



HU000030072T2

(19) **HU**(11) Lajstromszám: **E 030 072**(13) **T2****MAGYARORSZÁG**
Szellemi Tulajdon Nemzeti Hivatala**EURÓPAI SZABADALOM**
SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 11 781299**
(22) A bejelentés napja: **2011. 05. 12.**

(51) Int. Cl.: **A61K 311/37** (2006.01)
A61P 5/24 (2006.01)

(96) Az európai bejelentés bejelentési száma:
EP 20110781299

(86) A nemzetközi (PCT) bejelentési szám:
PCT/US 11/036311

(97) Az európai bejelentés közzétételi adatai:
EP 2568806 A1 **2011. 11. 17.**

(87) A nemzetközi közzétételi szám:
WO 11143469

(97) Az európai szabadalom megadásának meghirdetési adatai:
EP 2568806 B1 **2016. 05. 11.**

(30) Elsőbbségi adatok:
334095 P **2010. 05. 12.** **US**

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(54) **Terápiás előírások**

Az európai szabadalom ellen, megadásának az Európai Szabadalmi Közlönyben való meghirdetésétől számított kilenc hónapon belül, felszólalást lehet benyújtani az Európai Szabadalmi Hivatalnál. (Európai Szabadalmi Egyezmény 99. cikk(1))

A fordítást a szabadalmat az 1995. évi XXXIII. törvény 84/H. §-a szerint nyújtotta be. A fordítás tartalmi helyességét a Szellemi Tulajdon Nemzeti Hivatala nem vizsgálta.

(19)



(11)

EP 2 568 806 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
11.05.2016 Bulletin 2016/19

(21) Application number: **11781299.0**

(22) Date of filing: **12.05.2011**

(51) Int Cl.:
A61K 31/137 ^(2006.01) **A61P 5/24** ^(2006.01)

(86) International application number:
PCT/US2011/036311

(87) International publication number:
WO 2011/143469 (17.11.2011 Gazette 2011/46)

(54) **THERAPEUTIC REGIMENS**

THÉRAPIEPLÄNE

SCHÉMAS THÉRAPEUTIQUES

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME

(30) Priority: **12.05.2010 US 334095 P**

(43) Date of publication of application:
20.03.2013 Bulletin 2013/12

(60) Divisional application:
16163037.1

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US-A1- 2007 155 664 US-A1- 2008 114 048
US-A1- 2010 105 733

EP 2 568 806 B1

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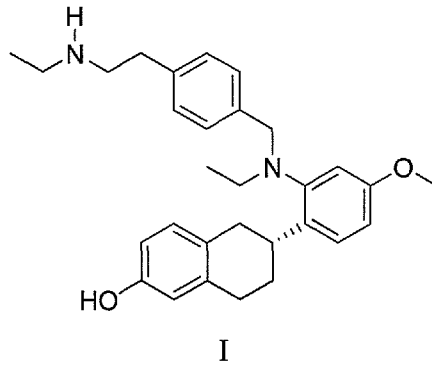
Description

RELATED APPLICATION

5 [0001] This application claims the benefit of U.S. Provisional Application No. 61/334,095, filed on May 12, 2010.

BACKGROUND OF THE INVENTION

10 [0002] The compound of formula I ((R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)-benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol) and its salts are described and claimed in U.S. Patent No. 7,612,114 B2.



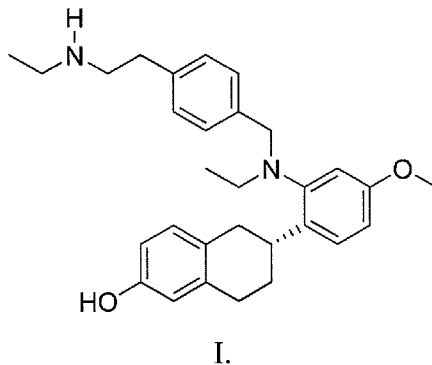
25 [0003] Use of the compound formula I for the treatment of vasomotor symptoms is described in WO2008/002490 and WO2009137104 discloses the administration of 20mg daily. While the effectiveness of compound 1 and its salts in the treatment of vasomotor symptoms has been described, improved dosing regimens would benefit those suffering from vasomotor symptoms.

30 SUMMARY OF THE INVENTION

[0004] This invention relates to clinically useful therapeutic dosing regimens for the compound of formula I ((R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol) as its dihydrochloride salt.

35 [0005] This invention also includes unit dosage forms containing the compound of formula I ((R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol) as its dihydrochloride salt.

[0006] In certain embodiments, this invention includes a unit dosage form suitable for administration to a human comprising 10 mg of the compound of formula I as its dihydrochloride salt



[0007] In a particular embodiment, the 10 mg of the compound of Formula 1 is present as its dihydrochloride salt.

55 [0008] In certain embodiments, this invention includes a unit dosage form suitable for administration to a human comprising 5 mg of the compound of formula I as its dihydrochloride salt.

[0009] In certain embodiments, this invention includes a unit dosage form suitable for administration to a human comprising 2.5 mg of the compound of formula I as its dihydrochloride salt.

[0010] In certain embodiments, this invention includes a unit dosage form suitable for administration to a human

comprising 1 mg of the compound of formula I as its dihydrochloride salt.

[0011] In some embodiments, the unit dosage form comprising the compound of formula I contains 1mg, 2.5 mg, 5 mg or 10 mg as a dihydrochloride salt.

[0012] In some embodiments, the unit dosage form comprising the compound of formula I contains 1mg, 2.5 mg, 5 mg or 10 mg as a salt, wherein said salt is a hydrogen chloride salt wherein said hydrogen chloride is present in a stoichiometry of at least one hydrogen chloride molecule but no more than 2.1 hydrogen chloride molecules for each molecule of formula I.

[0013] In one aspect, the unit dosage form is for once daily administration. In another aspect, the unit dosage form is for oral administration. In yet another aspect the unit dosage form is suitable for once daily, oral administration.

[0014] In some instances, the unit dosage form further comprises one or more pharmaceutically acceptable excipients.

[0015] In certain embodiments, the dosage form unit is a tablet or capsule suitable for oral administration.

[0016] In certain embodiments, the dosage unit form, after administration, is essentially dissolved in the stomach prior to being released into the small intestines.

[0017] In some instances, the dosage form unit is not coated with an acid resistant coating.

[0018] In certain embodiments, the intended human is a woman.

[0019] This invention also includes treating vasomotor disturbances in a peri-or post-menopausal woman in need thereof comprising administering to the woman a unit dosage form comprising 10 mg of the compound of formula I ((R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol) as its dihydrochloride salt.

[0020] This invention also includes treating vasomotor disturbances in a post-menopausal woman in need thereof comprising administering to the woman a unit dosage form containing 10 mg of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol as its dihydrochloride salt.

[0021] In some instances, the methods of this invention comprise the once-daily, oral administration of 10 mg of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol as its dihydrochloride salt.

[0022] This invention also includes treating vasomotor disturbances in a peri-or post-menopausal woman in need thereof comprising administering to the woman a unit dosage form comprising 1 mg, 2.5 mg or 5 mg of the compound of formula I ((R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol) as its dihydrochloride salt.

[0023] This invention also includes treating vasomotor disturbances in a post-menopausal woman in need thereof comprising administering to the woman a unit dosage form containing 1 mg, 2.5 mg or 5 mg of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol as its dihydrochloride salt.

[0024] In some instances, the methods of this invention comprise the once-daily, oral administration of 1 mg, 2.5 mg or 5 mg of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol as its dihydrochloride salt.

[0025] In some embodiments, the dosage form unit is a tablet or capsule suitable for oral administration.

[0026] In some embodiments, the methods of this invention administer a unit dosage form that, after administration, is essentially dissolved in the stomach prior to being released into the small intestines.

[0027] In some instances, the methods of this invention administer a unit dosage form that is not coated with an acid resistant coating.

[0028] Described herein is the treatment of vasomotor disturbances in a perior post-menopausal woman comprising administering to the woman a compound of formula I ((R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol) or a salt thereof wherein said administration results in a steady state plasma C_{max} of from 0.40 ng/mL to 1.44, such as from 0.40 ng/mL to 1.43 ng/mL. In certain related embodiments, said administration results in a steady state C_{max} of from 0.22 ng/mL to 1.61 ng/mL. In one aspect, the compound of formula I is in the form of a salt (e.g., an acid addition salt, dihydrochloride salt or hydrogen chloride salt).

[0029] In another aspect, the compound of formula is orally administered, once-daily. In yet another aspect, the compound that is administered orally, once-daily is in a unit dosage form. In a further aspect, the unit dosage form is a tablet or a capsule.

[0030] Described herein is the treatment of vasomotor disturbances in a post-menopausal woman comprising administering to the woman a compound of formula I ((R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol) wherein said administration results in a steady state plasma C_{max} of from 0.40 ng/mL to 1.44 ng/mL, such as from 0.40 ng/mL to 1.43 ng/mL. In certain related embodiments, said administration results in a steady state C_{max} of from 0.22 ng/mL to 1.61 ng/mL. In one aspect, the compound is administered once-daily. In another aspect, the compound is administered orally, once-daily.

[0031] In some embodiments, (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol is administered as its dihydrochloride salt.

