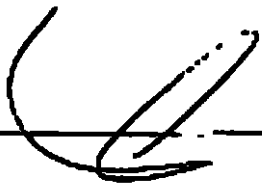
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(54) Title: RAZEDOXIMINE ASCORBATE AS SELECTIVE NITROGEN RECEPTOR MODULATOR

(57) Abstract: The present invention is directed to razedoxime ascorbate, compositions containing the same, dispersions thereof, preparations thereof, and uses thereof.

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## RAZEDOXIFENE ASCORBATE AS SELECTIVE ESTROGEN RECEPTOR MODULATOR

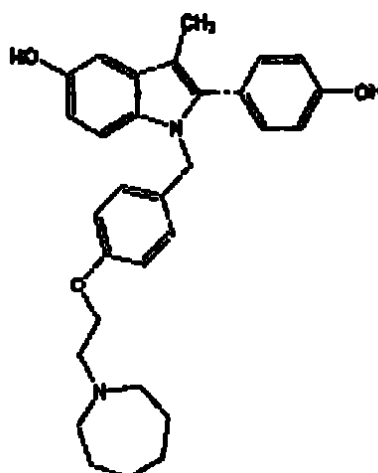
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## FIELD OF THE INVENTION

The present invention relates to the ascorbic acid salt of the selective estrogen receptor modulator 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (bazedoxifene), as well as compositions thereof and uses thereof.

## BACKGROUND OF THE INVENTION

Bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol ; or bazedoxifene free base), having the chemical formula shown below:



belongs to the class of drugs typically referred to as selective estrogen receptor modulators (SERMs). Consistent with its classification, bazedoxifene and its salts demonstrate affinity for estrogen receptors (ER) but show tissue selective estrogenic effects. For example, bazedoxifene acetate demonstrates little or no stimulation of uterine response in preclinical models of uterine stimulation. Conversely, bazedoxifene acetate demonstrates an estrogen agonist-like effect in preventing bone loss and reducing cholesterol in an ovariectomized rat model of osteoporosis. In an MCF-7 cell line (human breast cancer cell line), bazedoxifene acetate behaves as an estrogen antagonist. These data demonstrate that bazedoxifene is estrogenic on bone and cardiovascular lipid parameters and antiestrogenic on uterine and

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mammary tissue and thus has the potential for treating a number of different disease or disease-like states wherein the estrogen receptor is involved.

U.S. Pat. Nos. 5,998,402 and 6,479,535 report the preparation of bazedoxifene and salts thereof. The synthetic preparation of bazedoxifene and its salts has also appeared in the general literature. See, for example, Miller et al., *J. Med. Chem.*, 2001, 44, 1654-1657. Further description of the drug's biological activity has appeared in the general literature as well (e.g. Miller, et al. *Drugs of the Future*, 2002, 27(2), 117-121).

Because drug formulations showing, for example, improved stability, solubility, and bioavailability are consistently sought, there is an ongoing need for new forms of existing drug molecules. The ascorbic acid salt of bazedoxifene and compositions containing the same described herein helps meet these and other needs.

### SUMMARY OF THE INVENTION

The present invention provides an ascorbic acid salt of bazedoxifene and compositions comprising the same.

The present invention further provides methods of preparing bazedoxifene ascorbate comprising combining bazedoxifene free base and ascorbic acid.

The present invention further provides solid dispersions comprising bazedoxifene ascorbate dispersed in a dispersing agent.

The present invention further provides methods of preparing solid dispersions of bazedoxifene ascorbate, comprising: a) combining bazedoxifene ascorbate and a dispersing agent in solution; and b) removing solvent to yield the solid dispersion.

The present invention further provides methods of preparing solid dispersions of bazedoxifene ascorbate, comprising: a) combining bazedoxifene ascorbate with melted dispersing agent to form a liquid mixture; and b) solidifying the liquid mixture to form the solid dispersion.

The present invention further provides methods of treating a mammal having a disease or syndrome associated with estrogen deficiency or excess of estrogen comprising administering to the mammal a therapeutically effective amount of bazedoxifene ascorbate.

The present invention further provides methods of treating a mammal having a disease or disorder associated with proliferation or abnormal development of endometrial tissues comprising administering to the mammal a therapeutically effective amount of bazedoxifene ascorbate.

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The present invention further provides methods of lowering cholesterol in a mammal comprising administering to the mammal a therapeutically effective amount of bazedoxifene ascorbate.

5 The present invention further provides methods of inhibiting bone loss in a mammal comprising administering to the mammal a therapeutically effective amount of bazedoxifene ascorbate.

The present invention further provides methods of treating breast cancer in a mammal comprising administering to the mammal a therapeutically effective amount of bazedoxifene ascorbate.

10 The present invention further provides methods of treating postmenopausal woman for one or more vasomotor disturbances comprising administering to the postmenopausal woman a therapeutically effective amount of bazedoxifene ascorbate.

The present invention further provides bazedoxifene ascorbate for use in therapy.

15 The present invention further provides use of bazedoxifene ascorbate for the preparation of a medicament.

#### DETAILED DESCRIPTION

The present invention provides, *inter alia*, ascorbic acid salts of bazedoxifene, and solid dispersions and compositions thereof having improved properties relating to stability, solubility, bioavailability and the like. For example, bazedoxifene ascorbate incorporates the 20 antioxidant properties of ascorbic acid which can help resist decomposition (e.g., by oxidation) and prolong shelf-life. Bazedoxifene ascorbate also shows improved solubility compared with other forms of bazedoxifene which can result in increased bioavailability and lower dosages.

25 Bazedoxifene ascorbate can be characterized as an acid addition salt of bazedoxifene containing at least about one ascorbic acid molecule to every bazedoxifene molecule. For example, bazedoxifene ascorbate is characterized as having about a 1:1 molar ratio of bazedoxifene to ascorbic acid. In some embodiments, the bazedoxifene ascorbate salt of the invention can be amorphous, crystalline, other solid form or a mixture thereof. In further 30 embodiments, the bazedoxifene ascorbate salt can be anhydrous, hydrated (e.g., hemi-, mono-, di-hydrated, etc.), solvated or a mixture of two or more thereof.

Bazedoxifene ascorbate can be prepared by any suitable method resulting in formation the salt. In some embodiments, the bazedoxifene ascorbate is formed by combining bazedoxifene free base and ascorbic acid. For example, bazedoxifene free base

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and ascorbic acid can be combined in about equimolar amounts. The combining can be optionally carried out in a solvent in which at least one of bazedoxifene acetate and ascorbic acid has at least some solubility. For example, bazedoxifene free base and ascorbic acid can be dissolved together in a solvent, and then the solvent can be removed to yield the desired salt. Suitable solvents for forming the salts of the invention include organic solvents such as, for example, alcohols, ethers, hydrocarbons, halogenated hydrocarbons, nitriles, mixtures thereof, and the like. In some embodiments, the organic solvent is a volatile solvent such as methanol, ethanol, isopropanol, diethyl ether, pentane, hexane, benzene, dichloromethane, acetonitrile, mixtures thereof and the like. In some embodiments, the organic solvent is an alcohol such as methanol, ethanol, n-propanol, isopropanol, mixtures thereof and the like. In some embodiments, the organic solvent is ethanol.

Bazedoxifene ascorbate can also be prepared by replacing the anion of a different salt of bazedoxifene with ascorbate. For example, bazedoxifene acetate or other bazedoxifene salt can be treated with ascorbic acid or an ascorbate salt to form bazedoxifene ascorbate. This anion-replacement reaction can be optimally carried out in a solvent, such as an organic solvent described herein.

The present invention further provides solid dispersions of bazedoxifene ascorbate. The solid dispersions of the invention have increased solubility and bioavailability compared with, for example, bazedoxifene free base, crystalline bazedoxifene acetate and other salt forms of bazedoxifene. The increased bioavailability associated with solid dispersions has numerous advantages including allowing for administration of lower dosages, thereby lessening the chance for adverse side effects and reducing subject variability.

The compositions of the invention contain, for example, bazedoxifene ascorbate dispersed in a dispersing agent. In some embodiments, the weight ratio of bazedoxifene ascorbate to dispersing agent is about 1:99 to about 99:1. In some embodiments, the weight ratio of bazedoxifene ascorbate to dispersing agent is about 1:99 to about 75:25 or about 1:99 to about 60:40. In further embodiments, the weight ratio of bazedoxifene ascorbate to dispersing agent is about 1:99 to about 15:85; about 1:99 to about 10:90; or about 1:99 to about 5:95. In further embodiments, the weight ratio of bazedoxifene ascorbate to dispersing agent is about 5:95. In further embodiments, the weight ratio of bazedoxifene ascorbate to dispersing agent is about 25:75 to about 75:25, about 40:60 to about 60:40 or about 1:1. In some embodiments, the weight ratio of bazedoxifene ascorbate to dispersing agent is about 1:1.

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The "dispersing agent," as used herein, refers to any substance or mixture of substances that acts as a dispersing medium for molecules/particles of bazedoxifene ascorbate. The dispersing agent is typically composed of a pharmaceutically acceptable substance that does not substantially interfere with the pharmaceutical action of bazedoxifene ascorbate. The phrase "pharmaceutically acceptable" is employed herein to refer to those substances which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio. In some embodiments, the dispersing agent is a solid at room temperature (e.g., about 22 °C). In further embodiments, the dispersing agent melts at a temperature between about 20 and 100 °C. In further embodiments, the dispersing agent is soluble in an organic solvent.

Non-limiting examples of dispersing agents include polymers such as celluloses (e.g., carboxymethylcelluloses, methylcelluloses, hydroxypropylcelluloses, hydroxypropylmethylcelluloses); hyaluronates; alginates; polysaccharides, heteropolysaccharides (pectins); poloxamers; poloxamines; ethylene vinyl acetates; polyethylene glycols; dextrans; polyvinylpyrrolidones; chitosans; polyvinylalcohols; propylene glycols; polyvinylacetates; phosphatidylcholines (lecithins); triglycerols; polylactic acid; polyhydroxybutyric acid; mixtures thereof, copolymers thereof, derivatives thereof, and the like. Further example dispersing agents include copolymer systems such as polyethylene glycol-poly(lactic acid) (PEG-PLA), polyethylene glycol-polyhydroxybutyric acid (PEG-PHB), polyvinylpyrrolidone-polyvinylalcohol (PVP-PVA), and derivatized copolymers such as copolymers of N-vinyl pyrrolidone (or pyrimidine) derivatives and N-vinylpyrrolidone.

In some embodiments, the dispersing agent contains polyvinylpyrrolidone (PVP) or derivative thereof. PVP is a polyamide that forms complexes with a wide variety of substances and is considered to be chemically and physiologically inert. Examples of suitable PVPs include polyvinylpyrrolidones having an average molecular weight from about 10,000 to about 50,000. In some embodiments, the polyvinylpyrrolidone has an average molecular weight of about 10,000 to about 20,000. In further embodiments, the polyvinylpyrrolidone has a molecular weight of about 15,000 to about 20,000. An example of a suitable PVP is PVP K-17 (PLASDON® povidone, ISP Technologies, Ltd.). In some embodiments, the dispersing agent consists essentially of PVP or derivative thereof.

In some embodiments, the dispersing agent contains a block co-polymer of ethylene and propylene glycol, often referred to as a Poloxamer. Examples of suitable Poloxamers

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include Poloxamer 188 (TUTROL F 68, BASF), Poloxamer 407 (LUTROL F 127, BASF), and the like. In some embodiments, the dispersing agent is Poloxamer 188.

In some embodiments, the dispersing agent contains a polyethylene glycol (PEG). Suitable PEGs include PEG 200, 300, 400, 600, 1000, 1450, 3350, 4000, 6000, 8000, 10000, 20000, mixtures thereof and the like. In some embodiments, the dispersing agent is PEG 1450.

The hazedoxifene ascorbate dispersions of the invention can be made by any of numerous methods that result in, for example, a solid dispersion of amorphous hazedoxifene ascorbate. In an example method, hazedoxifene ascorbate (in any form, e.g., crystalline, amorphous, etc.) and the dispersing agent can be dissolved in a dispersing solvent (together, or separately and then combined) in the weight ratio desired and then the dispersing solvent is removed to yield the desired solid dispersion. The dispersing solvent can be an aqueous solvent or organic solvent. Suitable organic solvents include alcohols, ethers, hydrocarbons, halogenated hydrocarbons, nitriles, mixtures thereof, and the like. In some embodiments, the organic solvent is a volatile solvent such as methanol, ethanol, isopropanol, diethyl ether, pentane, hexane, benzene, dichloromethane, acetonitrile, mixtures thereof and the like. In some embodiments, the organic solvent is an alcohol such as methanol, ethanol, n-propanol, isopropanol, mixtures thereof and the like. In some embodiments, the organic solvent is ethanol.

