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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 May 2025 (22.05.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/106494 A1

(51) International Patent Classification:
A61K 31/395 (2006.01) *A61K 31/505* (2006.01)
A61K 31/18 (2006.01) *A61K 31/33* (2006.01)

(21) International Application Number:
PCT/US2024/055651

(22) International Filing Date:
13 November 2024 (13.11.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/599,019 15 November 2023 (15.11.2023) US

(72) Inventor; and
(71) Applicant: **KONG, Yanping** [US/US]; 3 Danville Circle, Merrimack, NH 03054 (US).

(74) Agent: **ZHANG, Yin, Philip**; Milstein Zhang & Wu LLC, 2000 Commonwealth Ave. Suite 400, Newton, MA 02466 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2025/106494 A1

(54) **Title:** COMPOSITIONS AND METHODS FOR TREATING ERECTILE DYSFUNCTION AND MALE HYPOGONADISM

(57) **Abstract:** The invention provides a novel pharmaceutical composition comprising sildenafil and cabergoline and method of use thereof for treating erectile dysfunction and/or male hypogonadism.

COMPOSITIONS AND METHODS FOR TREATING ERECTILE DYSFUNCTION AND MALE HYPOGONADISM

Priority Claims and Related Applications

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/599,019, filed November 15, 2023, the entire content of which is incorporated herein by reference for all purposes.

Technical Field of the Invention

[0002] The invention generally relates to novel therapeutic methods and pharmaceutical compositions for treating erectile dysfunction and male hypogonadism. More particularly, the invention relates to pharmaceutical compositions comprising sildenafil and cabergoline and uses thereof for treating erectile dysfunction and/or male hypogonadism.

Background of the Invention

[0003] Erectile dysfunction (ED) refers to an inability to achieve and/or maintain an erection satisfactory for the completion of sexual activity. ED is a highly prevalent condition and may affect 30% to 50% of men aged 40 to 70 years. The risk of ED increases with age and as the population continues to grow and age and it is estimated that there will be approximately 332 million men worldwide with ED by the year 2025. A normal level of libido, or sexual desire, is an important component of an individual's health and well-being. The primary naturally occurring hormone responsible for libido is testosterone. Male hypogonadism refers to diminished functional activity of the testicles that may result in diminished production of sex hormones. Abnormally low levels of testosterone also occur in male hypogonadism and are similarly associated with lack of libido and inability to produce or sustain erections. In males, the baseline testosterone level is a relatively constant throughout life while decreasing slowly in old age.

[0004] ED and male hypogonadism are common in elderly men and can lead to erection dysfunction, low libido and low energy. Increased longevity and population aging will increase

the number of men with late onset ED and hypogonadism. As common conditions, they often are underdiagnosed and undertreated, merely considered a normal part of aging.

[0005] The therapeutics and methods currently available for treating ED and/or male hypogonadism are inadequate and/or with significant side effects. There remains an urgent and ongoing need for novel and improved therapeutics to effectively treat ED and/or male hypogonadism and related diseases and conditions.

Summary of the Invention

[0006] The invention is based in part on the unexpected discovery of therapeutic methods and pharmaceutical compositions, as demonstrated herein, that can be used to treat ED and/or male hypogonadism. In particular, disclosed herein is a method using sildenafil and cabergoline together in specifically selected dosages in treatment and/or prevention of ED and/or male hypogonadism.

[0007] In one aspect, the invention generally relates to a method for treating erectile dysfunction, or a related disease or condition, comprising administering to a male subject in need thereof (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof.

[0008] In another aspect, the invention generally relates to a method for treating male hypogonadism, or a related disease or condition, comprising administering to a male subject in need thereof (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof.

[0009] In yet another aspect, the invention generally relates to a method for treating erectile dysfunction and male hypogonadism, or a related disease or condition, comprising administering to a male subject in need thereof (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof.

[0010] In yet another aspect, the invention generally relates to a pharmaceutical composition comprising (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable

form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof, and a pharmaceutically acceptable excipient, carrier, or diluent.

[0011] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition according to invention.

[0012] In yet another aspect, the invention generally relates to a kit comprising a unit dosage form of the invention and optionally a unit form of a further therapeutic agent and instructions for administration thereof.

[0013] In yet another aspect, the invention generally relates to use of (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof, for the manufacture of a medicament for the treatment of erectile dysfunction and/or male hypogonadism, or a related disease or condition.

[0014] In yet another aspect, the invention generally relates to use of (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof, for treating erectile dysfunction and male hypogonadism.

Definitions

[0015] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The following terms, unless indicated otherwise according to the context wherein the terms are found, are intended to have the following meanings.

[0016] When trade names are used herein, the trade name includes the product formulation, the generic drug, and the active pharmaceutical ingredient(s) of the trade name product, unless otherwise indicated by context.

[0017] Ranges provided herein are understood to be shorthand for all values within the range. For example, a range of 1 to 14 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14.

[0018] In this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference, unless the context clearly dictates otherwise.

[0019] Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein can be modified by the term about.

[0020] Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive.