[0032] Described herein is the treatment of vasomotor disturbances in a perior post-menopausal woman comprising

the administering of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol wherein said daily administration results in a steady state trough level of from 0.11 ng/mL to 0.79 ng/mL or from 0.12 ng/mL to 0.86 ng/mL. In some embodiments, (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol is administered as its salt (e.g., an acid addition salt, dihydrochloride salt or hydrogen chloride salt).

[0033] In some aspects, this invention also includes treating vasomotor disturbances in post-menopausal women comprising the daily administration of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol wherein said administration results in a steady state plasma C_{max} of from 0.40 ng/mL to 1.43 ng/mL or a steady state plasma C_{max} of from 0.22 ng/mL to 1.61 ng/mL and a steady state trough plasma level of from 0.11 ng/mL to 0.79 ng/mL or from 0.12 ng/mL to 0.86 ng/mL. In some embodiments, (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol is administered as its salt (e.g., an acid addition salt, dihydrochloride salt or hydrogen chloride salt).

[0034] In certain embodiments of this invention, the one or more delineated pharmacokinetic parameters are achieved by the administration of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol as a once-daily, oral administration of a unit dosage form. In some instances, the unit dosage form is a capsule or tablet. In certain embodiments, the capsule or tablet is essentially dissolved in the stomach prior to being released into the small intestines. In some embodiments, the dosage form unit is not coated with an acid resistant coating.

[0035] In some embodiments of this invention, the one or more delineated pharmacokinetic parameters are achieved by the administration of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol as a once-daily, oral administration of a dosage form unit comprising 10 mg of the compound as its dihydrochloride salt.

[0036] In some instances, the dosage form unit is a capsule or tablet. In certain embodiments, the capsule or tablet is essentially dissolved in the stomach prior to being released into the small intestines. In some embodiments, the dosage form unit is not coated with an acid resistant coating.

[0037] In some embodiments of this invention, the one or more delineated pharmacokinetic parameters are achieved by the administration of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol as a once-daily, oral administration of a dosage form unit comprising 1 mg, 2.5 mg or 5mg of the compound as its dihydrochloride salt.

[0038] In some instances, the dosage form unit is a capsule or tablet. In certain embodiments, the capsule or tablet is essentially dissolved in the stomach prior to being released into the small intestines. In some embodiments, the dosage form unit is not coated with an acid resistant coating.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039]

FIG. 1 is a graph showing the reduction in mean weekly frequency of moderate and severe hot flashes (Safety/Intent-to-treat population (ITT)).

FIG. 2 is a graph showing the reduction in mean weekly frequency of all hot flashes (ITT).

FIG. 3 is a graph showing reduction in mean severity of all hot flashes (ITT).

FIG. 4 is a graph showing the reduction in weekly composite scores.

DETAILED DESCRIPTION OF THE INVENTION

[0040] During the period immediately leading up to the menopausal period and usually for 1 or even many more years after, many women experience various central nervous system (CNS) disturbances associated with decreasing and/or fluctuating hormone levels (ie estrogens and progestins) brought on by the shutdown of ovarian function. The side effects are variously described but most prominently include an uncomfortable heating of the skin, usually on the upper body and most often in the face and neck. The sensations are transitory in nature, typically less than 30 minutes in duration. The sensation of heat can be accompanied by sweating, accelerated heart rate and a significant amount of physical discomfort. These sensations are typically referred to as hot flashes or hot flushes and may occur not only in the day but at night as well. Beyond the hot flashes or hot flushes associated with menopause, women might experience additional CNS disturbances. For example, some women experience depression, irritability, mood swings and other emotional or mood disorders as a consequence of the declining and/or fluctuating hormone levels associated with the menopause period. It has been known for some time that if women supplement their declining and/or fluctuating hormone levels with estrogens and/or progestins, these side effects can be largely, if not completely, eliminated. However, depending on the particular treatment modality being employed, the use of these hormones in postmenopausal women can be associated with certain side effects including the possibility of increased risk for breast cancer, uterine bleeding, uterine

cancer, stroke, blood clots and even heart disease. Not surprisingly, researchers have for some time been trying to find therapies that will treat the hormone-associated CNS effects of the menopausal period while avoiding some, and preferably all of the side effects.

5 [0041] The results of a phase 2a clinical study assessing the effects of the selective estrogen receptor modulator (SERM) (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol on women suffering from hot flashes are reported herein. The preclinical data for (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol indicate that it does not stimulate estrogen-dependent proliferation of mammary carcinoma cells (MCF-7) cells in the same way as prototypical estrogen agonists (e.g. estradiol) and in fact, is a potent antagonist of estradiol stimulation on these cells, suggesting that this compound will not increase the risk of breast cancer in women taking the drug and possibly could even decrease that risk. Moreover, in preclinical rat models measuring estrogenic agonist effects on the endometrium, (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride demonstrates negligible estrogen agonist stimulation effects. This indicates that (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride is unlikely to cause unacceptable uterine stimulation in postmenopausal women.

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15 [0042] For purposes of this invention, a dihydrochloride salt means that the base compound (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol has from 1.6 to 2 HCl's associated with the molecule. In some embodiments, a dihydrochloride salt refers to the base compound (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol wherein that base compound has from 1.8 to 2 HCl's associated with it. In certain embodiments, the term dihydrochloride refers to the base compound with approximately 2HCl's associated with it.

20 [0043] For purposes of this invention, a "unit dosage form" is a dosage form that is a discrete dosage formulation meaning that the entire drug content to be administered at a single time is contained in a single dosage form unit. For example, pills, tablets, lozenges, capsules are all dosage form units for purposes of this invention. Also contemplated in the scope of this definition is the possibility that the drug or some component of the drug formulation is not a single dosage form but only that the dose to be administered as a whole is a discrete unit. This means that a capsule may contain granules of the drug within the capsule but it is a single capsule that is to be administered. Likewise, a lozenge may contain the drug substance dissolved in a matrix but the drug form is the lozenge itself and thus is a unit dosage formulation.

25 [0044] The "unit dosage form" can be administered to a patient or preferably self-administered by a patient in a form that is generally acceptable in the pharmaceutical venue. In other word, the unit dosage form is pharmaceutically useful. By way of nonlimiting example, pharmaceutically useful dosage forms are suitable for oral delivery and include pills, tablets, buccal tablets, orally-disintegrating tablets, thin films, chewable tablets, lozenges, sublingual tablets or pills, liquid solutions, suspensions, syrups, powder or granules suitable for sprinkling in food or beverages capsules, food or candy with the drug contained within.

30 [0045] Pharmaceutically acceptable excipients include those excipients that are generally regarded as safe for administration to humans. Excipients especially suitable for formulations suitable for oral delivery include diluents (monosaccharides, disaccharides and polyhydric alcohols including starch, mannitol, dextrose, sucrose, microcrystalline cellulose, maltodextrin, sorbitol, xylitol, fructose and the like), binders (starch, gelatin, natural sugars, gums, waxes and the like), disintegrants (alginic acid, carboxymethylcellulose (calcium or sodium), cellulose, crocarmellose, crospovidone, microcrystalline cellulose, sodium starch glycolate, agar and the like), acidic or basic buffering agents (citrates, phosphates, gluconates, acetates, carbonates, bicarbonates and the like), chelating agents (edetic acid, edetate calcium, edetate disodium and the like), preservatives (benzoic acid, chlorhexidine gluconate, potassium benzoate, potassium sorbate, sorbic acid, sodium benzoate and the like), glidants and lubricants (calcium stearate, oils, magnesium stearate, magnesium trisilicate, sodium fumarate, colloidal silica, zinc stearate, sodium oleate, stearic acid, and the like), antioxidants and/or preservatives (tocopherols, ascorabtes, phenols, and the like) and acidifying agents (citric acid, fumaric acid, malic acid, tartaric acid and the like) as well as coloring agents, coating agents, flavoring agents, suspending agents, dessicants, humectants and other excipients known to those of skill in the art.

35 [0046] The unit dosage formulations or unit dosage forms of this invention can be prepared in different forms including most commonly, tablets and capsules. The tablets can be formulated by a wide variety of methods known to one of skill in the art including, for example, preparing a dry powder mixture of the drug substance in combination with one or more of the excipients granulating the mixture and pressing to together into a tablet and optionally coating the tablet with an enteric or non-enteric coating. The final coat typically includes a light protective pigment such as titanium oxide and a shellac or wax to keep the tablet dry and stable. While not intending to be limited by theory or example, in some instances it might be preferred to prepare the tablets by wet granulating the drug with one or more of the excipients and then extruding the granulated material.

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55 [0047] The unit dosage formulations or unit dosage forms of this invention also include capsules wherein the drug is enclosed inside the capsule either as a powder together with optional excipients or as granules containing usually

including one or more excipients together with the drug and wherein the granule in turn can be optionally coated, for example, enterically or non-enterically.

[0048] The formulations of this invention may be solids and when present as solids, they maybe of defined particle size. It maybe sometimes preferable to administer the compound with a certain particle size - a particle size with a preferred range where the average mean particle size diameter is under 100 microns, or 75 microns, or 50 microns, or 35 microns, or 10 microns or 5 microns.