In another example, hazedoxifene ascorbate and dispersing agent can be combined in the desired weight ratio when either or both the hazedoxifene ascorbate and dispersing agent is (are) in liquid form (e.g., a melt); and then the liquid mixture is solidified to form the desired solid dispersion. According to such embodiments, the hazedoxifene ascorbate and dispersing agent can be combined when at least one of the hazedoxifene ascorbate and dispersing agent is melted. The resulting mixture is then solidified by cooling to a temperature sufficient to solidify the mixture. In some embodiments, the mixture is cooled to about 25 °C or below. In some embodiments, hazedoxifene ascorbate is combined with melted dispersing agent and the resulting mixture cooled to a temperature below the melting point of the mixture to form the solid dispersion. In further embodiments, the dispersing agent is heated to a temperature between about 30 and 200 °C, between about 30 and 150 °C, or between about 30 and 100 °C, which is a temperature that is at or above the melting point of the dispersing agent. In further embodiments, the dispersing agent is heated to a temperature above about 30, above about 40, above about 50, above about 60, above about

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70, above about 80 or above about 90 °C. These and other methods are routine techniques suitable for the preparation of the bezafibrate ascorbate dispersions of the invention.

#### *Dosage and Formulation*

5 The salt forms and solid dispersions described herein can be formulated for administration in a patient in any of a variety of ways. In some embodiments, the salt forms and solid dispersions can be administered alone, i.e., without the addition of excipients or other additives. For example, solid dosage forms (e.g., tablet, capsules etc.) containing greater than about 95%, greater than about 98%, or greater than about 99% (by weight) of a  
10 salt form or solid dispersion described herein can be directly administered to a patient.

In some embodiments, the salt forms or solid dispersions are combined with one or more pharmaceutically acceptable carriers (excipients) to form a pharmaceutical composition for administration to a patient. The composition can contain any amount of salt form or solid dispersion. In some embodiments, the composition contains about 1 to about 99 % by  
15 weight of the salt form or solid dispersion. In further embodiments, the composition contains about 1 to about 50% by weight of the salt form or solid dispersion. In yet further embodiments, the composition contains about 1 to about 30% by weight of the salt form or solid dispersion. In yet further embodiments, the composition contains about 1 to about 20% by weight of the salt form or solid dispersion. In yet further embodiments, the composition  
20 contains about 1 to about 10% by weight of the salt form or solid dispersion.

Formulations containing the present salt forms and/or solid dispersions can be administered in daily doses ranging from 0.1 mg to 1000 mg of bezafibrate ascorbate to a person in need. Preferred dose ranges vary from 10 mg/day to about 600 mg/day, more preferably from 10 mg/day to about 60 mg/day. The dosing can be either in a single dose or  
25 two or more divided doses per day. Such doses can be administered in any manner that facilitates the compound's entry into the bloodstream including orally, via implants, parenterally, vaginally, rectally, and transdermally.

Transdermal administrations include all administrations across the surface of the body and the inner linings of body passages including epithelial and mucosal tissues. Such  
30 administration may be in the form of a lotion, cream, colloid, foam, patch, suspension, and the like.

Oral formulations containing the present salt forms or solid dispersions can comprise any conventionally used oral forms, including tablets, capsules, buccal forms, lozenges, lozenges and oral liquids, suspensions, and the like. Capsules or tablets of containing the

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present solid dispersion can also be combined with mixtures of other active compounds or inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, fibers, gelatins, gums, etc.

5 Tablet formulations can be made by conventional compression, wet granulation, or dry granulation methods and utilize pharmaceutically acceptable diluents (fillers), binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginate acid, arabic gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, disodium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations used herein may utilize standard delay or time release formulations or spacers. Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the  
10 suppositories melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

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 solvent and a plasticizer. Additional ingredients such as wetting agents, sugars, flavors, oils and lubricants can be  
20 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 or diluent can comprise any substance known in the art that is useful for the preparation of solid oral formulations. Pharmaceutically acceptable fillers can be selected  
25 from, for example, lactose, microcrystalline cellulose, sucrose, mannitol, calcium phosphate, calcium carbonate, powdered cellulose, maltodextrin, sorbitol, starch, xylitol, and the like.

The present formulations can also include disintegrant agents. These disintegrants can be selected from those known in the art, including pregelatinized starch, sodium starch glycolate and the like. Other useful disintegrants include croscarmellose sodium, crospovidone, starch, alginate acid, sodium alginate, clays (e.g. veegum or xanthan gum), cellulose floc, 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,  
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potassium carbonate, ammonium carbonate, etc.). The disintegrant(s) useful herein can 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 can have multiple functions in the formulations of this invention, acting e.g. as both a filler and a disintegrant, and its function in a specific formulation may be singular even though its properties may allow multiple functionality.

The pharmaceutical formulations and excipient systems herein can also contain an antioxidant or a mixture of antioxidants, such as ascorbic acid. Other antioxidants which can be used include sodium ascorbate and ascorbyl palmitate, optionally in conjunction with an amount of ascorbic acid. An example range for the antioxidant(s) is from about 0.05% to about 15% by weight, from about 0.5% to about 15% by weight, or from about 0.5% to about 5% by weight. In some embodiments, the pharmaceutical formulations contain substantially no antioxidant.

Pharmaceutical compositions of bazedoxifene ascorbate can also be formulated with steroidal estrogens, such as conjugated estrogens, USP. The amount of bazedoxifene ascorbate used in the formulation can be adjusted according to the particular solid dispersion used, the amount and type of steroidal estrogen in the formulation as well as the particular therapeutic indication being considered. In general, the bazedoxifene ascorbate can be used in an amount sufficient to antagonize the effect of the particular estrogen to the level desired. The dose range of conjugated estrogens can be from about 0.3 mg to about 2.5 mg, about 0.3 mg to about 1.25 mg, or about 0.3 mg to about 0.625 mg. An example range for amount of bazedoxifene ascorbate in a combination formulation is about 10 mg to about 40 mg. For the steroidal estrogen mestranol, a daily dosage can be from about 1 µg to about 150 µg, and for ethinyl estradiol a daily dosage of from about 1 µg to 200 µg can be used. In some embodiments, the daily dose is between about 2 µg and about 150 µg.

An example oral formulation contains the present salt form or solid dispersion and the following excipient systems:

- a) a filler and disintegrant together comprising from about 1% to about 99% by weight (wt) of the total formulation, preferably between about 20% and about 85% of the formulation, of which from about 4% to about 45% by weight of the total formulation; and
- b) a lubricant comprising from about 0.2% to about 15% of the composition (wt), where the lubricant is 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 butyrate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulfates or sodium chloride.

The percentages listed above for the filler, disintegrant, and lubricants are based on final pharmaceutical composition. The remainder of the final composition are comprised of the salt form or solid dispersion and a pharmaceutically acceptable surface covering, such as a coating or capsule, as described herein. In some embodiments of this invention, the salt form or solid dispersion comprises from about 1 % to about 99 %, about 10 to about 93 %, or about 20 to about 90% by weight, of the final composition; and the coating or capsule comprises up to about 8 %, by weight, of the formulation.

Additional numerous various excipients, dosage forms, dispersing agents and the like that are suitable for use in connection with the salt forms of the invention are known in the art and described in, for example, *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1945, which is incorporated herein by reference in its entirety.

#### Methods

As described in U.S. Pat. No. 5,998,402, bazedoxifene and salts thereof are selective estrogen agonists with affinity for the estrogen receptor. Unlike other types of estrogen agonists, bazedoxifene and salts thereof are antiestrogenic in the uterus and can antagonize the trophic effects of estrogen agonists in uterine tissues. Accordingly, the salt forms and solid dispersions of the invention, and compositions containing the same, can find many uses related to treating or preventing disease states or syndromes associated with an estrogen deficiency or an excess of estrogen. They may also be used in methods of treatment for diseases or disorders which result from proliferation or abnormal development, actions or growth of endometrial or endometrial-like tissues.

Bazedoxifene ascorbate has the ability to behave like an estrogen agonist by lowering cholesterol and preventing bone loss. Accordingly, the salt form or solid dispersion of the invention is useful for treating many malady which result from estrogen effects and estrogen excess or deficiency including osteoporosis, prostatic hypertrophy, male pattern baldness, vaginal and skin atrophy, acne, dysfunctional uterine bleeding, endometrial polyps, benign breast disease, uterine leiomyomas, adenomyosis, ovarian cancer, infertility, breast cancer, endometriosis, endometrial cancer, polycystic ovary syndrome, cardiovascular disease, contraception, Alzheimer's disease, cognitive decline and other CNS disorders, as well as certain cancers including melanoma, prostate cancer, cancers of the colon, CNS

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cancers, among others. Additionally, the solid dispersion can be used for contraception in pre-menopausal women, as well as hormone replacement therapy in post-menopausal women (such as for treating vasomotor disturbances such as hot flush) or in other estrogen deficiency states where estrogen supplementation would be beneficial. It can also be used in disease  
5 states where amenorrhea is advantageous, such as leukemia, endometrial ablations, chronic renal or hepatic disease or coagulation diseases or disorders.

The salt forms and solid dispersions of the invention can also be used in methods of treatment for and prevention of bone loss, which can result from an imbalance in a individual's formation of new bone tissues and the resorption of older tissues, leading to a net  
10 loss of bone. Such bone depletion results in a range of individuals, particularly in post-menopausal women, women who have undergone bilateral oophorectomy, those receiving or who have received extended corticosteroid therapies, those experiencing gonadal dysgenesis, and those suffering from Cushing's syndrome. Special needs for bone, including teeth and oral bone, replacement can also be addressed using the solid dispersion in individuals with  
15 bone fractures, defective bone structures, and those receiving bone-related surgeries and/or the implantation of prosthesis. In addition to the problems described above, the solid dispersion can be used in treatments for osteoarthritis, hypocalcemia, hypercalcemia, Paget's disease, osteomalacia, osteoblastarosis, multiple myeloma and other forms of cancer having deleterious effects on bone tissues.

20 Methods of treating the diseases and syndromes listed herein are understood to involve administering to an individual in need of such treatment a therapeutically effective amount of the salt form or solid dispersion of the invention, or composition containing the same. As used herein, the term "treating" in reference to a disease is meant to refer to preventing, inhibiting and/or ameliorating the disease.

25 As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a  
30 tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

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(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

5 (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting or slowing further development of the pathology and/or symptomatology); and

10 (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

15

## EXAMPLES

### Example 1: Preparation of Bazedoxifene Ascorbate

#### Synthesis 1

20 To a solution of 0.0713 g of ascorbic acid (crystalline powder) in 3 mL of ethanol heated on a water bath to 70 °C then cooled to about 40°C, was added with mixing 0.2001 g of bazedoxifene free base. The resulting suspension was heated to about 50 °C for 10 min forming a colorless solution which was cooled to room temperature. A faint yellow liquid layer formed at the base of the reaction vial.

25 2 mL of anhydrous ether was added to the cooled mixture to form a faint yellow precipitate. The supernatant liquid was decanted and the pasty precipitate was triturated with ether (2 x 1 mL) to form a creamy powder of about 0.1628 g of bazedoxifene ascorbate. The powder was kept in the dark and flushed with nitrogen in a closed container.

#### Synthesis 2

30 A solution of 0.7491 g (0.0042499 mole) of ascorbic acid (crystalline powder) in 32 mL of ethanol with stirring (magnetic stirrer) was heated to 70 °C until all solids were dissolved. The solution was cooled to 50°C. To the cooled solution, 2.04 g (0.0042499 mole) of bazedoxifene free base was added at once, stirred, and heated 3 hours at 60 °C forming a

clear yellow-brown solution. The reaction was checked by HPLC with UV detection at 220 nm for bazedoxifene and 245 nm and 265 nm for ascorbic acid.

The resulting clear solution was cooled and solvents were evaporated under reduced pressure to dryness to give yellow-brown solid. Monitoring by HPLC showed that reaction progression at 1 hour at 60 °C was substantially the same as at 3 hours at 60 °C. The yellow solid was milled with mortar and pestle to give 2.84 g of bazedoxifene ascorbate.

#### *Purification 1*

82 mg of the bazedoxifene ascorbate was dissolved in 1 mL of ethanol/water with some heat. The solution was precipitated by diethyl ether to give yellow amorphous powder.

#### *Purification 2*

To a few mg of bazedoxifene ascorbate was added isopropyl alcohol followed by a few drops of acetone. The resulting mixture was heated to 50 °C for 3-5 min to form a clear yellow solution. The solution was then cooled to about 4 °C to forming a yellow-brown precipitate (not crystalline).

#### *Purification 3*

About 1 g of bazedoxifene ascorbate was placed in conical flask and about 25 mL of acetone was added with mixing. A few drops (5 drops) of water were added with mixing to give a reddish-brown solution. Filter was added (about 15 mL) to precipitate the salt forming a cloudy, brown, gummy precipitate. Trituration with ether gave a brown precipitate (about 0.95 g). This brown fine solid was stored in a desiccator under vacuum at room temperature.