[0049] For purposes of this invention, a dose description of 10 mg when referring to (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride means about 10 mg of the entire weight of the compound as its salt (e.g., an acid addition salt, dihydrochloride salt or hydrogen chloride salt) such as its dihydrochloride salt. Small variations about the 10 mg should be considered to fall within the 10 mg description of this invention. For example, differences in weighing, humidity, small impurities of the synthesis, etc means that a dose range from 9 mg to 11 mg will be considered equal to 10 mg for purpose of the description in this invention.

[0050] For purposes of this invention, a dose description of 1 mg, 2.5 mg or 5 mg when referring to (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride means about 1 mg, 2.5 mg or 5 mg of the entire weight of the compound as its salt (e.g., an acid addition salt, dihydrochloride salt or hydrogen chloride salt), such as its dihydrochloride salt. Small variations about the 1 mg, 2.5 mg or 5 mg should be considered to fall within the weight description of this invention. For example, differences in weighing, humidity, small impurities of the synthesis, etc means that a dose range from .9 mg to 1.1 mg will be considered equal to 1 mg for purpose of the description in this invention or 2.2 mg to 2.8 mg will be considered equal to 2.5 mg for purpose of the description in this invention, or 4.4 mg to 5.6 mg will be considered equal to 5 mg for purpose of the description in this invention.

[0051] For purposes of this invention, the compound (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride may vary to a certain degree with regard to the amount of the (S)-enantiomer that may be present in the drug product. For example, when (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride is referred to, it should be understood that it generally will contain at least 95% of the R-enantiomer and up to 5% of the S-enantiomer. For purposes of calculating the desired dosaging amount, the S-enantiomer will be included in the total weight of the drug provided it does not exceed the 5% preferred limit set in this definition. However, if the drug substance is dosed having >5% of the (S)-enantiomer, then the (S)-enantiomer will be subtracted from the total weight of the drug substance for purposes of dosaging calculations.

[0052] For purposes of this invention, the phrase "essentially dissolved in the stomach" means that after oral administration of a dosage form of this invention or a method of this invention, the compound (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol is more than 50% dissolved in the stomach prior to being released into the duodenum. In certain embodiments of this invention, the phrase "essentially dissolved in the stomach" means that after oral administration of a dosage form of this invention or a method of this invention, the compound (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol is more than 70% dissolved in the stomach prior to being released into the duodenum. In certain embodiments of this invention, the phrase "essentially dissolved in the stomach" means that after oral administration of a dosage form of this invention or a method of this invention, the compound (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol is more than 90% dissolved in the stomach prior to being released into the duodenum. The dissolution of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol in the stomach can be affected by different parameters, particularly those related to the excipients that the compound is co-formulated with and especially to whether the dosage formulation form is coated with a material that prevents dissolution of the coating material in the acid environment of the stomach. In some embodiments of this invention, it should be noted that the dosage form is not coated with an acid resistant coating. For purposes of this invention, an acid resistant coating refers to a coating on a tablet, granule, tablet, capsule or any other particle that contains (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol within it. An acid resistant material means that the coating is resistant to pH's of up to about 5.5. Acid resistant coating materials are well known by those of ordinary skill in the art and include materials such as polymeric acids such as methacrylic acid polymers, and the like. Acid resistant materials also include such materials as waxes, shellacs, fatty acids, polymeric acids, plant fibers and the like.

[0053] In some embodiments of this invention, it may be preferable to provide the drug in a form that avoids or largely avoids exposure of the drug substance in the person's stomach being treated. For example, a patient suffering from gastritis or some other form of irritation in the stomach may prefer to take a dosage formulation that largely or completely bypasses the direct exposure of the drug to the stomach lining. In this regard, a coating may be added to the drug dosage form such as an enteric coating that is stable in the acidic pH in the stomach but is more readily dissolved in the less acidic environment of the small intestine. Acid resistant materials also include such materials as waxes, shellacs, fatty acids, polymeric acids, plant fibers and the like.

[0054] For purposes of this invention, the term "vasomotor disturbances" refers to the constellation of central nervous system disturbances associated with the peri- and postmenopausal period. In particular, vasomotor disturbances includes hot flashes and/or hot flushes that are severe, moderate or mild. Vasomotor disturbances may also include inappropriate sweating and/or sweating at night. Vasomotor disturbances is sometimes referred to in the art as "vasomotor symptoms" associated with the peri- or postmenopause periods.

[0055] For purposes of this invention, a "perimenopausal woman" is a woman who is transitioning into menopause. The perimenopausal period is not strictly defined but rather is understood by one of skill in the medical arts to include women whose estrogen levels have begun to fluctuate unevenly often leading to irregular menstrual cycles. The perimenopausal period typically begins several years before true menopause and includes up to one year after the woman's final menstrual period. From a functional perspective with regard to treating a perimenopausal woman with the compositions and methods of this invention, the perimenopausal period is most easily identified by the symptoms associated with it. If a woman is still having her menstrual periods or has within one year had a menstrual period but yet she is at least 30 years of age and more likely at least 40 years of age and is experiencing hot flashes/flushes, night sweats, unusual anxiety, depression and/or mood swings then she can be considered as a perimenopausal woman for who this invention can be of value.

[0056] For purposes of this invention description, the term "postmenopausal woman" refers to any woman who has is at least 40 years of age and is naturally amenorrheic for a period of at least one year or has elevated FSH levels (>25 mIU in some embodiments, >30 mIU in some embodiments and >50 mIU in other embodiments). In some embodiments of this invention, the term "postmenopausal woman" refers to women who are amenorrheic through surgical removal of the ovaries. In yet other aspects of this invention, the term "postmenopausal woman" refers to women who are amenorrheic through treatment with an agent that causes suppression of ovarian function such as leutinizing hormone agonists (eg leuprolide), antagonists or gonadotropin hormone releasing hormone antagonists such (eg ganirelix).

EXAMPLE

[0057] A phase 2a study was undertaken to assess the effect of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride (referred to as "drug" in tables below) to alleviate hot flashes in postmenopausal women. The study design and objectives are detailed below.

Study Objectives:

[0058] The overall objectives of the study were to assess the clinical safety and efficacy of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride in postmenopausal women with frequent, moderate to severe vasomotor symptoms. Changes in frequency and severity of symptoms were assessed. Data was evaluated to analyze the effect of increasing doses of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride on overall efficacy.

The specific objectives of this study are to:

- Monitor the effects of 28-days of treatment with (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride on frequency and severity of hot flashes in postmenopausal women with frequent, moderate to severe vasomotor symptoms.
- Monitor the safety and tolerability of 28-days of dosing with (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride in postmenopausal women with frequent, moderate to severe vasomotor symptoms.

Study Population:

Planned Inclusion Criteria:

[0059] Postmenopausal women from 40 to 75 years of age (inclusive) who meet the study entry criteria and have provided written informed consent will be eligible for the study. The women will be established to be postmenopausal on the basis of menstrual history (one year of amenorrhea) and/or serum FSH levels. Women with documented surgical menopause who meet the study entry criteria will also be eligible 6 months after surgery. The principal entry criterion is a documented history of moderate to severe hot flashes with an event frequency of 7 per day or 50 per week. All patients are to be in good general health as determined by medical history, physical examination (including pelvic examination and Pap test) and clinical laboratory testing. Pelvic ultrasound should also demonstrate no clinically significant abnormality. Breast health should be confirmed by mammogram in the past 6 months or at screening. Body Mass Index (BMI) of 18 - 30 kg/m² (inclusive). The resting 12-lead ECG obtained during screening should have no clinically significant

EP 2 568 806 B1

abnormality and a QTc (Bazett's correction) of ≤ 450 msec.

Planned Exclusion Criteria:

5 [0060] Patients reporting recent use (within 6 months of enrollment) of estrogens, SERMs, or other estrogen preparations might be excluded, as will those with recent (within 3 months of enrollment) use of any medication known to reduce or enhance vasomotor symptoms. Women with a history of thrombosis or blood clotting disorders, chronic medical or psychiatric illness, and breast, uterine or other cancer might be excluded. Patients with known substance abuse problems will also be excluded and patients who have received an investigational drug product in the past 12 months might be excluded.

10 [0061] Patients must have understood and agreed to comply with all study requirements and had signed the written Informed Consent Form (ICF).

Study Design and Methodology:

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Number of Patients:

[0062] A total of 100 patients are planned to be enrolled in the study.

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Design:

[0063] This is a randomized, placebo-controlled, double-blind, parallel-group, Phase 2, multi-center, dose-finding study to evaluate the effects of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride in the treatment of vasomotor symptoms in postmenopausal women.

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[0064] A total of 100 eligible patients will be randomized to receive one of 5 blinded treatment regimens. (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride at doses 0, 10, 25, 50 or 100 mg will be dosed for 28-days. The dosages of study medications and the number of patients randomized to each treatment regimen are shown in Table 1.

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Table 1

Treatment Regimen	Study Medication	Daily Dose (PO)	Number of Patients
1	drug	10 mg	20
2	drug	25 mg	20
3	drug	50 mg	20
4	drug	100 mg	20
5	Placebo	--	20
		Total	100

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Study Visits:

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[0065] The study periods and number of clinic visits are summarized in Table 2.

Table 2

Study Period	Duration of Study Period	Scheduled Visits (#)
Screening	≤ 2 weeks	2
Treatment	4 weeks	4
Follow-up	1 month	1
Total	~ 10 Weeks	7

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Planned Procedures and Assessments:

Efficacy:

5 **[0066]** Patients will document in real time hot flash frequency and severity according to a predetermined scale, in the provided electronic or paper Study Diary. Study Diary entries of hot flash frequency and severity and associated symptoms will be reviewed at each study visit. Serum markers of estrogen effect will be measured at specific study visits while on treatment.

10 Safety:

[0067] Safety evaluations include physical examinations, vital signs, 12-lead ECG, clinical laboratory tests, and adverse events. Study specific algorithms for management of vaginal bleeding and clinically significant breast tenderness have been included.

15 **[0068]** Safety laboratory assessments will be performed at specific study visits during the treatment period and the final visit. All patients will be monitored for cardiac safety (QTc interval assessment) at specific study visits using a standardized 12-lead ECG.

Endpoints and Data Analysis:

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[0069] The efficacy endpoints assessed are:

- Change in frequency of hot flashes over time
- Change in severity of hot flashes over time;
- 25 • Change in composite score of hot flashes over time (frequency x severity)

[0070] The safety data includes the incidence and severity of adverse events by dose and cumulative dose, and the pathological changes in hematology, chemistry and urinalysis data. Changes in physical examination, vital signs, ECG and clinical laboratory tests will be summarized using descriptive statistics. Shift frequencies will be summarized for clinical laboratory tests.

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[0071] Treatment groups will be assessed for uniformity at baseline (baseline characteristics, medical history, physical examination, vital signs, and ECG).

Treatments Administered:

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[0072] (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride was provided by sponsor in capsule form for oral administration. All doses (0, 10, 25, 50 and 100 mg) were provided as identical presentations. Each patient was provided with 2 containers of 28-capsules each at the start of treatment and took one capsule from each container every day for 28-days. Placebo contained the same excipients as active medication, but without (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride. The patients were instructed to take the capsules orally in the fasted state (morning).

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Capsule Formulations

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[0073] The capsules containing (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride were prepared in dosage strengths of 0 mg, 10 mg, 25 mg and 50 mg. The composition of the capsules is shown in Table 3.

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Table 3

Strength of capsule**	Content (drug)	Prosolv®*	Total weight
0 mg	0 mg	69.1 mg	69.1 mg
10 mg	10.3 mg	58.8 mg	69.1 mg
25 mg	25.8 mg	43.3 mg	69.1 mg

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EP 2 568 806 B1

(continued)

Strength of capsule**	Content (drug)	Prosolv®*	Total weight
50 mg	51.5 mg	17.6 mg	69.1 mg

*Silicified microcrystalline cellulose, as a combination of 98% microcrystalline cellulose (MCC) and 2% colloidal silicon dioxide (CSD). SMCC 50 (JRS Pharma; Holzmühle 1 D-73494 Rosenberg (Germany); 2981 Route 22, Suite 1 Patterson, NY 12563-2359 (USA)).

**Capsules used were Capsugel (100 Route 206 North/Pfizer Way, Peapack, NJ 07977 USA) Coni-Snap® gelatin capsules, size 4, white opaque.

[0074] A slight excess of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride was used in order to compensate for residual impurities and moisture in the drug product. Each patient self-administered two capsules to which they were blinded with regard to the capsule contents. The placebo group received 2- 0 mg capsules; the 10 mg group received 1- 10 mg capsule and 1- 0 mg capsule; the 25 mg group received 1- 25 mg capsule and 1- 0 mg capsule; the 50 mg group received 1- 50 mg capsule and 1- 0 mg capsule; and the 100 mg group received 2- 50 mg capsules.

[0075] Capsules containing 1, 2.5 and 5 mg of drug can be similarly prepared.

Planned Duration of Patient Participation:

[0076] The maximum duration of study participation for an individual patient is approximately 10-weeks (72 days) from the initial Screening visit to the completion of final study evaluations. Patients will complete screening procedures during the Screening Period within 14 days prior to the first dose of study medication. After completion of the Screening Period, patients will be randomized if they meet the entrance criteria and will receive the first dose of study medication on Day 1 of the Treatment Period. The Treatment Period will be 28 days in duration and will involve daily oral self-administration of (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride or its Placebo and documentation of hot flashes/symptoms using a Study Diary. After completion of 28 days of dosing, patients will return to the clinic for the End-of Treatment Visit (Day 29) and enter the Follow-up Period of 30 days. The end of patient participation will be at the End-of-Study Visit, scheduled at the end of the Follow-up Period.

Study Results

[0077] Analyzed: A total of 136 patients were screened of which 36 (26.5%) were screen failures; therefore, 100 patients were enrolled and randomized in the study. Of the 100 patients enrolled, 100 were included in the Safety/Intent-to-Treat (ITT) population and 81 were included in the Per-Protocol Population (PP).

Duration of Treatment:

[0078] The treatment period duration was 4 weeks. The maximum duration of study participation for an individual patient was approximately 10 weeks (72 days) from the initial Screening visit to the completion of final study evaluations.

Efficacy:

[0079] Efficacy was assessed by evaluating change including baseline and percent change from baseline for the following primary endpoints:

- Frequency of hot flashes
- Severity of hot flashes
- Composite score of hot flashes over time (frequency × severity)
- drug levels

STATISTICAL METHODS:

[0080] The following analysis populations were analyzed in this study: Safety population (Safety/Intent-to-treat [ITT]), defined as all patients who received one or more doses of study drug, and Per-Protocol Population (PP) defined as all patients of the ITT Population who met all entrance criteria or had a waiver of unmet criterion, had not used any prohibited

concomitant medications, met study drug compliance of 90%, provided acceptably complete (25 days of full data) diary information, and met assessment and visit compliance at baseline and End-of-Treatment Visits. All efficacy endpoints were to be analyzed for the ITT and PP populations, with the exception of the drug levels (analyzed for the ITT population only). Safety endpoints were to be analyzed for the Safety/ITT population.

5 **[0081]** Continuous, quantitative variable summaries included the number of patients (N) (with non missing values), mean, standard deviation, median, minimum, maximum, and 95% confidence interval. Categorical, qualitative variable summaries included the frequency and percentage of patients who were in the particular category. In general, the denominator for the percentage calculation was to be based upon the total number of patients in the study population for the treatment groups at the specific timepoint, unless otherwise specified. Descriptive summaries were to be presented for the number and percentage of patients in each study population (overall and by center), disposition of patients (including number of patients screened, screen failure patients, and patients randomized, completed and withdrawn), and study withdrawals by reason of withdrawal. Summaries of demographics and baseline characteristics were to include the following: age, race, height, weight, BMI, medical history (time since last menses and number of months of hot flash history), hot flash history (moderate, severe, and moderate and severe), and concomitant medication at baseline, Baseline physical examination (abnormal and normal), vital signs (systolic and diastolic blood pressure, pulse rate, temperature, respiratory rate), and 12-lead ECG (abnormal and normal). Summaries of AEs, clinical laboratory investigations (chemistries, hematology, coagulation, serum estradiol, and urinalysis), vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), physical examinations, ECG investigations, and pelvic ultrasound were to be provided. Adverse events of vaginal bleeding and breast tenderness (and related breast events) were to be tabulated separately.

10 **[0082]** Changes in the efficacy endpoints of frequency, severity, and composite score of hot flashes over time; associated hot flash symptoms (palpitations, insomnia, joint aches, and headaches), PD markers of estrogen effect (FSH, LH, and lipid profile), drug levels, and MRS were to be summarized using descriptive statistics. Frequency, severity, and composite score of hot flashes over time were to be analyzed using repeated measures analysis of variance (ANOVA) with factors for treatment (treatment groups), time (study day) and their interaction. A linear trend test for treatment groups (placebo, and 10, 25, 50, 100 mg doses of drug) and for study day as well as any potential interaction between the two was to be included as part of the analyses by including both dose and time as continuous variables in the ANOVA model. Pair-wise comparisons of change from baseline were to be tested between the placebo group and each drug dose group for each timepoint; the mean difference together with a 95% confidence interval of the difference was to be presented for placebo compared with each active treatment group. Nominal p-values at Week 4 were to be presented.

15 **[0083]** Additional exploratory, post-hoc analyses were to be performed as appropriate to complement the overall understanding of study results.

20 **[0084]** Descriptive summaries of actual (absolute) values and changes from baseline values by study visit were to be presented for hematology, chemistry, coagulation, serum estradiol, and urinalysis by treatment for the safety population. Additionally, for each laboratory parameter, shifts in assessments from baseline to End-of Treatment Visit and End-of-Study Visit were to be presented (shift tables).