### **Example 2: Characterization of Bazedoxifene Ascorbate**

#### *Proton Nuclear Magnetic Resonance (1H-NMR)*

The proton NMR spectrum of bazedoxifene ascorbate prepared according to Example 1 in deuterated dimethyl sulfoxide (DMSO-d<sub>6</sub>) was consistent with the structure of bazedoxifene ascorbate.

#### *Mass Spectrum*

Bazedoxifene ascorbate prepared according to Example 1 gave M+H:471.3 (MW=470.3) for bazedoxifene; 2M+H:941.6; M'+H : 177.1 for ascorbic acid.

*High Performance Liquid Chromatography (HPLC)*

Bazedoxifene ascorbate prepared according to Example 1 was analyzed by HPLC run under the following conditions:

- Column: Prodigy ODS-2, 5  $\mu$ m of 150 cm x 4.6 mm  
5 Detector: Ultraviolet (UV) at 220 nm  
Column Temperature: 30 °C  
Flow Rate: 1.5 mL/min  
Mobile Phase: 680 mL of: 2 L of water containing 6.8 g monobasic potassium phosphate (adjusted to pH 3.0 with phosphoric acid); and 320 mL of acetonitrile.

10

The retention times for bazedoxifene and ascorbic acid were consistent with the structure.

*Powder X-ray Diffraction (XRPD)*

- 15 XRPD analyses were carried out on a Scintag X2 X-ray powder diffractometer using Cu K  $\alpha$  radiation. The tube power and amperage were set at 45 kV and 40 mA, respectively. The divergence and scattering slits were set at 1° and the receiving slit was set at 0.2 mm. The theta-two theta continuous scan at 3° /min (0.4 sec/0.02° step) from 3 to 40 °2 $\theta$  was used. Samples were packed in a quartz sample holder.

- 20 Powder X-ray diffraction of bazedoxifene ascorbate prepared according to Example 1 showed an amorphous material.

*Differential Scanning Calorimeter (DSC)*

- 25 3.542 mg of bazedoxifene ascorbate prepared according to Example 1 were placed in PERKIN ELMER Pyris 1 DSC with autosampler and heated from 25 °C to 150 °C at a rate of 5 °C/min. The output was measured in a sealed aluminum pan.

The material appeared to be amorphous with a glass transition (T<sub>g</sub>) at 50.02 °C.

*Thermogravimetric Analysis (TGA)*

- 30 1.377 mg of bazedoxifene ascorbate prepared according to Example 1 was placed in a PERKIN ELMER Pyris 1 TGA with an open sample pan flushed with nitrogen. The sample was scanned from 25 °C to 300 °C at a rate of 5 °C/min.

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The bazedoxifene ascorbate sample lost about 11 % up to 100°C (corresponding to about one molecule of water) and then another loss of weight occurred between 105°C and 160°C.

5 **Example 3: Equilibrium Solubility of Bazedoxifene Ascorbate in 0.0005 M acetic acid at 37°C.**

Each of 10.1, 10.0, and 9.8 milligrams of bazedoxifene ascorbate, prepared according to Example 1, were put in 3 mL of 0.0005 M acetic acid and then placed in a water bath at 37 °C. The samples were rotated at 50 rotation/min for 18 hours. All samples were filtered  
10 through 0.2 µm (Nylon Acrodisc) filter. Samples were analyzed by HPLC.

The equilibrium solubility of bazedoxifene ascorbate was determined to be 1.66 mg/mL.

**Example 4: Bulk stability**

15 A batch of bazedoxifene ascorbate prepared according to Example 1 was stored for a time in a vial on the bench top covered with aluminum foil. At 1 month and at 75 days, several mg were analyzed by HPLC. At the 1 month time point, HPLC showed 99.86% recovery. At the 75 day time point, HPLC showed 95.3% recovery.

20 **Example 5: Bazedoxifene Ascorbate Solid Dispersion with PVP (1:1 w/w)**  
*Preparation*

0.5128 g of PVP K17 (PLASDONE C-15 "Povidone USP"; ISP Technologies, Inc.) was dissolved in 10 mL of ethanol. Then 0.5032 g of bazedoxifene ascorbate prepared according to Example 1 was added with magnetic stirring. The flask was flushed with  
25 nitrogen gas and put in a water bath at 70 °C for 10 minutes. The mixture turned clear brown solution and was left in the water bath without heating for 30 minutes. Solvents were evaporated under reduced pressure for 6 hours.

The resulting solid-glassy brown material was grinded with mortar and pestle to give brown-beige fine powder of 0.9244 g with a very good fluidity which did not solidify  
30 overnight.

The HPLC retention times and UV spectra were consistent with the composition of the dispersion. XRPD showed that the dispersion was amorphous. TGA revealed 2.7% weight loss up until about 100°C believed to be due to loss of one molecule of water.

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**Example 6: Solubility of Bazedoxifene Ascorbate Solid Dispersion with PVP (1:1 w/w) in 0.0005 M acetic acid at 37 °C**

Samples of bazedoxifene ascorbate solid dispersion of Example 5 (ca. 20 mg each) were placed in vials to which 1 mL of 0.0005 M acetic acid was added. The mixture was shaken by hand for 10 seconds and then placed in a water bath of 37 °C at 50 rotations/minute for 18 hours. The samples were then filtered through syringe disc filters (13 mm of 0.2 µm Nylon (Whatman)). Results: 12.364 mg/mL.

**Example 7: Bulk Stability of Solid Dispersion**

Bulk stability of bazedoxifene ascorbate solid dispersion with PVP (1:1 w/w) of Example 5 was assessed at 1 month and at 3 months according to the following procedure. Samples of 5-6 g of bazedoxifene ascorbate solid dispersion in vials wrapped with foil were placed on a benchtop at room temperature for one month or for three months. The samples were then analyzed by HPLC to give the following results:

Initial 44.79% (use at value);  
1 month at room temperature: 43.14% (use at value);  
3 month at room temperature: 44.44% (use at value).

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each of the publications and references, including books and patents, cited in the present application is incorporated herein by reference in its entirety.

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What is claimed is:

1. An ascorbic acid salt of bazedoxifene.
2. A composition comprising the salt of claim 1 and a pharmaceutically acceptable carrier.
3. A method of preparing the salt of claim 1 comprising combining bazedoxifene free base and ascorbic acid.
4. The method of claim 3 wherein about equimolar amounts of bazedoxifene free base and ascorbic acid are combined.
5. The method of claim 3 or claim 4 wherein said combining is carried out in a solvent.
6. The method of claim 5 wherein said solvent comprises an alcohol.
7. The method of claim 6 wherein said alcohol comprises ethanol.
8. A salt prepared by the method of any one of claims 3 to 7.
9. A solid dispersion comprising the salt of claim 1 and a dispersing agent.
10. The solid dispersion of claim 9 wherein said dispersing agent comprises a cellulose, hyaluronate, alginate, polysaccharide, heteropolysaccharide, poloxamers, poloxamines, ethylene vinyl acetate, polyethylene glycol, dextran, polyvinylpyrrolidone, chitosan, polyvinylalcohol, propylene glycol, polyvinylacetate, phosphatidylcholines, miglyol, polylactic acid, polyhydroxybutyric acid, mixture of two or more thereof or copolymer thereof.
11. The solid dispersion of claim 9 wherein said dispersing agent comprises polyvinylpyrrolidone.
12. The solid dispersion of any one of claims 9 to 11 wherein the weight ratio of said salt to said dispersing agent is about 1:99 to about 99:1.

13. The solid dispersion of any one of claims 9 to 11 wherein the weight ratio of said salt to said dispersing agent is about 1:99 to about 60:40.
14. The solid dispersion of any one of claims 9 to 11 wherein the weight ratio of said salt to said dispersing agent is about 1:99 to about 10:90.
15. The solid dispersion of any one of claims 9 to 11 wherein the weight ratio of said salt to said dispersing agent is about 5:95.
16. The solid dispersion of any one of claims 9 to 11 wherein the weight ratio of said salt to said dispersing agent is about 40:60 to about 60:40.
17. The solid dispersion of any one of claims 9 to 11 wherein the weight ratio of said salt to said dispersing agent is about 1:1.
18. A method of preparing the solid dispersion of any one of claims 9 to 17 comprising:  
a) combining said salt and said dispersing agent in solution, wherein said solution comprises a solvent; and  
b) removing said solvent to yield said solid dispersion.
19. The method of claim 18 wherein said solvent is an organic solvent.
20. The method of claim 19 wherein said organic solvent comprises an alcohol.
21. The method of claim 20 wherein said alcohol comprises ethanol.
22. A solid dispersion prepared by the method of any one of claims 18 to 21.
23. A method of preparing the solid dispersion of any one of claims 9 to 17 comprising:  
a) combining said salt with melted dispersing agent to form a liquid mixture; and  
b) solidifying said liquid mixture to form said solid dispersion.

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24. The method of claim 23 wherein said melted dispersing agent is prepared by heating said dispersing agent to a temperature above about 30 °C.
25. The method of claim 23 wherein said solidifying comprises cooling said liquid mixture to a temperature at or below about 25 °C.
26. A solid dispersion prepared by the method of claim 23.
27. A composition comprising the solid dispersion of any one of claims 9 to 17 and a pharmaceutically acceptable carrier.
28. A method of treating a mammal having a disease or syndrome associated with estrogen deficiency or excess of estrogen comprising administering to said mammal a therapeutically effective amount of the salt of claim 1.
29. A method of treating a mammal having a disease or disorder associated with proliferation or abnormal development of endometrial tissues comprising administering to said mammal a therapeutically effective amount of the salt of claim 1.
30. A method of lowering cholesterol in a mammal comprising administering to said mammal a therapeutically effective amount of the salt of claim 1.
31. A method of inhibiting bone loss in a mammal comprising administering to said mammal a therapeutically effective amount of the salt of claim 1.
32. A method of treating breast cancer in a mammal comprising administering to said mammal a therapeutically effective amount of the salt of claim 1.
33. A method of treating postmenopausal woman for one or more vasomotor disturbances comprising administering to said postmenopausal woman a therapeutically effective amount of the salt of claim 1.
34. The method of claim 33 wherein said vasomotor disturbance is hot flush.

35. Use of a compound according to claim 1 in the preparation of a medicament for treating a mammal having a disease or syndrome associated with estrogen deficiency or excess of estrogen; or  
treating a mammal having a disease or disorder associated with proliferation or abnormal development of endometrial tissues; or  
lowering cholesterol in a mammal; or  
inhibiting bone loss in a mammal; or  
treating breast cancer in a mammal; or  
treating postmenopausal women for one or more vasomotor disturbances.

# **ASCORBATO DE BAZEDOXIFENO COMO MODULADOR DEL RECEPTOR DE ESTRÓGENO SELECTIVO**

## **CAMPO DE LA INVENCION**

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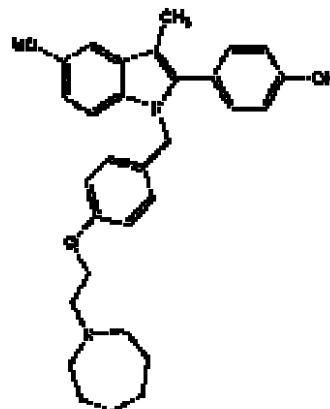
La presente invención se refiere a la sal de ácido ascórbico del modulador de receptor de estrógeno selectivo 1-[4-(2-azepan-1-il-etoxi)-bencil]-2-(4-hidroxi-fenil)-3-metil-1H-indol-5-ol (bazedoxifeno), así como composiciones del mismo y usos del mismo.

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## **ANTECEDENTES DE LA INVENCION**

Bazedoxifeno 1-[4-(2-azepan-1-il-etoxi)-bencil]-2-(4-hidroxi-fenil)-3-metil-1H-indol-5-ol; o base libre de bazedoxifeno), que tiene la fórmula química mostrada a continuación:

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pertenece a la clase de fármacos típicamente referidos como moduladores de receptor de estrógeno selectivo (SERMs). Consistente con su clasificación, el bazedoxifeno y sus sales demuestran afinidad para receptores de estrógeno (ER) pero muestran efectos estrogénicos selectivos de tejido. Por ejemplo, el acetato de bazedoxifeno demuestra poca o nada de estimulación de respuesta uterina en modelos preclínicos de estimulación uterina. Por el contrario, el acetato de bazedoxifeno demuestra un efecto similar al agonista de estrógeno para prevenir pérdida de hueso y reducción de colesterol en un

modelo de rata ovariectomizada de osteopenia. En una línea de células MCF-7 (línea de células de cáncer de mama humana), el acetato de bazedoxifeno se comporta como un antagonista de estrógeno. Estos datos demuestran que el bazedoxifeno es estrogénico sobre parámetros de lípidos de hueso y cardiovasculares y antiestrogénico sobre tejido uterino y de mama y por lo tanto tiene el potencial para tratar un número de diferentes estados de enfermedad o similares a enfermedad en donde el receptor de estrógeno está implicado.