40 **Results:**

Pharmacokinetic Evaluation

45 **[0085]**

Table 4

Mean Trough Level of Drug (ng/mL) (ITT)					
Visit	Placebo	10 mg (SD)	25 mg (SD)	50 mg (SD)	100 mg (SD)
Day 8	0.00	0.45 (0.34)	1.33 (0.52)	3.11 (1.66)	6.91 (4.39)
Day 15	0.00	0.49 (0.37)	1.49 (0.71)	3.39 (2.01)	6.66 (4.60)
Day 29	0.00	0.34 (0.26)	1.18 (0.73)	3.23 (2.41)	6.03 (4.46)
SD = standard deviation in ng/mL					

Table 5

Peak Level of drug (ng/mL) (ITT)					
Visit	Placebo	10 mg (SD)	25 mg (SD)	50 mg (SD)	100 mg (SD)
Day 1	0.00	0.56 (0.34)	1.41 (0.63)	2.83 (1.72)	8.39 (4.04)
Day 8	0.00	0.92 (0.52)	2.53 (0.74)	6.36 (2.58)	15.47 (7.14)
Day 15	0.00	0.92 (0.69)	2.97 (1.09)	6.22 (3.46)	12.76 (5.28)

SD = standard deviation in ng/mL

[0086] Values for ranges of steady state trough levels and steady state Cmax can be derived from Tables 4 and 5. Steady state values are the values listed for days 8 and 15. The ranges were derived from the mean number listed in the table plus or minus one standard deviation (the number in parenthesis after each mean value). For example a steady state trough level ranging from 0.11 ng/mL to 0.79 ng/mL is derived from Table 4 by taking the trough level for 10 mg, 0.45 ng/mL, adding 0.34 to get the upper value of 0.79 and subtracting 0.34 to get the lower value of 0.11. Other ranges for steady state trough levels and ranges for Cmax can be similarly derived from the data in Tables 4 and 5.

Hot Flash Frequency

Moderate and Severe Hot Flash Frequency

[0087] The total number of hot flashes rated as moderate and severe were reported as a weekly mean for each treatment group. As can be seen in Table 6, the 10 mg treatment group demonstrated the best treatment effect.

Table 6

Weekly Mean Frequency of Moderate and Severe Hot Flash Numbers (ITT)							
Timepoint	Statistic	Treatment Group					Total N=100
		Placebo N=19	10 mg N=22	25 mg N=20	50 mg N=21	100 mg N=18	
Baseline	N Mean (SD)	18 61.3 (12.84)	22 63.1 (14.23)	19 65.9 (44.30)	21 71.9 (36.92)	17 58.5 (12.67)	97 64.4 (27.81)
Week 1	N Mean (SD)	18 41.2 (24.39)	22 30.4 (18.92)	17 57.7 (50.49)	20 41.7 (23.79)	17 41.9 (24.23)	94 41.9 (30.37)
Week 2	N Mean (SD)	17 36.6 (25.48)	20 18.5 (13.34)	17 42.3 (49.73)	18 32.8 (25.52)	17 35.6 (28.06)	89 32.7 (30.72)
Week 3	N Mean (SD)	17 33.6 (24.80)	20 14.5 (11.92)	17 43.3 (57.15)	18 29.6 (25.09)	16 24.5 (24.06)	88 28.7 (32.62)
Week 4	N Mean (SD)	16 29.5 (24.53)	20 13.4 (11.54)	17 37.4 (54.76)	18 29.4 (26.53)	15 18.6 (19.16)	86 25.4 (31.29)

Abbreviations: (SD) = standard deviation

[0088] The graphical representation of the data from table 6 is shown in FIG. 1. The 10 mg group demonstrated the greatest reduction in hot flashes at each weekly time point.

Total Hot Flash Frequency

[0089] The total number of hot flashes rated as mild, moderate and severe (all hot flashes) were reported as a weekly

EP 2 568 806 B1

mean for each treatment group. As can be seen in Table 7, the 10 mg treatment group demonstrated the greatest reduction in hot flashes at each weekly time point and once again demonstrates the best treatment effect.

Table 7

Weekly Mean Frequency of Mild, Moderate and Severe Hot Flash Numbers (ITT)							
Timepoint	Statistic	Treatment Group					Total N=100
		Placebo N=19	10 mg N=22	25 mg N=20	50 mg N=21	100 mg N=18	
Baseline	N Mean (SD)	18 65.2 (13.29)	22 66.0 (13.89)	19 75.8 (46.46)	21 76.0 (36.96)	17 63.6 (13.23)	97 69.5 (28.66)
Week 1	N Mean (SD)	18 46.7 (23.56)	22 36.0 (18.97)	17 64.4 (48.88)	20 54.0 (27.15)	17 48.6 (23.32)	94 49.3 (30.45)
Week 2	N Mean (SD)	17 40.1 (23.88)	20 27.2 (15.16)	17 48.0 (48.80)	18 45.8 (25.16)	17 41.6(27.37)	89 40.1 (30.03)
Week 3	N Mean (SD)	17 38.7 (25.25)	20 21.2 (12.99)	17 46.6 (56.27)	18 40.5 (22.37)	16 29.4 (23.91)	88 34.9 (31.91)
Week 4	N Mean (SD)	16 34.9 (30.84)	20 19.1 (12.95)	17 42.4 (53.18)	18 37.9 (23.45)	15 23.1 (19.45)	86 31.3 (31.52)

Abbreviations: (SD) = standard deviation

[0090] The graphical representation of the data from Table 7 is shown in FIG. 2.

Hot Flash Severity

[0091] Hot flashes were also scored according to their severity with a mild hot flash scored a "1", a moderate hot flash scored a "2" and a severe hot flash scored a "3". A mean hot flash severity can be derived by taking the sum of the total obtained by multiplying the total frequency of hot flashes in each group (mild, moderate or severe) by the severity assigned to that type of hot flash (1, 2 or 3, respectively) and then dividing the total by the frequency of all hot flashes. This gives the mean severity and is averaged over a week period and presented in Table 8. A graph of the data from Table 8 is shown in FIG. 3. The 10 mg dose had the greatest reduction in severity of hot flashes at all time points.

Table 8

Mean Severity Scores by Week (ITT)							
Timepoint	Statistic	Treatment Group					Total N=100
		Placebo N=19	10 mg N=22	25 mg N=20	50 mg N=21	100 mg N=18	
Baseline	N Mean (SD)	18 2.36 (0.430)	22 2.37 (0.347)	19 2.26 (0.348)	21 2.14 (0.313)	17 2.21 (0.330)	97 2.27 (0.359)
Week 1	N Mean (SD)	18 2.12 (0.397)	22 1.99 (0.460)	17 2.12 (0.392)	20 1.92 (0.402)	17 2.04 (0.334)	94 2.03 (0.401)
Week 2	N Mean (SD)	17 2.11 (0.446)	20 1.80 (0.514)	17 2.09 (0.447)	17 1.88 (0.535)	17 2.01 (0.406)	88 1.97 (0.478)
Week 3	N	16	19	16	18	16	85

EP 2 568 806 B1

(continued)

Mean Severity Scores by Week (ITT)							
		Treatment Group					
Timepoint	Statistic	Placebo N=19	10 mg N=22	25 mg N=20	50 mg N=21	100 mg N=18	Total N=100
	Mean (SD)	2.00 (0.482)	1.84 (0.570)	2.14 (0.408)	1.86 (0.544)	1.88 (0.473)	1.94 (0.503)
Week 4	N	14	18	16	18	15	81
	Mean (SD)	1.94 (0.504)	1.86 (0.562)	2.06 (0.404)	1.83 (0.568)	1.89 (0.484)	1.91 (0.505)

Abbreviations: (SD) = standard deviation

Hot Flash Composite Score

[0092] A composite score that takes into account both the total frequency and the mean severity was calculated by multiplying together that patient's mean weekly severity with that patient's total hot flash frequency to give the composite score. The composite index is a helpful measure of the overall alleviation of hot flash burden. Table 9 lists the composite scores for the treatment groups. FIG. 4 is a graphical representation of the data in Table 9. The composite score indicates that the 10 mg group had the greatest composite score reduction at each weekly timepoint.

Table 9

Composite Scores by Week (ITT)							
		Treatment Group					
Timepoint	Statistic	Placebo N=19	10 mg N=22	25 mg N=20	50 mg N=21	100 mg N=18	Total N=100
Baseline	N	18	22	19	21	17	97
	Mean (SD)	155.17 (47.09)	156.45 (38.91)	165.47 (119.10)	162.19 (76.44)	140.35 (36.82)	156.40 (69.97)
Week 1	N	18	22	17	20	17	94
	Mean (SD)	98.44 (54.65)	73.68 (41.67)	142.71 (125.55)	104.35 (55.52)	104.35 (68.35)	102.98 (74.70)
Week 2	N	17	20	17	18	17	89
	Mean (SD)	86.24 (57.05)	47.75 (24.95)	102.82 (118.57)	87.78 (54.61)	87.18 (74.31)	81.25 (72.30)
Week 3	N	17	20	17	18	16	88
	Mean (SD)	80.29 (55.48)	37.15 (21.96)	102.59 (139.75)	77.67 (51.87)	59.75 (62.00)	70.52 (77.19)
Week 4	N	16	20	17	18	15	86
	Mean (SD)	69.31 (57.98)	34.35 (23.48)	89.59 (134.32)	75.06 (55.82)	43.67 (40.32)	61.92 (73.76)

Abbreviations: (SD) = standard deviation

[0093] Taken in sum, the data presented herein demonstrate the unexpected and surprisingly consistent reduction on hot flash incidence and severity of the lowest dose tested (10 mg) compared to placebo and three higher doses. This discovery is not only unexpected and surprising but potentially beneficial as well. In general, the ability to use a lower dose suggests a lower cost of goods as well as decreased likelihood of side effects or off target effects that tend to increase as dosage of any drug is increased.