Las patentes de E.U.A. Nos. 5,998,402 y 6,479,535 reportan la preparación de bazedoxifeno y sales del mismo. La preparación sintética de bazedoxifeno y sus sales también ha aparecido en la literatura general. Véase, por ejemplo, Miller et al., *J. Med. Chem.*, 2001, 44, 1654-1657. Una descripción adicional de la actividad biológica del fármaco también ha aparecido en la literatura general (v.gr., Miller, et al. *Drugs of the Future*, 2002, 27(2), 117-121).

Debido a que las formulaciones de fármaco que muestran, por ejemplo, estabilidad, solubilidad y biodisponibilidad mejoradas se buscan consistentemente, existe una necesidad actual de nuevas formas de moléculas de fármaco existentes. La sal de ácido ascórbico de bazedoxifeno y composiciones que contienen el mismo aquí descritas ayuda a cumplir estas y otras necesidades.

### **BREVE DESCRIPCION DE LA INVENCION**

La presente invención provee una sal de ácido ascórbico de bazedoxifeno y composiciones que comprenden el mismo.

La presente invención además provee métodos para preparar ascorbato de bazedoxifeno que comprende combinar una base libre de bazedoxifeno y ácido ascórbico.

La presente invención además provee dispersiones sólidas que comprenden

ascorbato de bazedoxifeno disperso en un agente dispersante.

La presente invención además provee métodos para preparar dispersiones  
sólidas de ascorbato de bazedoxifeno, que comprenden: a) combinar  
ascorbato de bazedoxifeno y un agente dispersante en solución; y b) remover  
5 solvente para dar la dispersión sólida.

La presente invención además provee métodos para preparar dispersiones  
sólidas de ascorbato de bazedoxifeno, que comprenden: a) combinar  
ascorbato de bazedoxifeno con agente dispersante fundido para formar una  
mezcla líquida; y b) solidificar la mezcla líquida para formar la dispersión  
10 sólida.

La presente invención además provee métodos para tratar a un mamífero que  
tiene una enfermedad o síndrome asociado con deficiencia de estrógeno o  
exceso de estrógeno que comprende administrar al mamífero una cantidad  
terapéuticamente efectiva de ascorbato de bazedoxifeno.

15 La presente invención además provee métodos para tratar a un mamífero que  
tiene una enfermedad o trastorno asociado con proliferación o desarrollo  
anormal de tejidos endometriales que comprende administrar al mamífero una  
cantidad terapéuticamente efectiva de ascorbato de bazedoxifeno.

La presente invención además provee métodos para reducir colesterol en un  
20 mamífero que comprende administrar al mamífero una cantidad  
terapéuticamente efectiva de ascorbato de bazedoxifeno.

La presente invención además provee métodos para inhibir pérdida de hueso  
en un mamífero que comprende administrar al mamífero una cantidad  
terapéuticamente efectiva de ascorbato de bazedoxifeno.

25 La presente invención además provee métodos para tratar cáncer de mama  
en un mamífero que comprende administrar al mamífero una cantidad  
terapéuticamente efectiva de ascorbato de bazedoxifeno.

La presente invención además provee métodos para tratar a mujeres  
postmenopáusicas para una o más perturbaciones vasomotoras que

comprende administrar a mujeres postmenopáusicas una cantidad terapéuticamente efectiva de ascorbato de bazedoxifeno.

La presente invención además provee ascorbato de bazedoxifeno para usarse en terapia.

- 5 La presente invención además provee el uso de ascorbato de bazedoxifeno para la preparación de un medicamento.

### **DESCRIPCION DETALLADA DE LA INVENCION**

- 10 La presente invención provee, entre otras, sales de ácido ascórbico de bazedoxifeno, y dispersiones sólidas y composiciones de las mismas que tienen propiedades mejoradas relacionadas con su estabilidad solubilidad, biodisponibilidad y similares. Por ejemplo, el ascorbato de bazedoxifeno
- 15 ayudar a resistir la descomposición (v.gr., por oxidación) y prolongar la vida de anaquel. El ascorbato de bazedoxifeno también muestra solubilidad mejorada comparada con otras formas de bazedoxifeno que pueden dar por resultado biodisponibilidad incrementada y dosis reducidas.

- El ascorbato de bazedoxifeno se pueden caracterizar como una sal ácida de
- 20 adición de bazedoxifeno que contiene por lo menos aproximadamente una molécula de ácido ascórbico a cada molécula de bazedoxifeno. Por ejemplo, el ascorbato de bazedoxifeno se caracteriza por tener aproximadamente una relación molar de 1:1 de bazedoxifeno a ácido ascórbico. En algunas modalidades, la sal de ascorbato de bazedoxifeno de la invención puede ser
- 25 amorfa, cristalina, otra forma sólida o una mezcla de las mismas. En modalidades adicionales, la sal de ascorbato de bazedoxifeno puede ser anhidra, hidratada (v.gr., hemi-, mono-, di-hidratada, etc.), solvatada o una mezcla de dos o más de las mismas.

El ascorbato de bazedoxifeno se puede preparar por cualquier método

adecuado que dé por resultado la formación de la sal. En algunas modalidades, el ascorbato de bazedoxifeno se forma al combinar base libre de bazedoxifeno y ácido ascórbico. Por ejemplo, la base libre de bazedoxifeno y ácido ascórbico se pueden combinar en cantidades aproximadamente equimolares. La combinación se puede llevar a cabo opcionalmente en un solvente en el cual por lo menos uno de acetato de bazedoxifeno y ácido ascórbico tenga por lo menos alguna solubilidad. Por ejemplo, la base libre de bazedoxifeno y ácido ascórbico se pueden disolver juntos en un solvente, y después el solvente se puede remover para dar la sal deseada. Los solventes adecuados para formar las sales de la invención incluyen solventes orgánicos tales como, por ejemplo, alcoholes, éteres, hidrocarburos, hidrocarburos halogenados, nitrilos, mezclas de los mismos, y similares. En algunas modalidades, el solvente orgánico es un solvente volátil tal como metanol, etanol, isopropanol, éter dietílico, pentano, hexano, benceno, diclorometano, acetonitrilo, mezclas de los mismos y similares. En algunas modalidades, el solvente orgánico es un alcohol tal como metanol, etanol, n-propanol, isopropanol, mezclas de los mismos y similares. En algunas modalidades, el solvente orgánico es etanol.

El ascorbato de bazedoxifeno también se puede preparar reemplazando el anión de una sal de bazedoxifeno diferente con ascorbato. Por ejemplo, el acetato de bazedoxifeno u otra sal de bazedoxifeno se puede tratar con ácido ascórbico o una sal de ascorbato para formar ascorbato de bazedoxifeno. Esta reacción de reemplazo de anión se puede llevar a cabo opcionalmente en un solvente, tal como un solvente orgánico aquí descrito.

La presente invención además provee dispersiones sólidas de ascorbato de bazedoxifeno. Las dispersiones sólidas de la invención tienen solubilidad y biodisponibilidad incrementadas en comparación con, por ejemplo, base libre de bazedoxifeno, acetato de bazedoxifeno cristalino y otras formas de sal de bazedoxifeno. La biodisponibilidad incrementada asociada con dispersiones

sólidas tiene numerosas ventajas incluyendo permitir la administración de dosis más bajas, reduciendo así la probabilidad de efectos colaterales adversos y reducción de la variabilidad del sujeto.

Las composiciones de la invención contienen, por ejemplo, ascorbato de  
5 bazodoxifeno disperso en un agente dispersante. En algunas modalidades, la relación en peso de ascorbato de bazodoxifeno a agente dispersante es de aproximadamente 1:99 a aproximadamente 99:1. En algunas modalidades, la relación en peso de ascorbato de bazodoxifeno a agente dispersante es de aproximadamente 1:99 a aproximadamente 75:25 o de aproximadamente 1:99  
10 a aproximadamente 60:40. En modalidades adicionales, la relación en peso de ascorbato de bazodoxifeno a agente dispersante es de aproximadamente 1:99 a aproximadamente 15:85; de aproximadamente 1:99 a aproximadamente 10:90; o de aproximadamente 1:99 a aproximadamente 5:95. En modalidades adicionales, la relación en peso de ascorbato de  
15 bazodoxifeno a agente dispersante es de aproximadamente 5:95. En modalidades adicionales, la relación en peso de ascorbato de bazodoxifeno a agente dispersante es de aproximadamente 25:75 a aproximadamente 75:25, de aproximadamente 40:60 a aproximadamente 60:40 o de aproximadamente 1:1. En algunas modalidades, la relación en peso de ascorbato de  
20 bazodoxifeno a agente dispersante es de aproximadamente 1:1.

El "agente dispersante," como se usa aquí, se refiere a cualquier sustancia o mezcla de sustancias que actúa como un medio dispersante para moléculas/partículas de ascorbato de bazodoxifeno. El agente dispersante está compuesto típicamente de una sustancia farmacéuticamente aceptable  
25 que no interfiere sustancialmente con la acción farmacéutica de ascorbato de bazodoxifeno. La frase "farmacéuticamente aceptable" se utiliza aquí para referirse a aquellas sustancias que están dentro del alcance del juicio médico sólido, adecuadas para usarse en contacto con los tejidos de seres humanos y animales sin toxicidad excesiva, irritación, respuesta alérgica u otro

problema o complicación, en proporción con una relación de riesgo/beneficio razonable. En algunas modalidades, el agente dispersante es un sólido a temperatura ambiente (v.gr., aproximadamente 22°C). En modalidades adicionales, el agente dispersante se funde a una temperatura entre  
5 aproximadamente 30 y 100°C. En modalidades adicionales, el agente dispersante es soluble en un solvente orgánico.

Ejemplos no limitantes de agentes dispersantes incluyen polímeros tales como celulosas (v.gr., carboximetilcelulosas, metilcelulosas, hidroxipropilcelulosas, hidroxipropilmetilcelulosas); hialuronatos; alginatos; polisacáridos,  
10 heteropolisacáridos (pectinas); poloxámeros; poloxaminas; etileno-acetatos de vinilo; polietilenglicol; dextranos; polivinilpirrolidonas; quitosanes; alcoholes polivinílicos; propilenglicoles; acetatos de polivinilo; fosfatidilcolinas (lecitinas); miglioles; ácido poliláctico; ácido polihidroxibutírico; mezclas de los mismos, copolímeros de los mismos, derivados de los mismos, y similares. Agentes  
15 dispersantes de ejemplo adicionales incluyen sistemas de copolímero tales como polietilenglicol-ácido poliláctico (PEG-PLA), polietilenglicol-ácido polihidroxibutírico (PEG- PHB), polivinilpirrolidona-alcohol polivinílico (PVP-PVA), y copolímeros derivados tales como copolímeros de N-derivados de vinilpurina (o pirimidina) y N-vinylpirrolidona.

20 En algunas modalidades, el agente dispersante contiene polivinilpirrolidona (PVP) o derivado del mismo. PVP es una poliamida que forma complejos con una amplia variedad de sustancias y se considera que es químicamente y fisiológicamente inerte. Ejemplos de PVPs adecuadas incluyen polivinilpirrolidonas que tiene un peso molecular promedio de  
25 aproximadamente 10,000 a aproximadamente 50,000. En algunas modalidades, la polivinilpirrolidona tiene un peso molecular promedio de aproximadamente 10,000 a aproximadamente 20,000. En modalidades adicionales, la polivinilpirrolidona tiene un peso molecular de aproximadamente 15,000 a aproximadamente 20,000. Un ejemplo de una

PVP adecuada es PVP K-17 (PLASDONE povidona, ISP Technologies, Ltd.).

En algunas modalidades, el agente dispersante consiste esencialmente de PVP o derivado de la misma.

En algunas modalidades, el agente dispersante contiene un copolímero de  
5 bloque de etileno y propilenglicol, a menudo referido como un poloxámero. Ejemplos de poloxámeros adecuados incluyen Poloxamer 188 (LUTROL F 88, BASF), Poloxamer 407 (LUTROL F 127, BASF), y similares. En algunas modalidades, el agente dispersante es Poloxamer 188.

En algunas modalidades, el agente dispersante contiene un polietilenglicol  
10 (PEG). Los PEGs adecuados incluyen PEG 200, 300, 400, 600, 1000, 1450, 3350, 4000, 6000, 8000, 10000, 20000, mezclas de los mismos y similares. En algunas modalidades, el agente dispersante es PEG 1450.