[0094] When the effect of the compound of formula I at 10 mg is analyzed by concentration of drug in the plasma and compared to its efficacy, it was observed that the lower concentration cohort experienced similar efficacy as the higher concentration cohort. For example, in one analysis, a cohort with a 2 hour postdose plasma concentration range of

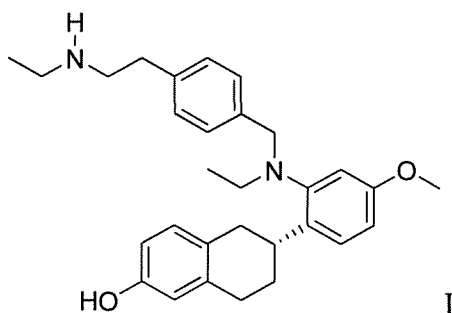
between 0.43 ng/mL to 0.53 ng/mL of the compound of formula I had a similar efficacy in hot flush frequency reduction (-75%) as the higher concentration cohort having a range of 0.66 ng/mL to 1.34 ng/mL (-77%). This indicates that lower dosages of the compound of formula I such as 5 mg, 2.5 mg or 1 mg can be effective.

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Claims

1. A unit dosage form comprising from 0.9 to 1.1 mg, from 2.2 to 2.8 mg, from 4.4 to 5.6 mg or from 9 to 11 mg of the compound of formula I as its dihydrochloride salt

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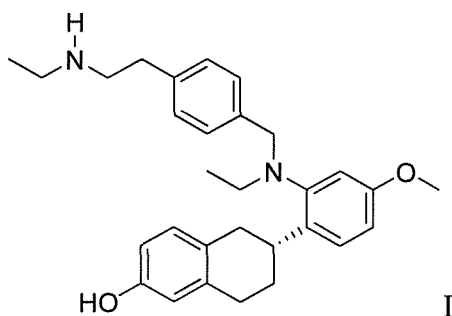
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for use in a method of treating vasomotor disturbances in a peri-menopausal or postmenopausal woman in need thereof, wherein the method comprises the once-daily administration of said unit dosage form to the patient.

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2. The use of a compound of formula I as its dihydrochloride salt

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in the manufacture of a medicament for treating vasomotor disturbances in a perimenopausal or postmenopausal woman in need thereof, wherein the medicament is a unit dosage form comprising from 0.9 to 1.1 mg, from 2.2 to 2.8 mg, from 4.4 to 5.6 mg or from 9 to 11 mg of said compound, and wherein the method comprises the once-daily administration of said unit dosage form to the patient.

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3. The unit dosage form for use according to claim 1, or the use according to claim 2, wherein the unit dosage form comprises 1, 2.5, 5 or 10 mg of the compound of formula I as its dihydrochloride salt.

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4. The unit dosage form for use according to claim 1, or the use according to claim 2, wherein the unit dosage form comprises 10 mg of the compound of formula I as its dihydrochloride salt.

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5. The unit dosage form for use or use according to claims 1 to 4, further comprising one or more pharmaceutically acceptable excipients.

6. The unit dosage form according to claim 5, wherein the unit dosage form is a tablet or capsule suitable for oral administration.

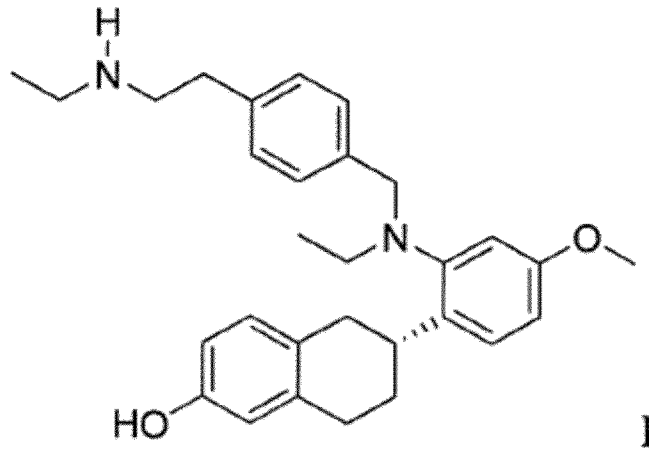
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7. The unit dosage form according to claim 6, wherein following oral administration the unit dosage form, is more than 50% dissolved in the stomach prior to being released into the small intestines.

8. The unit dosage form according to claim 7, wherein the unit dosage form is not coated with an acid resistant coating.
9. The unit dosage form for use or use according to any one of claims 1 to 4, wherein the unit dosage form is administered orally, once-daily; and optionally wherein the unit dosage form is a tablet or capsule suitable for oral administration.
10. The unit dosage form for use or use according to claim 9, wherein the unit dosage form is a tablet or capsule suitable for oral administration, and is more than 50% dissolved in the stomach prior to being released into the small intestines, optionally wherein the unit dosage form is not coated with an acid resistant coating.

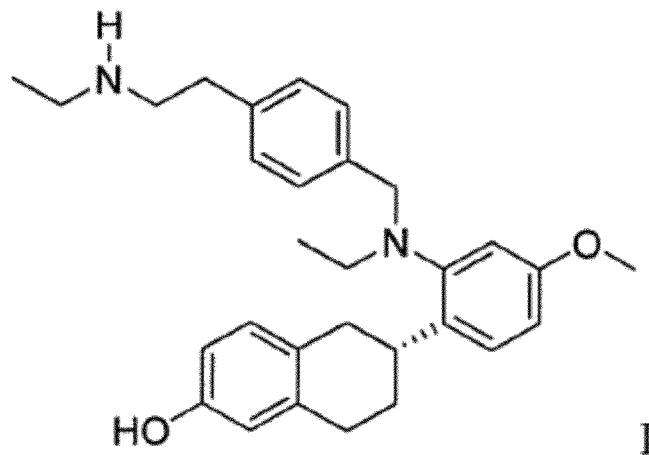
Patentansprüche

1. Einheitsdosierungsform, umfassend von 0,9 bis 1,1 mg, von 2,2 bis 2,8 mg, von 4,4 bis 5,6 mg oder von 9 bis 11 mg der Verbindung mit Formel I in Form ihres Dihydrochloridsalzes



zur Verwendung in einem Verfahren für die Behandlung vasomotorischer Störungen bei einer perimenopausalen oder postmenopausalen Frau, die eine solche Behandlung benötigt, wobei das Verfahren die einmal tägliche Verabreichung der Einheitsdosierungsform an die Patientin umfasst.

2. Verwendung einer Verbindung mit Formel I in Form ihres Dihydrochloridsalzes

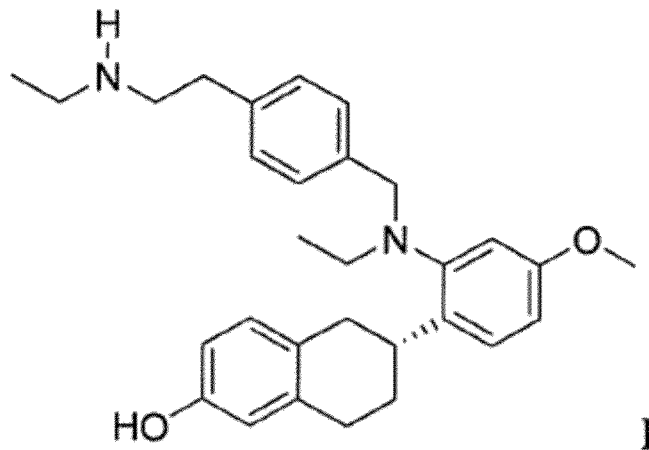


bei der Herstellung eines Arzneimittels für die Behandlung vasomotorischer Störungen bei einer perimenopausalen oder postmenopausalen Frau, die eine solche Behandlung benötigt, wobei das Arzneimittel eine Einheitsdosierungsform ist, umfassend von 0,9 bis 1,1 mg, von 2,2 bis 2,8 mg, von 4,4 bis 5,6 mg oder von 9 bis 11 mg der Verbindung und wobei das Verfahren die einmal tägliche Verabreichung der Einheitsdosierungsform an die Patientin umfasst.

3. Einheitsdosierungsform zur Verwendung nach Anspruch 1 oder Verwendung nach Anspruch 2, wobei die Einheitsdosierungsform 1, 2,5, 5 oder 10 mg der Verbindung mit Formel I in Form ihres Dihydrochloridsalzes umfasst.
- 5 4. Einheitsdosierungsform zur Verwendung nach Anspruch 1 oder die Verwendung nach Anspruch 2, wobei die Einheitsdosierungsform 10 mg der Verbindung mit Formel I in Form ihres Dihydrochloridsalzes umfasst.
5. Einheitsdosierungsform zur Verwendung nach Anspruch 1 bis 4, ferner umfassend einen oder mehrere pharmazeutisch unbedenkliche Trägerstoffe.
- 10 6. Einheitsdosierungsform nach Anspruch 5, wobei die Einheitsdosierungsform eine Tablette oder Kapsel ist, die für die orale Verabreichung geeignet ist.
7. Einheitsdosierungsform nach Anspruch 6, wobei die Einheitsdosierungsform nach der oralen Verabreichung zu mehr als 50 % im Magen gelöst ist, bevor sie im Dünndarm freigesetzt wird.
- 15 8. Einheitsdosierungsform nach Anspruch 7, wobei die Einheitsdosierungsform nicht mit einer säureresistenten Beschichtung überzogen ist.
9. Einheitsdosierungsform zur Verwendung oder Verwendung nach einem der Ansprüche 1 bis 4, wobei die Einheitsdosierungsform einmal täglich oral verabreicht wird; und wahlweise wobei die Einheitsdosierungsform eine Tablette oder Kapsel ist, die für die orale Verabreichung geeignet ist.
- 20 10. Einheitsdosierungsform zur Verwendung oder Verwendung nach Anspruch 9, wobei die Einheitsdosierungsform eine Tablette oder Kapsel ist, die für die orale Verabreichung geeignet ist und zu mehr als 50 % im Magen gelöst ist, bevor sie im Dünndarm freigesetzt wird, wahlweise wobei die Einheitsdosierungsform nicht mit einer säureresistenten Beschichtung überzogen ist.
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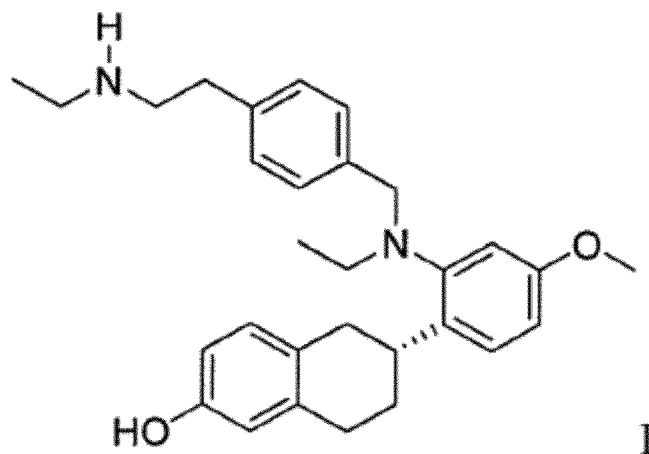
30 **Revendications**

1. Forme pharmaceutique unitaire comprenant entre 0,9 et 1,1 mg, entre 2,2 et 2,8 mg, entre 4,4 et 5,6 mg ou entre 9 et 11 mg du composé de formule I sous la forme de son sel de dichlorhydrate



50 pour une utilisation dans un procédé de traitement de troubles vasomoteurs chez une femme périménopausée ou postménopausée en ayant besoin, dans laquelle le procédé comprend l'administration journalière de ladite forme pharmaceutique unitaire à la patiente.

- 55 2. Utilisation d'un composé de formule I sous la forme de son sel de dichlorhydrate



20 dans la fabrication d'un médicament pour le traitement de troubles vasomoteurs chez une femme pérимénopausée ou postménopausée en ayant besoin, dans laquelle le médicament est une forme pharmaceutique unitaire comprenant entre 0,9 et 1,1 mg, entre 2,2 et 2,8 mg, entre 4,4 et 5,6 mg ou entre 9 et 11 mg dudit composé, et dans laquelle le procédé comprend l'administration journalière de ladite forme pharmaceutique unitaire à la patiente.

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3. Forme pharmaceutique unitaire pour une utilisation selon la revendication 1, ou utilisation selon la revendication 2, laquelle forme pharmaceutique unitaire comprend 1, 2,5, 5 ou 10 mg du composé de formule I sous la forme de son sel de dichlorhydrate.
 4. Forme pharmaceutique unitaire pour une utilisation selon la revendication 1, ou utilisation selon la revendication 2, laquelle forme pharmaceutique unitaire comprend 10 mg du composé de formule I sous la forme de son sel de dichlorhydrate.
 5. Forme pharmaceutique unitaire pour une utilisation ou utilisation selon les revendications 1 à 4, comprenant en outre un ou plusieurs excipients pharmaceutiquement acceptables.
 6. Forme pharmaceutique unitaire selon la revendication 5, laquelle forme pharmaceutique unitaire est un comprimé ou une capsule approprié(e) pour l'administration par voie orale.
 7. Forme pharmaceutique unitaire selon la revendication 6, laquelle forme pharmaceutique unitaire, après l'administration par voie orale, est dissoute à plus de 50 % dans l'estomac avant d'être libérée dans l'intestin grêle.
 8. Forme pharmaceutique unitaire selon la revendication 7, laquelle forme pharmaceutique unitaire n'est pas recouverte d'un enrobage acido-résistant.
 9. Forme pharmaceutique unitaire pour une utilisation ou utilisation selon l'une quelconque des revendications 1 à 4, laquelle forme pharmaceutique unitaire est administrée par voie orale, une fois par jour ; et facultativement laquelle forme pharmaceutique unitaire est un comprimé ou une capsule approprié(e) pour l'administration par voie orale.
 10. Forme pharmaceutique unitaire pour une utilisation ou utilisation selon la revendication 9, laquelle forme pharmaceutique unitaire est un comprimé ou une capsule approprié(e) pour l'administration par voie orale, et est dissoute à plus de 50 % dans l'estomac avant d'être libérée dans l'intestin grêle, facultativement laquelle forme pharmaceutique unitaire n'est pas recouverte d'un enrobage acido-résistant.