Las dispersiones de ascorbato de bazedoxifeno de la invención se pueden hacer por cualesquiera métodos adecuados que den por resultado, por  
15 ejemplo, una dispersión sólida de ascorbato de bazedoxifeno amorfo. En un método de ejemplo, el ascorbato de bazedoxifeno (en cualquier forma, v.gr., cristalina, amorfa, etc.) y el agente dispersante se pueden disolver en un solvente dispersante (juntos, o por separado y después combinarse) en la relación en peso deseada y después el solvente dispersante es removido para  
20 dar la dispersión sólida deseada. El solvente dispersante puede ser un solvente acuoso o solvente orgánico. Los solventes orgánicos adecuados incluyen alcoholes, éteres, hidrocarburos, hidrocarburos halogenados, nitrilos, mezclas de los mismos, y similares. En algunas modalidades, el solvente orgánico es un solvente volátil tal como metanol, etanol, isopropanol, éter dietílico, pentano, hexano, benceno, diclorometano, acetonitrilo, mezclas de  
25 los mismos y similares. En algunas modalidades, el solvente orgánico es un alcohol tal como metanol, etanol, n-propanol, isopropanol, mezclas de los mismos y similares. En algunas modalidades, el solvente orgánico es etanol. En otro ejemplo, el ascorbato de bazedoxifeno y agente dispersante se

pueden combinar en la relación en peso deseada cuando cualquiera o ambas del ascorbato de bazedoxifeno y agente dispersante esté (están) en forma líquida (v.gr., un material fundido); y después la mezcla líquida es solidificada para formar la dispersión de sólido deseada. De conformidad con dichas

5 modalidades, el ascorbato de bazedoxifeno y agente dispersante se pueden combinar cuando por lo menos uno del ascorbato de bazedoxifeno y agente dispersante se funden. La mezcla resultante es después solidificada enfriando a una temperatura suficiente para solidificar la mezcla. En algunas

10 modalidades, la mezcla se enfría a aproximadamente 25°C o menor. En algunas modalidades, el ascorbato de bazedoxifeno se combina con agente dispersante fundido y la mezcla resultante se enfría a temperatura por debajo del punto de fusión de la mezcla para formar la dispersión sólida. En modalidades adicionales, el agente dispersante se calienta a una temperatura entre aproximadamente 30 y 200°C, entre aproximadamente 30 y 150°C, o

15 entre aproximadamente 30 y 100°C, que es una temperatura que está en o por arriba del punto de fusión del agente dispersante. En modalidades adicionales, el agente dispersante se calienta a una temperatura por arriba de aproximadamente 30, por arriba de aproximadamente 40, por arriba de aproximadamente 50, por arriba de aproximadamente 60, por arriba de

20 aproximadamente 70, por arriba de aproximadamente 80 o por arriba de aproximadamente 90°C. Estos y otros métodos son técnicas de rutina adecuadas para la preparación de dispersiones de ascorbato de bazedoxifeno de la invención.

## 25 Dosificación y formulación

Las formas de sal y dispersiones de sal aquí descritas se pueden formular para administrarse a un paciente en cualquiera de una variedad de formas. En algunas modalidades, las formas de sal y dispersiones sólidas se pueden administrar solas, es decir, sin la adición de excipientes u otros aditivos. Por

ejemplo, las formas de dosis sólidas (v.gr., tabletas, cápsulas etc.) que contienen más que aproximadamente 95%, más que aproximadamente 98% o más que aproximadamente 99% (en peso) de una forma de sal o dispersión sólida aquí descritos se pueden administrar directamente a un paciente.

- 5 En algunas modalidades, las formas de sal o dispersiones sólidas se combinan con uno o más vehículos (excipientes) farmacéuticamente aceptables para formar una composición farmacéutica para administrarse a un paciente. La composición puede contener cualquier cantidad de forma de sal o dispersión sólida. En algunas modalidades, las composiciones contienen
- 10 aproximadamente 1 a aproximadamente 99% en peso de la forma de sal o dispersión sólida. En modalidades adicionales, la composición contiene aproximadamente 1 a aproximadamente 50% en peso de la forma de sal o dispersión sólida. En modalidades adicionales, la composición contiene aproximadamente 1 a aproximadamente 30% en peso de la forma de sal o
- 15 dispersión sólida. En modalidades adicionales, la composición contiene aproximadamente 1 a aproximadamente 20% en peso de la forma de sal o dispersión sólida. En modalidades adicionales, la composición contiene aproximadamente 1 a aproximadamente 10% en peso de la forma de sal o dispersión sólida.
- 20 Las formulaciones que contienen las presentes formas de sales y/o dispersión sólida se pueden administrar en dosis diarias que varían de 0.1 mg a 1000 mg de ascorbato de bazodoxifeno a una persona que las necesita. Los intervalos de dosis preferidos varían de 10 mg/día a aproximadamente 600 mg/día, muy preferiblemente de 10 mg/día a aproximadamente 60 mg/día. La dosificación
- 25 puede ser ya sea en una sola dosis o en dos o más dosis divididas por día. Dichas dosis se pueden administrar de cualquier manera que facilite la entrada del compuesto al torrente sanguíneo incluyendo oral, mediante implantes, parenteral, vaginal, rectal y transdérmica.

Las administraciones transdérmicas incluyen todas las administraciones a

través del cuerpo y los revestimientos internos del cuerpo incluyendo tejidos epitelial y de la mucosa. Dicha administración puede ser en forma de una loción, crema, coloide, espuma, parche, suspensión y similares.

Las formulaciones orales que contienen las presentes formas de sal o  
5 dispersión sólida pueden comprender cualesquiera formas orales  
convencionalmente usadas, incluyendo tabletas, cápsulas, formas bucales,  
troscos, pastillas y líquidos, suspensiones y similares orales. Las cápsulas o  
tabletas que contienen la presente dispersión sólida también se pueden  
combinar con mezclas de otros compuestos activos o filtros y/o diluyentes  
10 inertes tales como los almidones farmacéuticamente aceptables (v.gr.,  
almidón de maíz, papa o tapioca), azúcares, agentes edulcorantes artificiales,  
celulosas en polvo, tales como celulosas cristalina y microcristalina, harinas,  
gelatinas, gomas, etc.

Las formulaciones de tableta se pueden hacer mediante compresión  
15 convencional, granulación en húmedo o métodos de granulación por secado y  
utilizan diluyentes (llenadores) farmacéuticamente aceptables, agentes  
aglutinantes, lubricantes, desintegrantes, agentes de suspensión o  
estabilizadores, incluyendo, pero sin limitarse a, estearato de magnesio, ácido  
esteárico, talco, laurilsulfato de sodio, celulosa microcristalina,  
20 carboximetilcelulosa de calcio, polivinilpirrolidona, gelatina, ácido algínico,  
goma acacia, goma de xantano, citrato de sodio, silicatos complejos,  
carbonato de calcio, glicina, dextrina, sacarosa, sorbitol, fosfato de dicalcio,  
sulfato de calcio, lactosa, caolina, manitol, cloruro de sodio, talco, almidones  
secos y azúcar en polvo. Las formulaciones orales usadas aquí pueden utilizar  
25 formulaciones de liberación retardada o liberación con el tiempo estándares o  
*spansules*. Las formulaciones de supositorio se pueden hacer de materiales  
tradicionales, incluyendo manteca de cacao, con o sin la adición de ceras para  
alterar el punto de fusión de los supositorios, y glicerina. También se pueden  
usar bases de supositorio solubles en agua, tales como polietilenglicol de

varios pesos moleculares.

En la técnica se conocen revestimientos de película útiles con las presentes formulaciones y generalmente consisten de un polímero (usualmente un tipo de polímero de celulosa), un colorante y un plastificante. Ingredientes  
5 adicionales tales como agentes humectantes, azúcares, sabores, aceites y lubricantes se pueden incluir en formulaciones de revestimiento de película para impartir ciertas características al revestimiento de película. Las composiciones y formulaciones aquí también se pueden combinar y procesar como un sólido, después procesar en forma de una cápsula, tal como una  
10 cápsula de gelatina.

El llenador o diluyente puede comprender cualquier sustancia conocida en la técnica que sea útil para la preparación de formulaciones orales sólidas. Llenadores farmacéuticamente aceptables se pueden seleccionar, por ejemplo, de lactosa, celulosa microcristalina, sacarosa, manitol, fosfato de  
15 calcio, carbonato de calcio, celulosa en polvo, maltodextrina, sorbitol, almidón, xilitol y similares.

Las presentes formulaciones también pueden incluir agentes desintegrantes. Estos desintegrantes se pueden seleccionar de aquellos conocidos en la técnica, incluyendo almidón pregelatinizado, glicolato de almidón de sodio y  
20 similares. Otros desintegrantes útiles incluyen croscarmelosa de sodio, crospovidona, almidón, ácido algínico, alginato de sodio, arcillas (v.gr. Veegum o goma de xantano), flóculo de celulosa, resinas de intercambio de iones, o sistemas efervescentes, tales como aquellos que utilizan ácidos alimenticios (tales como ácido cítrico, ácido tartárico, ácido málico, ácido  
25 fumárico, ácido láctico, ácido adípico, ácido ascórbico, ácido aspártico, ácido eritórico, 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.). Los desintegrantes útiles aquí pueden comprender de aproximadamente 4% a

aproximadamente 40% de la composición en peso, preferiblemente de aproximadamente 15% a aproximadamente 35%, muy preferiblemente de aproximadamente 20% a aproximadamente 35%.

Algunos componentes pueden tener funciones múltiples en las formulaciones de la invención, actuando v.gr., tanto como llenador como desintegrante, y su función en una formulación específica puede ser singular aun cuando sus propiedades puedan permitir funcionalidad múltiple.

Las formulaciones farmacéuticas y sistemas de excipiente aquí también pueden contener un antioxidante o una mezcla de antioxidantes, tales como ácido ascórbico. Otros antioxidantes que se pueden usar incluyen ascorbato de sodio y palmitato de ascorbilo, preferiblemente junto con una cantidad de ácido ascórbico. Un intervalo de ejemplo para el antioxidante(a) es de aproximadamente 0.05% a aproximadamente 15% en peso, de aproximadamente 0.5% a aproximadamente 15% en peso, o de aproximadamente 0.5% a aproximadamente 5% en peso. En algunas modalidades, las formulaciones farmacéuticas sustancialmente no contienen antioxidante.

Las composiciones farmacéuticas de ascorbato de bazedoxifeno también se pueden formular con estrógenos esteroideos, tales como estrógenos conjugados, USP. La cantidad de ascorbato de bazedoxifeno usado en la formulación se puede ajustar de conformidad con la dispersión sólida particular usada, la cantidad y tipo de estrógeno esteroideo en la formulación así como la indicación terapéutica particular que se esté considerando. En general, el ascorbato de bazedoxifeno se puede usar en una cantidad suficiente para antagonizar el efecto del estrógeno particular al nivel deseado. El intervalo de dosis de estrógenos conjugados puede ser de aproximadamente 0.3 mg a aproximadamente 2.5 mg, aproximadamente 0.3 mg a aproximadamente 1.25 mg, o aproximadamente 0.3 mg a aproximadamente 0.625 mg. Un intervalo de ejemplo para la cantidad de

ascorbato de bazedoxifeno en una formulación de combinación es aproximadamente 10 mg a aproximadamente 40 mg. Para el estrógeno esteroideo mestranol, una dosis diaria puede ser de aproximadamente 1  $\mu$ g a aproximadamente 150  $\mu$ g, y para etinilestradiol se puede usar una dosis diaria de aproximadamente 1  $\mu$ g a 300  $\mu$ g. En algunas modalidades, la dosis diaria es entre aproximadamente 2  $\mu$ g y aproximadamente 150  $\mu$ g.

Una formulación oral de ejemplo contiene la presente forma de sal o dispersión sólida y los siguientes sistemas de excipiente:

- a) un llenador y desintegrante juntos que comprenden de aproximadamente 1% a aproximadamente 99% en peso (p) de la formulación total, preferiblemente entre aproximadamente 20% y aproximadamente 85% de la formulación, de la cual de aproximadamente 4% a aproximadamente 45% en peso de la formulación total; y
- b) un lubricante que comprende de aproximadamente 0.2% a aproximadamente 15% de la composición (p), en donde el lubricante es estearato de magnesio u otros estearatos metálicos (v.gr., estearato de calcio o estearato de zinc), ésteres de ácido graso (v.gr., estearilfumarato de sodio), ácidos grasos (v.gr., ácido esteárico), alcoholes grasos, behenato de glicerilo, aceite mineral, parafinas, aceites vegetales hidrogenados, leucina, polietilenglicol, laurilsulfatos metálicos y cloruro de sodio.

Los porcentajes anteriormente listados para el llenador, desintegrante y lubricantes se basan en la composición farmacéutica final. El resto de la composición final está compuesto de la forma de sal o dispersión sólida y una cubierta de superficie farmacéuticamente aceptable, tal como un revestimiento o cápsula, como se describe aquí. En algunas modalidades de esta invención, la forma de sal o dispersión sólida comprende de aproximadamente 1% a aproximadamente 99%, aproximadamente 10 a aproximadamente 95 % o aproximadamente 20 a aproximadamente 90% en peso, de la composición final; el revestimiento o cápsula comprende hasta aproximadamente 8%, en

peso, de la formulación.

Numerosos excipientes, formas de dosis, agentes dispersantes y similares adicionales que son adecuados para usarse en conexión con las formas de sal de la invención son conocidos en la técnica y se describen, por ejemplo, en Remington's Pharmaceutical Sciences, 17a. ed., Mack Publishing Company, Easton, Pa., 1965, que se incorpora aquí por referencia en su totalidad.

### Métodos

Como se describe en la patente de E.U.A. No. 5,998,402, bazedoxifeno y sales del mismo son agonistas de estrógeno selectivos con afinidad para el receptor de estrógeno. A diferencia de otros tipos de agonistas de estrógeno, bazedoxifeno y sales del mismo son antiestrogénicos en el útero y pueden antagonizar los efectos tróficos de agonistas de estrógeno en tejidos uterinos. Por consiguiente, las formas de sal y dispersiones sólidas de la invención, y composiciones que contiene las mismas, pueden encontrar muchos usos relacionados con el tratamiento o prevención de estados de enfermedad o síndromes asociados con una deficiencia de estrógeno o un exceso de estrógeno. También se pueden usar en métodos de tratamiento para enfermedades o trastornos que resultan de proliferación o desarrollo anormal, acciones o crecimiento de tejido endometrial o similar al endometrial.

El ascorbato de bazedoxifeno tiene la capacidad para comportarse como un agonista de estrógeno al reducir el colesterol e inhibir la pérdida de hueso. Por consiguiente, la forma de sal o dispersión sólida de la invención es útil para tratar muchos padecimientos que resultan de efectos de estrógeno y exceso o deficiencia de estrógeno incluyendo osteoporosis, hipertrofia prostática, calvicie de patrón masculino, atrofia vaginal y de la piel, acné, sangrado uterino disfuncional, pólipos endometriales, enfermedad de mama benigna, leiomiomas uterinos, adenomiosis, cáncer de ovario, infertilidad, cáncer de

mama, endometriosis, cáncer del endometrio, síndrome de ovario poliquístico, enfermedad cardiovascular, contracepción, enfermedad de Alzheimer, declinación cognitiva y otros trastornos del SNC, así como ciertos cánceres incluyendo melanoma, cáncer de próstata, cáncer de colon, cánceres del  
5 SNC, entre otros. Además, la dispersión sólida se puede usar para contracepción en mujeres pre-menopáusicas, así como terapia de reemplazo de hormonas en mujeres postmenopáusicas (tales como para tratar perturbaciones vasomotoras tales como rubor caliente) o en otros estados de deficiencia de estrógeno en donde sería benéfica la complementación de  
10 estrógeno. También se puede usar en estados de enfermedad en donde la amenorrea es ventajosa, tales como leucemia, ablación endometrial, enfermedad renal o hepática crónica o enfermedades o trastornos de coagulación.

Las formas de sal y dispersiones sólidas de la invención también se puede  
15 usar en métodos de tratamiento y prevención de pérdida de hueso, que puede resultar de un desequilibrio en la formación de un individuo de tejidos óseos nuevos y la reabsorción de tejidos más viejos, conduciendo a una pérdida neta de hueso. Dicho agotamiento de hueso da por resultado una gama de individuos, particularmente en mujeres postmenopáusicas, mujeres que han  
20 sufrido ooforectomía bilateral, aquellas que reciben o que han recibido terapias con corticosteroides prolongadas, aquellas que experimentan disgenesia gonadal, y aquellas que padecen síndrome de Cushing. En necesidades especiales de hueso, incluyendo dientes y hueso oral, el reemplazo también se puede enfrentar usando la dispersión sólida en  
25 individuos con fracturas de hueso, estructuras de hueso defectuosas, y aquellos que reciben cirugías relacionadas con hueso y/o la implantación de prótesis. Además de los problemas anteriormente descritos, la dispersión sólida se puede usar en tratamientos de osteoartritis, hipocalcemia, hipercalcemia, enfermedad de Paget, osteomalacia, osteomalacia, osteomalacia,

mieloma múltiple y otras formas de cáncer que tiene efectos deletéreos sobre tejidos óseos.

Se entiende que los métodos de tratamiento de las enfermedades y síndromes aquí listados implican la administración a un individuo que necesita  
5 dicho tratamiento de una cantidad terapéuticamente efectiva de la forma de sal o dispersión sólida de la invención, o composición que contiene el mismo. Como se usa aquí, por el término "tratamiento", en referencia a una enfermedad, se entiende que se refiere a prevenir, inhibir y/o aliviar la enfermedad.

10 Como se usa aquí, el término "individuo" o "paciente," usado de manera intercambiable, se refiere a cualquier animal, incluyendo mamíferos, preferiblemente ratones, ratas, otros roedores, conejos, perros, gatos, cisnes, ganado vacuno, ovejas, caballos o primates, y muy preferiblemente humanos. Como se usa aquí, la frase "cantidad terapéuticamente efectiva" se refiere a la  
15 cantidad de compuesto activo o agente farmacéutico que induce la respuesta biológica o medicinal en respuesta a un tejido, sistema, animal, individuo o humano que está siendo buscado por un investigador, veterinario, médico u otro médico de clínica, que incluye uno o más de los siguientes:

(1) prevenir la enfermedad; por ejemplo, prevenir una enfermedad, condición o  
20 trastorno en un individuo que pueda estar predispuesto a la enfermedad, condición o trastorno pero aún no experimenta o despliega la patología o sintomatología de la enfermedad;

(2) inhibir la enfermedad; por ejemplo, inhibir una enfermedad, condición o trastorno en un individuo que está experimentando o desplegando la patología  
25 o sintomatología de la enfermedad, condición o trastorno (es decir, detener o hacer más lento el desarrollo posterior de la patología y/o sintomatología); y

(3) aliviar la enfermedad; por ejemplo, aliviar una enfermedad, condición o trastorno en un individuo que está experimentando o desplegando la patología o sintomatología de la enfermedad, condición o trastorno (es decir, revirtiendo

la patología y/o sintomatología).

La invención se describirá con mayor detalle a manera de ejemplos específicos. Los siguientes ejemplos se ofrecen para propósitos ilustrativos, y no deben considerarse para limitar la invención de ninguna manera. Los  
5 expertos en la técnica reconocerán fácilmente una variedad de parámetros no críticos que pueden ser cambiados o modificados para dar esencialmente los mismos resultados.

## **EJEMPLOS**

10

### **EJEMPLO 1**

#### **Preparación de ascorbato de bazedoxifeno**

##### **Síntesis 1**

A una solución de 0.0713 g de ácido ascórbico (polvo cristalino) en 3 ml de  
15 etanol calentado sobre un baño de agua a 70°C después enfriado a aproximadamente 40°C, se añadió mezclando 0.2001 g de base libre de bazedoxifeno. La suspensión resultante se calentó a aproximadamente 50°C durante 10 minutos formando una solución incolora que se enfrió a temperatura ambiente. Una capa líquida amarilla pálida se formó en la base  
20 de del vial de reacción.

2 ml de éter anhidro se añadió a la mezcla enfriada para formar un precipitado amarillo pálido. El líquido sobrenadante se decantó y el precipitado pastoso se  
trituyó con éter (2 x 1 ml) para formar un polvo cremoso de aproximadamente 0.1628 g de ascorbato de bazedoxifeno. El polvo se mantuvo en la oscuridad  
25 y se lavó a chorro con nitrógeno en un contenedor cerrado.

##### **Síntesis 2**

Una solución de 0.7494 g (0.0042499 moles) de ácido ascórbico (polvo cristalino) en 32 ml de etanol con agitación (agitador magnético) se calentó a

70°C hasta que todos los sólidos se disolvieron. La solución se enfrió a 50°C. A la solución enfriada se añadió de una sola vez 2.04 g (0.0042499 moles) de base libre de bazedoxifeno, se agitó y se calentó 3 horas a 60°C formando una solución café-amarillo claro. La reacción se verificó por CLAR con  
5 detección de UV a 220 nm para bazedoxifeno y 245 nm y 265 nm para ácido ascórbico.

La solución clara resultante se enfrió y los solventes se evaporaron bajo presión reducida hasta sequedad para dar un sólido amarillo-café. El monitoreo por CLAR mostró que la progresión de reacción a 1 hora a 60°C fue  
10 sustancialmente el mismo que a 3 horas a 60°C. El sólido amarillo se molió con mortero y pistilo para dar 2.84 g de ascorbato de bazedoxifeno.

#### Purificación 1

82 mg del ascorbato de bazedoxifeno se disolvió en 1 ml de etanol/agua con algo de calor. La solución se precipitó con éter dietílico para dar polvo amorfo  
15 amarillo.

#### Purificación 2

A unos cuantos miligramos de ascorbato de bazedoxifeno se añadió alcohol isopropílico seguido por unas cuantas gotas de acetona. La mezcla resultante  
20 se calentó a 50°C durante 3-5 minutos para formar una solución amarilla clara. La solución después se enfrió a aproximadamente 4°C para formar un precipitado amarillo-café (no cristalino).

#### Purificación 3

Aproximadamente 1 g de ascorbato de bazedoxifeno se colocó en un matraz cónico y aproximadamente 25 ml de acetona se añadió con mezclado. Unas  
25 cuantas gotas (5 gotas) de agua se añadieron con mezclado para dar una solución café rojiza. Se añadió éter (aproximadamente 15 ml) para precipitar

la sal formando un precipitado turbio, café, gomoso. La trituración con éter dio un precipitado café (aproximadamente 0.95 g). Este sólido fino café se almacenó en un desecador bajo vacío a temperatura ambiente.

5

## **EJEMPLO 2**

### **Caracterización de ascorbato de bazedoxifeno**

#### **Resonancia magnética nuclear de protones (H-RMN)**

El espectro de RMN de protones de ascorbato de bazedoxifeno preparado de conformidad con el ejemplo 1 en sulfóxido de dimetilo desnaturalizado (DMSO<sub>d</sub><sub>6</sub>) fue consistente con la estructura de ascorbato de bazedoxifeno.

#### **Espectro de masa**

El ascorbato de bazedoxifeno preparado de conformidad con el ejemplo 1 dio M+H:471.3 (PM=470.3) para bazedoxifeno; 2M+H:941.6; M'+H: 177.1 para ácido ascórbico.

#### **Cromatografía de líquidos de alto rendimiento (CLAR)**

El ascorbato de bazedoxifeno preparado de conformidad con el ejemplo 1 se analizó por corrida de CLAR bajo las siguientes condiciones:

20 Columna: Prodigy ODS-2, 5 µm de 150 cm x 4.6 mm

Detector: Ultravioleta (UV) a 220 nm

Temperatura de columna: 30°C

Velocidad de flujo: 1.5 ml/min

Fase móvil: 680 ml de: 2 l de agua que contenía 6.8 g de fosfato de potasio monobásico (ajustado a pH 3.0 con ácido fosfórico); y 320 ml de acetonitrilo.

Los tiempos de retención para bazedoxifeno y ácido ascórbico fueron consistentes con la estructura.

### Difracción de rayos X en polvo (XRPD)

Se llevaron a cabo análisis de XRPD en un difractómetro de rayos X en polvo Scintag X2 usando radiación de Cu K  $\alpha$ . El polvo del tubo y el amperaje se fijaron a 45 kV y 40 mA, respectivamente. Las ranuras de divergencia y dispersión se fijaron a 1° y la ranura receptora se fijó a 0.2 mm. Se usó escudriñamiento teta-dos teta continuo a 3°/min (0.4 seg/0.02° de paso) de 3 a 40°2 $\theta$ . Las muestras se empacaron en un soporte de muestras de cuarzo. La difracción de rayos X en polvo de ascorbato de bazedoxifeno preparado de conformidad con el ejemplo 1 mostró un material amorfo.

10

### Calorímetro de escudriñamiento diferencial (DSC)

3.542 mg de ascorbato de bazedoxifeno preparado de conformidad con el ejemplo 1 se prepararon en PERICIN ELMER Pyris 1 DSC con un auto-muestreador y se calentaron de 25°C a 150°C a un régimen de 5°C/min. La salida se midió en una charola de aluminio sellada. El material pareció ser amorfo con una transición de vidrio (Tv) a 50.02°C.

15

### Análisis termogravimétrico (TGA)

1.377 mg de ascorbato de bazedoxifeno preparado de conformidad con el ejemplo 1 se colocó en un PERICIN ELMER Pyris 1 TGA con una charola de muestra abierta lavada a chorro con nitrógeno. La muestra se escudrió de 25°C a 300°C a un régimen de 5°C/min.

La muestra de ascorbato de bazedoxifeno perdió aproximadamente 11% a 100°C (correspondiente a aproximadamente una molécula de agua) y después ocurrió otra pérdida de peso entre 105°C y 160°C.

25

## EJEMPLO 3

### Solubilidad en equilibrio de ascorbato de bazedoxifeno en ácido acético

0.0005 M a 37°C

Cada uno de 10.1, 10.0 y 9.8 miligramos de ascorbato de bazedoxifeno, preparado de conformidad con el ejemplo 1, se puso en 3 ml de ácido acético 0.0005 M y después se colocó en un baño de agua a 37°C. Las muestras se  
5 hicieron girar a 50 rotaciones/minuto durante 18 horas. Las muestras de AU se filtraron a través de un filtro de 0.2  $\mu$ m (Nylon Acrodisc). Las muestras se analizaron por CLAR. La solubilidad en equilibrio de ascorbato de bazedoxifeno se determinó que era de 1.66 mg/ml.