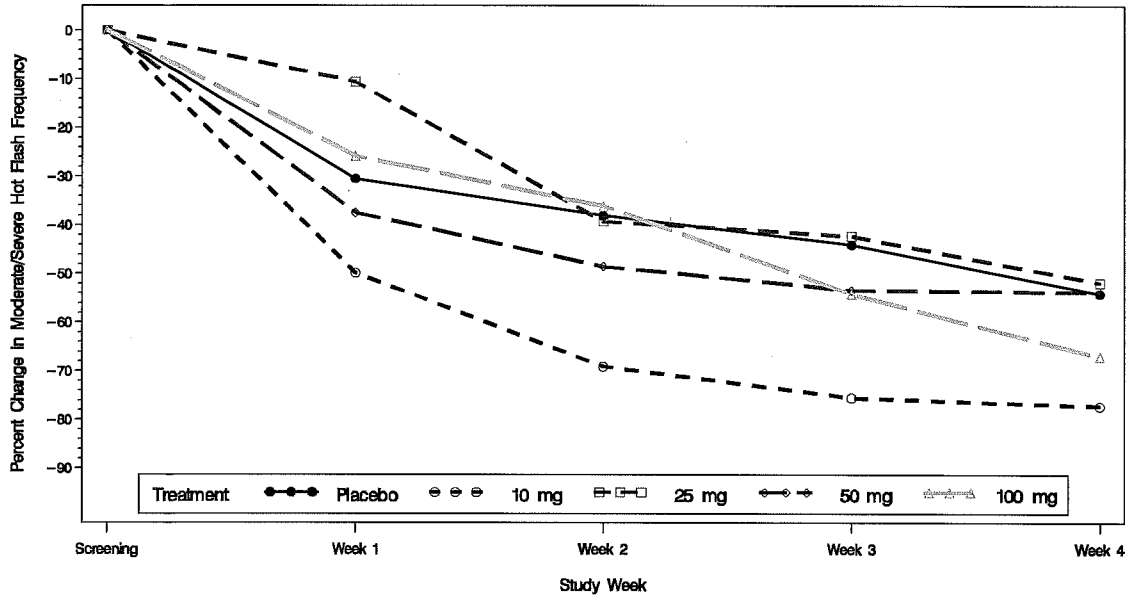


FIG. 1

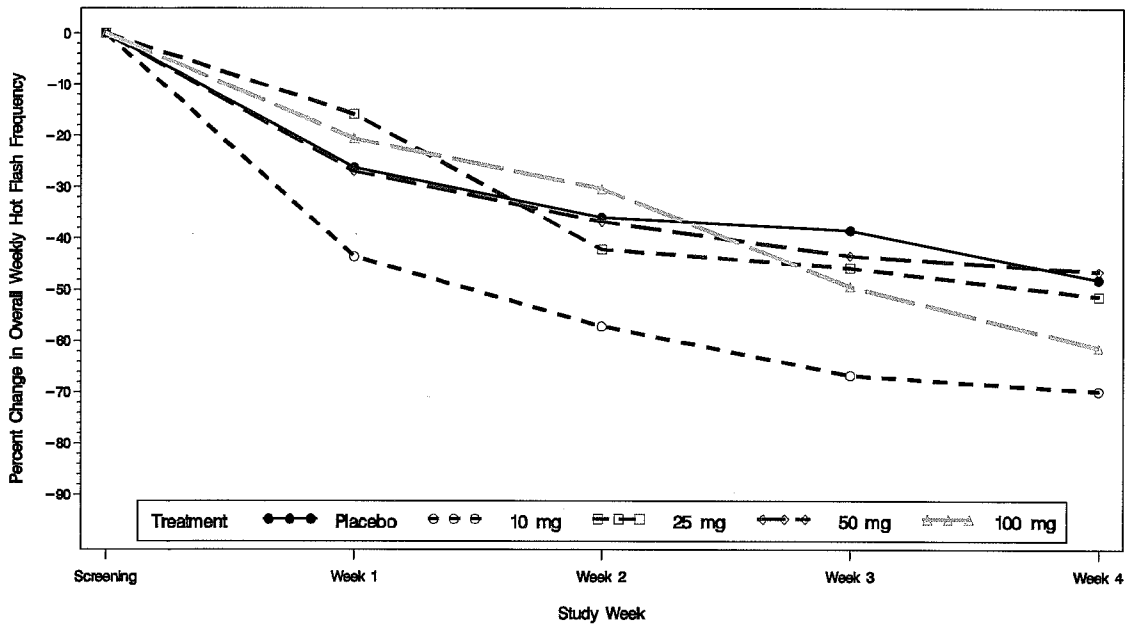


FIG. 2

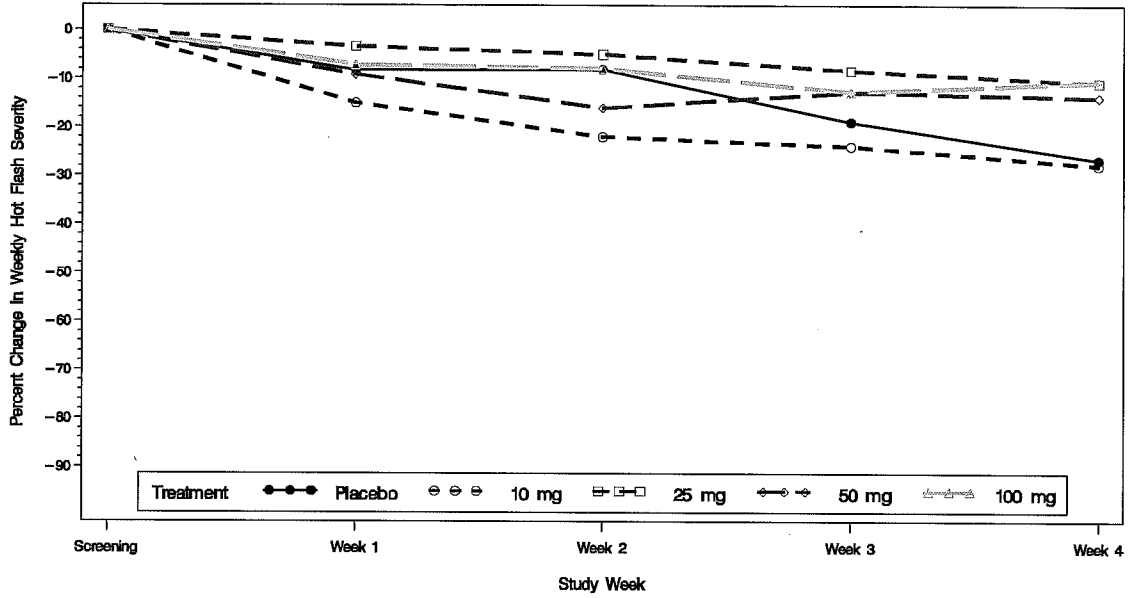


FIG. 3

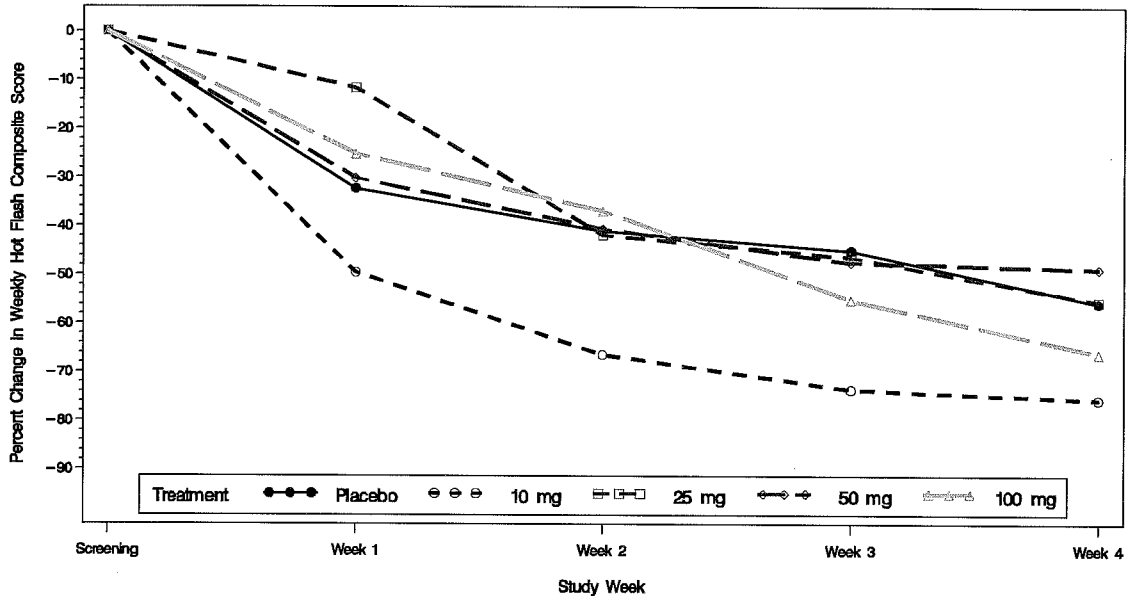


FIG. 4

REFERENCES CITED IN THE DESCRIPTION

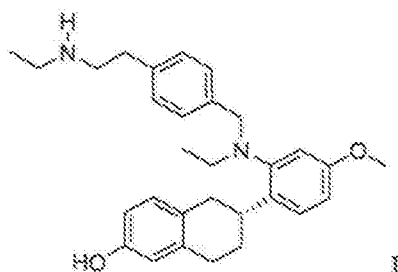
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- US 7612114 B2 [0002]
- WO 2008002490 A [0003]
- WO 2009137104 A [0003]

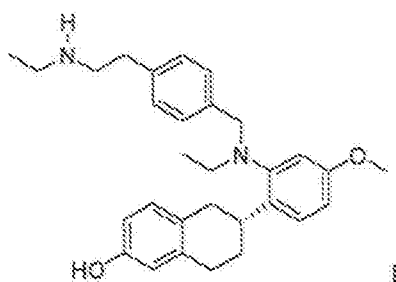
Szabadalmi igénypontok

1. Egység dózis forma, amely 0,9 - 1,1 mg, 2,2 - 2,8 mg, 4,4 - 5,6 mg vagy 9 - 11 mg I képletű vegyületet foglal magában dihidroklorid-só alakban



peri-menopauzális vagy postmenopauzális vazomotoros zavarok kezelésére szolgáló eljárásban egy arra szoruló nőnél történő alkalmazásra, ahol az eljárás a paciensnek az egység dózis forma napi egyszeri adagolását jelenti.

2. Az I képletű vegyület alkalmazása dihidroklorid-só alakban



egy arra szoruló nőnél peri-menopauzális vagy postmenopauzális vazomotoros zavarok kezelésére szolgáló gyógyszer előállítására, ahol a gyógyszer egy egység dózis forma, amely 0,9 - 1,1 mg, 2,2 - 2,8 mg, 4,4 - 5,6 mg vagy 9 - 11 mg vegyületet foglal magában, és ahol az eljárás a paciensnek az egység dózis forma napi egyszeri adagolását jelenti.

3. Az egység dózis forma az 1. igénypont szerinti alkalmazásra, vagy a 2. igénypont szerinti alkalmazás, ahol az egység dózis forma 1, 2,5, 5 vagy 10 mg I képletű vegyületet foglal magában dihidroklorid-só alakban.

4. Az egység dózis forma az 1. igénypont szerinti alkalmazásra, vagy a 2. igénypont szerinti alkalmazás, ahol az egység dózis forma 10 mg I képletű vegyületet foglal magában dihidroklorid-só alakban.

5. Az egység dózis forma az 1-4. igénypontok szerinti alkalmazásra vagy alkalmazás, amely továbbá tartalmaz egy vagy több gyógyszerészetileg elfogadható kötőanyagot.

6. Az 5. igénypont szerinti egység dózis forma, ahol a dózis forma szájon át történő adagolásra alkalmas tablettá vagy kapszula.

7. A 6. igénypont szerinti egység dózis forma, ahol a szájon át történt adagolást követően több, mint 50% feloldódik a gyomorban mielőtt a vékonybélbe bocsátódna ki.

8. A 7. igénypont szerinti egység dózis forma, ahol az egység dózis forma nincs bevonva saválló bevonattal.

9. Az egység dózis forma az 1-4. igénypontok bármelyike szerinti alkalmazásra vagy alkalmazás, ahol az egység dózis formát szájon át adagoljuk, egyszer naponta; és adott esetben ahol az egység dózis forma szájon át történő adagolásra alkalmas tabletta vagy kapszula.

10. Az egység dózis forma a 9. igénypont szerinti alkalmazásra vagy alkalmazás, ahol az egység dózis forma szájon át történő adagolásra alkalmas tabletta vagy kapszula, és több, mint 50%-a feloldódik a gyomorban mielőtt a vékonybélbe bocsátódna ki, adott esetben ahol az egység dózis forma nincs bevonva saválló bevonattal.

A meghatalmazott:

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