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#### **EJEMPLO 4**

##### **Estabilidad del lote**

Un lote de ascorbato de bazedoxifeno preparado de conformidad con el ejemplo 1 se almacenó durante un tiempo en un vial sobre una mesa cubierto  
15 en la parte superior con lámina delgada de aluminio. A 1 mes y a 75 días, se analizaron varios miligramos por CLAR. En el punto de tiempo de 1 mes, CLAR mostró 99.86% de recuperación. En el punto de tiempo de 75 días, CLAR mostró 95.3% de recuperación.

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#### **EJEMPLO 5**

##### **Dispersión sólida de ascorbato de bazedoxifeno con PVP (1:1 p/p)**

##### **Preparación**

0.5128 g de PVP KI 7 (PLASDONE C-15 "Povidona USP"; ISP Technologies, Inc.) se disolvió en 10 ml de etanol. Después, 0.5032 g de ascorbato de  
25 bazedoxifeno preparado de conformidad con el ejemplo 1 se añadió con agitación magnética. El matraz se lavó a chorro con nitrógeno gaseoso y se puso en un baño de agua a 70°C durante 10 minutos. La mezcla se volvió una solución café clara y se dejó en el baño de agua sin calentar durante 30

minutos. Los solventes se evaporaron bajo presión reducida durante 6 horas.

El material café vítreo sólido resultante se molió con un mortero y pistilo para dar un polvo fino café-beige de 0.9244 g con una fluidez muy buena que no se solidificó durante la noche.

- 5 Los tiempos de retención de CLAR y los espectros de UV fueron consistentes con la composición de la dispersión. XRPD mostró que la dispersión fue amorfa. TGA reveló que 2.7% de pérdida de peso hasta aproximadamente 100°C se creyó que se debió a pérdida de una molécula de agua.

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#### **EJEMPLO 6**

##### **Solubilidad de dispersión sólida de ascorbato de bazedoxifeno con PVP**

**(1:1 p/p) en ácido acético 0.0005 M a 37°C**

- Muestras de dispersión sólida de ascorbato de bazedoxifeno del ejemplo 5
- 15 (aprox. 20 mg cada una) se colocaron en viales a los cuales se añadió 1 ml de ácido acético 0.0005 M. La mezcla se agitó manualmente durante 10 segundos y después se colocó en un baño de agua de 37°C a 50 rotaciones/minuto durante 18 horas. Las muestras después se filtraron a través de filtros de disco de jeringa (13 mm de Nylon de 0.2  $\mu$ m (Whatman)).
- 20 Resultados: 12.364 mg/ml.

#### **EJEMPLO 7**

##### **Estabilidad del volumen de dispersión sólida**

- 25 La estabilidad del volumen de dispersión sólida de ascorbato de bazedoxifeno con PVP (1:1 p/p) del ejemplo 5 se evaluó a 1 mes y a 3 meses de conformidad con el siguiente procedimiento. Muestras de 5-6 g de dispersión sólida de ascorbato de bazedoxifeno en viales envueltos en lámina delgada se colocaron sobre una mesa a temperatura ambiente durante un mes o durante

tres meses. Las muestras después se analizaron por CLAR para dar los siguientes resultados:

Inicial 44.79% (uso a valor);

1 mes a temperatura ambiente: 43.14% (uso a valor);

5 3 meses a temperatura ambiente: 44.44% (uso a valor).

Varias modificaciones de la invención, además de aquellas descritas aquí, serán evidentes para los expertos en la técnica a partir de la descripción anterior. Se pretende que dichas modificaciones también caigan dentro del alcance de las reivindicaciones anexas. Cada una de las publicaciones y,  
10 referencias, incluyendo libros y patentes, citados en la presente solicitud se incorpora aquí por referencia en su totalidad.

### **NOVEDAD DE LA INVENCION**

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### **REIVINDICACIONES**

- 1.- Una sal de ácido ascórbico de bazedoxifeno.
- 2.- Una composición que comprende la sal de la reivindicación 1 y un vehículo farmacéuticamente aceptable.
- 20 3.- Un método para preparar la sal de la reivindicación 1, caracterizado además porque comprende combinar la base libre de bazedoxifeno y ácido ascórbico.
- 4.- El método de conformidad con la reivindicación 3, caracterizado además porque cantidades aproximadamente equimolares de base libre de  
25 bazedoxifeno y ácido ascórbico se combinan.
- 5.- El método de conformidad con la reivindicación 3 o la reivindicación 4, caracterizado además porque dicha combinación se lleva a cabo en un solvente.
- 6.- El método de conformidad con la reivindicación 5, caracterizado además

porque el solvente comprende un alcohol.

7.- El método de conformidad con la reivindicación 6, caracterizado además porque el alcohol comprende etanol.

8.- Una sal preparada por el método de cualquiera de las reivindicaciones 3 a 5 7.

9.- Una dispersión sólida que comprende la sal de la reivindicación 1 y un agente dispersante.

10.- La dispersión sólida de conformidad con la reivindicación 9, caracterizada además porque el agente dispersante comprende una celulosa, hialuronato, 10 alginato, polisacárido, heteropolisacárido, poloxámeros, poloxaminas, etilenoacetato de vinilo, polietilenglicol, dextrano, polivinilpirrolidona, quitosán, alcohol polivinílico, propilenglicol, acetatos de polivinilo; fosfatidilcolinas, miglitol, ácido poliláctico; ácido polihidroxibutírico; mezcla de los mismos o copolímeros de los mismos.

15 11.- La dispersión sólida de conformidad con la reivindicación 9, caracterizada además porque el agente dispersante comprende polivinilpirrolidona.

12.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 9 a 11, caracterizada además porque la relación en peso de la sal al agente dispersante es de aproximadamente 1:99 a aproximadamente 20 99:1.

13.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 9 a 11, caracterizada además porque la relación en peso de la sal al agente dispersante es de aproximadamente 1:99 a aproximadamente 60:40.

25 14.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 9 a 11, caracterizada además porque la relación en peso de la sal al agente dispersante es de aproximadamente 1 : 99 a aproximadamente 10:90.

15.- La dispersión sólida de conformidad con cualquiera de las

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reivindicaciones 9 a 11, caracterizada además porque la relación en peso de la sal al agente dispersante es de aproximadamente 5:95.

16.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 9 a 11, caracterizada además porque la relación en peso de la sal al agente dispersante es de aproximadamente 40:60, a aproximadamente 60:40.

17.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 9 a 11, caracterizada además porque la relación en peso de la sal al agente dispersante es de aproximadamente 1:1.

18.- Un método para preparar la dispersión sólida de conformidad con cualquiera de las reivindicaciones 9 a 17, que comprende: a) combinar la sal y el agente dispersante en solución, en donde la solución comprende un solvente; y b) remover solvente para dar la dispersión sólida.

19.- El método de conformidad con la reivindicación 18, caracterizado además porque el solvente es un solvente orgánico.

20.- El método de conformidad con la reivindicación 19, caracterizado además porque el solvente comprende un alcohol.

21.- El método de conformidad con la reivindicación 20, caracterizado además porque el alcohol comprende etanol.

22.- Una dispersión sólida preparada por el método de cualquiera de las reivindicaciones 18 a 21.

23.- Un método para preparar la dispersión sólida de conformidad con cualquiera de las reivindicaciones 9 a 17 que comprende: a) combinar la sal con agente dispersante fundido para formar una mezcla líquida; y b) solidificar la mezcla líquida para formar la dispersión sólida.

24.- El método de conformidad con la reivindicación 23, caracterizado además porque el agente dispersante fundido se prepara calentando el agente dispersante a una temperatura por arriba de aproximadamente 30°C.

25.- El método de conformidad con la reivindicación 23, caracterizado además

porque la solidificación comprende enfriar la mezcla líquida a una temperatura en o por debajo de aproximadamente 25°C.

26.- Una dispersión sólida preparada por el método de conformidad con la reivindicación 23.

5 27.- Una composición que comprende la dispersión sólida de conformidad con cualquiera de las reivindicaciones 9 a 17 y un vehículo farmacéuticamente aceptable.

28.- Un método para tratar a un mamífero que tiene una enfermedad o síndrome asociado con deficiencia de estrógeno o exceso de estrógeno que  
10 comprende administrar al mamífero una cantidad terapéuticamente efectiva de la sal de la reivindicación 1.

29.- Un método para tratar a un mamífero que tiene una enfermedad o trastorno asociado con proliferación o desarrollo anormal de tejidos endometriales que comprende administrar al mamífero una cantidad  
15 terapéuticamente efectiva de la sal de la reivindicación 1.

30.- Un método para reducir colesterol en un mamífero que comprende administrar al mamífero una cantidad terapéuticamente efectiva de la sal de la reivindicación 1.

31.- Un método para inhibir pérdida de hueso en un mamífero que comprende  
20 administrar al mamífero una cantidad terapéuticamente efectiva de la sal de la reivindicación 1.

32.- Un método para tratar cáncer de mama en un mamífero que comprende administrar al mamífero una cantidad terapéuticamente efectiva de la sal de la reivindicación 1.

25 33.- Un método para tratar a mujeres postmenopáusicas para una o más perturbaciones vasomotoras que comprende administrar a dichas mujeres postmenopáusicas una cantidad terapéuticamente efectiva de la sal de la reivindicación 1.

34.- El método de conformidad con la reivindicación 33, caracterizado además

porque dicha perturbación vasomotora es rubor caliente.

35.- El uso de un compuesto de conformidad con la reivindicación 1, en la preparación de un medicamento para tratar a un mamífero que tiene una enfermedad o síndrome asociado con deficiencia de estrógeno o exceso de estrógeno; o para tratar a un mamífero que tiene una enfermedad o trastorno asociado con proliferación o desarrollo anormal de tejidos endometriales; o reducir colesterol en un mamífero; o inhibir pérdida de hueso en un mamífero; o tratar cáncer de mama en un mamífero; o tratar a mujeres postmenopáusicas para una o más perturbaciones vasomotoras.

**RESUMEN DE LA INVENCION**

La presente invención está dirigida a ascorbato de bazedoxifeno,  
composiciones que contienen el mismo, dispersiones del mismo,  
5 preparaciones del mismo y usos del mismo.

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P06/1574F

## PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To: COZEN O'CONNOR  
 Attn: Goddard, Christine A.  
 1900 Market Street  
 Philadelphia, Pennsylvania 19103  
 UNITED STATES OF AMERICA

RECEIVED  
 COZEN IP DEPT

NOTIFICATION OF TRANSMITTAL OF  
 THE INTERNATIONAL SEARCH REPORT AND  
 THE WRITTEN OPINION OF THE INTERNATIONAL  
 SEARCHING AUTHORITY, OR THE DECLARATION

AUG 08 2005

DUE DATE 9-2-05

MAX DATE 10-2-05

DOCKETED BY 1-2-05

supp  
 10/2/05  
 Art. 34 & max date 10/3  
 (PCT Rule 44.1)

Date of mailing  
 (day/month/year)

02/08/2005

Applicant's or agent's file reference

AM101505 PCT WYTH0092-500 L163175

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2005/011663

International filing date  
 (day/month/year)

07/04/2005

Applicant

WYETH

WYETH  
 AUG 15 2005  
 PATENT DEPT.

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 18:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 48):

When? The time limit for filing such amendments is normally 3 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes  
 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.88

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 18 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 30 months from the priority date, participate in the national phase 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 18 months.

See the Annex to Form PCT/ISA/220 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.O. Box 1 Patentkanal 2  
 NL-6800 HV Rijswijk  
 Tel. (+31-70) 340-0040, Tx. 31 851 890 rlx  
 Fax (+31-70) 340-3016

Authorized officer

Angela Lopez Navarro

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## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 18. 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 these 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 18

The applicant has, after having received the international search report, the 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 18 except where, e.g. the applicant wants the claim 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 provision of protection is available in some States only.

## What parts of the international application may be amended?

Under Article 18, 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 20 or, where applicable, Article 41.

## When?

Within 2 months from the date of transmittal of the international search report or 18 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 40.1).

## 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 Examining Authority (Rule 40.5).

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

## How?

Either by cancelling one or more of the 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 amended, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 703.1j).

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

## What documents may/may not accompany the amendments?

Letter (Section 203(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 18(1)" (see below, under "Statement under Article 18(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.



## PATENT COOPERATION TREATY

## PCT

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## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|                                                              |                                                                                               |                                                                |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Applicant's or agent's file reference<br><b>AKI01585 PCT</b> | <b>FOR FURTHER ACTION</b><br>see Form PCT/ISA/220 as well as, where applicable, Item 5 below. |                                                                |
| International application No.<br><b>PCT/US2005/011663</b>    | International filing date (day/month/year)<br><b>07/04/2005</b>                               | (Earliest) Priority Date (day/month/year)<br><b>08/04/2004</b> |
| Applicant<br><b>WYETH</b>                                    |                                                                                               |                                                                |

This International Search Report has been prepared by the 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 4 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 31.2(b)).

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosure in the international application, see Box No. 1.

2. ☒ Certain claims were found unsearchable (See Box III).

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:

**RAZEDUXIFENE ASSOCIATE AS SELECTIVE ESTROGEN RECEPTOR MODULATOR**

## 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

 Int. Serial Application No. 111158  
 PCT/US2005/011663

## A. CLASSIFICATION OF SUBJECT MATTER

IPC / C07D209/12 A61K31/55 A61P5/24

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

## B. FIELDS SEARCHED

Magnetic documents searched (classification system followed by classification symbols)  
IPC 7 C07D

Documentation searched other than magnetic documentation to the extent that such documents are included in the fields searched

Electronic data bases consulted during the international search phase of data base and, where pertinent, search terms used

EPO-Internal, CIBM A95 Data, WPI Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages                                                                       | Relevant to claim No. |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X        | WO 02/03987 A2 (AMERICAN HOME PRODUCTS CORPORATION, USA)<br>17 January 2002 (2002-01-17)<br>see p. 33, l. 21 to 32; p. 37, w/ granulation and example 3; | 1-35                  |

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

## \* Special categories of cited documents:

- \*A\* documents defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier documents that published on or after the international filing date
- \*L\* documents which may throw doubts on priority claimed or which is cited to establish the publication date of another claim or other special reason (to be specified)
- \*O\* documents 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 documents published after the international filing date or priority date and not in conflict with the application but cited to further extend 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 considered with one or more other such documents, upon consideration being given to a person skilled in the art.

\*A\* document number of the same patent family

Date of the actual completion of the international search

25 July 2005

Date of mailing of the international search report

02/08/2005

Name and mailing address of the ISA

 European Patent Office, P.O. Box 2911  
 NL - 2200 HP Rijswijk  
 Tel. (+31-70) 340-2040, Te. 31 881 00 00  
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Authorized officer

Traegler-Goeldel, M

49

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2005/011663

11/17/05 7/9

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

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

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 28-35 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 13.4(a).

## Box II 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 extra 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 claim Nos.:

Remarks on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Indicate on parent family members

In related Application No. 0111970  
PCT/US2005/011663

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| WO 0203987                                | A2                  | 17-01-2002                 |                     |
|                                           |                     | AU 7174101 A               | 21-01-2002          |
|                                           |                     | BR 0112242 A               | 24-05-2003          |
|                                           |                     | CA 2415058 A1              | 17-01-2002          |
|                                           |                     | CN 1450895 A               | 22-10-2003          |
|                                           |                     | EP 1309327 A2              | 14-05-2003          |
|                                           |                     | HU 0301422 A2              | 29-09-2003          |
|                                           |                     | JP 2004502733 T            | 29-01-2004          |
|                                           |                     | MX PA02012891 A            | 24-10-2003          |
|                                           |                     | NO 20030030 A              | 03-03-2003          |
|                                           |                     | PL 365875 A1               | 10-01-2005          |
|                                           |                     | US 2002031548 A1           | 14-03-2002          |
|                                           |                     | ZA 200301004 A             | 05-05-2004          |

## PCT COOPERATION TREATY

11/11/06

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From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

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/220FOR FURTHER ACTION  
See paragraph 2 belowInternational application No.  
PCT/US2005/011663International filing date (day/month/year)  
07.04.2005Priority date (day/month/year)  
08.04.2004International Patent Classification (IPC) or both national classification and IPC  
C07D209/12, A61K31.65, A61P6/24Applicant  
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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D-53208 Munich  
Tel. +49 89 2369 - 0 Fax: 622689 opma: d  
Fax: +49 89 2369 - 4485

Authorized Officer:

Trösgler-Goschke, M  
Telephone No. +49 89 2369-6271



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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
PCT/US2005/011663**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. mode of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to 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:

non/3

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
PCT/US2005/011863**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. 28-35 with respect to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 28-35 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.
- ☐ 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-6is of the Administrative Instructions.
- ☐ See separate sheet for further details

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/011663

**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 | 3-7, 11, 16-17, 19-21, 23-25,    |
|                               | No: Claims  | 1, 2, 8-10, 12-14, 18, 22, 27-35 |
| Inventive step (IS)           | Yes: Claims |                                  |
|                               | No: Claims  | 1-35                             |
| Industrial applicability (IA) | Yes: Claims | 1-27                             |
|                               | No: Claims  |                                  |

**2. Citations and explanations**

see separate sheet

**Box No. VI Certain documents cited**

**1. Certain published documents (Rules 43bis.1 and 70.10)**

and/or

**2. Non-written disclosures (Rules 43bis.1 and 70.9)**

see form 210

00065

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

International application No.

PCT/US2005/011663

**re item III:**

Claims 28 to 35 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).

**re item V:****1. State of the art**

The substantive examination is being performed on the basis of the documents cited in the International Search Report:

D1: WO 02/03987 A2 (AMERICAN HOME PRODUCTS CORPORATION, USA) 17  
January 2002 (2002-01-17)

**2. Novelty**

The novelty of claims 1, 2, 9, 10, 12-14, 18, 22, 27-35 is destroyed by the disclosure of example 3 and the wet granulation on p. 37 according to table 1, wherein the drug and ascorbic acid is mixed and sodium lauryl sulfate is dissolved in water and this solution is used to granulate that mixture. This procedure results inevitably in a certain amount of ascorbic acid salt of bazodoxifene being formed. Therefore claims 1, 2, 8 (directed to a product), 9, 10, 12-14, 18, 22 and 27 to 35 do not fulfil the requirements of Art. 33 (2) PCT.

**3. Inventive step**

The present application is concerned with the ascorbic acid of bazodoxifene, a potent selective estrogen receptor modulator, widely known from the prior art. If the problem underlying the present application were to be seen in the provision of a further salt of bazodoxifene, the solution of this problem is obvious, since the salt with ascorbic acid is known from the prior art, as set out above under item 2. Also the method of preparing said salt according to claim 3 is in principle already known from D1, p. 33: there is disclosed a pharmaceutical composition which comprises 0.1%-25% bazodoxifene and 0.5% to 15%

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

International application No.

PCT/US2005/011663

ascorbic acid. Whether the problem of providing a further salt of bazedoxifene (presumed it were novel), showing an unexpected effect as compared to the closest prior art acetate salt, has been solved, cannot be decided since no such data are given in the specification. Therefore claims 1-35 do not fulfil the requirements of Art. 33 (3) PCT.

**4. Industrial applicability**

For the assessment of the present claims 28 to 35 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. Presumed the claims were in accord with Art. 33 (2) and (3), no objection arises with respect to claims 1 to 27.

**in item VII:**

1. According to the PCT International Search and Examination Guidelines, chapter 5.26 and 5.27, a claim, which defines a product in terms of the process by which it is made, is as a whole directed to a product. Such a claim is not novel if a prior art product, even if made by an undisclosed process, appears to be inherently the same, as it is the case in the present application. Therefore, since claims 9 and 22 are formulated as a product by process, these claims not being novel, are not admissible according to Art. 6.
2. According to the PCT International Search and Examination Guidelines, chapter 5.40, claims 3, 12-17, 24 and 25 are not admissible under Art. 6 PCT, due to the use of the term "about", rendering the claims unclear.

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

(19) World Intellectual Property Organization  
International Bureau

WORLD INTELLECTUAL PROPERTY ORGANIZATION

(43) International Publication Date  
17 January 2003 (17.01.2002)

PCT

(10) International Publication Number  
WO 02/03987 A2(51) International Patent Classification: A61K 31/404,  
8:20(74) Agent: MIŁOWSKY, Arnold, S., et al.; American  
Home Products Corporation, Patent Law Department, Five  
Chalks Farm, Madison, NJ 07940 (US).

(21) International Application Number: PCT/US01/20993

(22) International Filing Date: 29 June 2001 (29.06.2001)

(23) Filing Language: English

(24) Publication Language: English

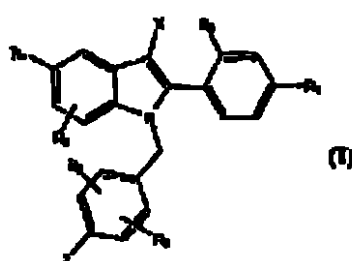
(30) Priority Date: 6 July 2000 (06.07.2000) US  
60/216,193(71) Applicant: AMERICAN HOME PRODUCTS COR-  
PORATION (US/US); Five Chalks Farm, Madison, NJ  
07940-0874 @ (US).(72) Inventors: BENJAMIN, Eric, Jost; 4 Hobbs Court,  
Parsippany, NJ 08970 (US); DULIN, Wendy, Ann; 25  
Richard Street, Slacksburg, NY 10974 (US); SURYAWAN-  
SHI, Jiwaji, Guleshr; 3 Downen Court, Rockaway, NJ  
07866 (US).(51) Designated States (optional): AE, AQ, AL, AM, AR, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GR, GU, HK,  
HM, HR, HU, ID, IL, IN, IS, JP, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,  
SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.(54) Designated States (optional): ARIPO patent (CH, DM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BR, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

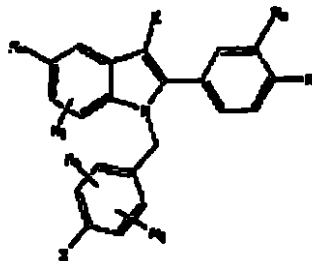
— without international search report and to be republished  
upon receipt of that report

(Continued on next page)

(54) Title: PHARMACEUTICAL COMPOSITIONS OF ESTROGENIC AGENTS



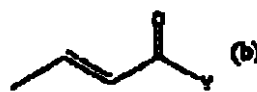
(I)



(II)



(a)



(b)



(c)



(d)

(57) Abstract: This invention comprises novel pharmaceutical carrier or excipient systems and oral pharmaceutical formulations comprising as an active ingredient raloxifene, amoxifen, doxofen, estradiol, estrone, or CP 134,155, or analog thereof, or a compound of formula (I) or (II), wherein Z is a moiety selected from the group of formulas (a), (b) or (c), wherein R<sub>1</sub> is selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> ester alkyl ethers thereof, benzyl, or halogen; or C<sub>1</sub>-C<sub>4</sub> halogenated ethers; R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are H, OH or C<sub>1</sub>-C<sub>12</sub> ester or alkyl ether thereof, halogen, or C<sub>1</sub>-C<sub>4</sub> halogenated ethers, cyano, C<sub>1</sub>-C<sub>4</sub> alkyl, or CF<sub>3</sub>, with the proviso that, when R<sub>1</sub> is H, R<sub>2</sub> is not OH; Y is the moiety: formula (d), wherein R<sub>7</sub> and R<sub>8</sub> are alkyl or concatenated together to form an optionally substituted, nitrogen-containing ring; or a pharmaceutically acceptable salt thereof; and excipients chosen from: pharmaceutical fillers, glidants, lubricants, wetting agents and antioxidants.

WO 02/03987 A2

WYTH0092-500  
163477

PATENT COOPERATION TREATY

MPS/CAE  
PCT/US05/011853  
11/11/05

From the INTERNATIONAL BUREAU

AM101585 WO PCT

NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

GOCCARD, Christine A  
Cohen O'Connor  
1900 Market Street  
Philadelphia, PA 19103  
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)  
23 June 2005 (23.06.2005)

Applicant's or agent's file reference  
AM101585 PCT

International application No.  
PCT/US05/011853

International publication date (day/month/year)

Applicant

WYETH et al

IMPORTANT NOTIFICATION

International filing date (day/month/year)  
07 April 2005 (07.04.2005)

Priority date (day/month/year)  
08 April 2004 (08.04.2004)

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) referred to in the application(s) whose priority is claimed. Unless otherwise indicated by the letters "N2" in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- If applicable) The letters "NR" appearing in the right hand column denotes a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office of the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under this Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- If applicable) An asterisk (\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit provided in Rule 17.1(a) or the request to receive and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office on the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date

Priority document No.

Country or region of Office  
of PCT receiving Office

Date of receipt  
of priority document

08 April 2004 (08.04.2004)

60/620,454

US

17 May 2005 (12.05.2005)

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

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Form PCT/IB/001 (January 2004)

Lebro folios 69, 70, 71 Tarjetas y Extracto

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE  
PCT**

PATENTE DE INVENCION

11

MODELO DE UTILIDAD [ ]

- ♦ Indicación de que se solicita la concesión de una patente [ ]
- ♦ Datos de Identificación del solicitante o de la persona que 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 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 un Esquema de Trazado [ ]
- ♦ Datos de Identificación del solicitante o de la persona que presenta la solicitud [ ]
- ♦ Representación gráfica del esquema trazado [ ]
- ♦ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ]

INCOMPLETA [ ]

  
Firma Responsable:

Fecha

06 OCT 2008

Carrera 13 No. 27-40 Piso 5, 7 y 10  
Commutador: 3 82 08 40  
Fax: 350 62 20  
E-mail: [info@alc.gov.co](mailto:info@alc.gov.co)  
[www.slc.gov.co](http://www.slc.gov.co)  
Bogotá, D.C., Colombia