[0021] The term "comprising", when used to define compositions and methods, is intended to mean that the compositions and methods include the recited elements, but do not exclude other elements. The term "consisting essentially of", when used to define compositions and methods, shall mean that the compositions and methods include the recited elements and exclude other elements of any essential significance to the compositions and methods. For example, "consisting essentially of" refers to administration of the pharmacologically active agents expressly recited and excludes pharmacologically active agents not expressly recited. The term consisting essentially of does not exclude pharmacologically inactive or inert agents, *e.g.*, pharmaceutically acceptable excipients, carriers or diluents. The term "consisting of", when used to define compositions and methods, shall mean excluding trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0022] As used herein, the terms "disease", "disorder" or "condition" are used interchangeably herein to refer to a pathological condition, for example, one that can be identified by symptoms or other identifying factors as diverging from a healthy or a normal state. The term "disease" includes disorders, syndromes, conditions, and injuries. Diseases include, but are not limited to, proliferative, inflammatory, immune, metabolic, infectious, and ischemic diseases.

[0023] As used herein, a "pharmaceutically acceptable form" of a disclosed compound includes, but is not limited to, pharmaceutically acceptable salts, esters, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives of disclosed compounds. In one embodiment, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable salts, esters, isomers, prodrugs and isotopically labeled derivatives of disclosed compounds. In some embodiments, a "pharmaceutically acceptable form" includes,

but is not limited to, pharmaceutically acceptable salts and isotopically labeled derivatives of disclosed compounds.

[0024] In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt. As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al. describes pharmaceutically acceptable salts in detail in J. *Pharmaceutical Sciences* (1977) 66:1-19. Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, besylate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, lactic acid, trifluoracetic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0025] The salts can be prepared in situ during the isolation and purification of the disclosed compounds, or separately, such as by reacting the free base or free acid of a parent compound with a suitable base or acid, respectively.

[0026] In certain embodiments, the pharmaceutically acceptable form is a "solvate" (e.g., a hydrate). As used herein, the term "solvate" refers to compounds that further include a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of a disclosed compound or a pharmaceutically acceptable salt thereof. Where the solvent is water, the solvate is a "hydrate". Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include 1 to about 100, or 1 to about 10, or 1 to about 2, about 3 or about 4, solvent or water molecules. It will be understood that the term "compound" as used herein encompasses the compound and solvates of the compound, as well as mixtures thereof.

[0027] In certain embodiments, the pharmaceutically acceptable form is a prodrug. As used herein, the term "prodrug" (or "pro-drug") refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable form of the compound. A prodrug can be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis (*e.g.*, hydrolysis in blood). In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs can increase the bioavailability of the compound when administered to a subject (*e.g.*, by permitting enhanced absorption into the blood following oral administration) or which enhance delivery to a biological compartment of interest (*e.g.*, the brain or lymphatic system) relative to the parent compound. Exemplary prodrugs include derivatives of a disclosed compound with enhanced aqueous solubility or active transport through the gut membrane, relative to the parent compound.

[0028] The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, Bundgard, H., *Design of Prodrugs* (1985), pp. 7- 9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series,* Vol. 14, and in *Bioreversible Carriers in Drug Design,* ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. Exemplary advantages of a prodrug can include, but are not limited to, its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it can enhance absorption from the digestive tract, or it can enhance drug stability for long-term storage.

[0029] As used herein, the term “pharmaceutically acceptable” excipient, carrier, or diluent refers to a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations. Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate, magnesium stearate, and polyethylene oxide-polypropylene oxide copolymer as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0030] As used herein, the terms “prevent”, “preventing”, or “prevention” refer to a method for precluding, delaying, averting, or stopping the onset, incidence, severity, or recurrence of a disease or condition. For example, a method is considered to be a prevention if there is a reduction or delay in onset, incidence, severity, or recurrence of a disease or condition or one or more symptoms thereof in a subject susceptible to the disease or condition as compared to a subject not receiving the method. The disclosed method is also considered to be a prevention if there is a reduction or delay in onset, incidence, severity, or recurrence of one or more symptoms of a disease or condition in a subject susceptible to the disease or condition after receiving the method as compared to the subject's progression prior to receiving treatment. The reduction or delay in onset, incidence, severity, or recurrence of cancer can be about a 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100%, or any amount of reduction in between.

[0031] Prevention and the like do not mean preventing a subject from ever getting the specific disease or disorder. Prevention may require the administration of multiple doses. Prevention can include the prevention of a recurrence of a disease in a subject for whom all disease symptoms were eliminated, or prevention of recurrence in a relapsing-remitting disease.

[0032] As used herein, the terms "subject" and "patient" are used interchangeably herein to refer to a living animal (human or non-human). The subject may be a mammal. The terms "mammal" or "mammalian" refer to any animal within the taxonomic classification mammalia. A mammal may be a human or a non-human mammal, for example, dogs, cats, pigs, cows, sheep, goats, horses, rats, and mice. The term "subject" does not preclude individuals that are entirely normal with respect to a disease or condition, or normal in all respects.

[0033] As used herein, the term "therapeutically effective amount" refers to the dose of a therapeutic agent or agents sufficient to achieve the intended therapeutic effect with minimal or no undesirable side effects. A therapeutically effective amount can be determined by a skilled physician, *e.g.*, by first administering a low dose of the pharmacological agent(s) and then incrementally increasing the dose until the desired therapeutic effect is achieved with minimal or no undesirable side effects.

[0034] As used herein, the terms "treatment" or "treating" a disease or disorder refers to a method of reducing, delaying or ameliorating such a condition, or one or more symptoms of such disease or condition, before or after it has occurred. Treatment may be directed at one or more effects or symptoms of a disease and/or the underlying pathology. The treatment can be any reduction and can be, but is not limited to, the complete ablation of the disease or the symptoms of the disease. As compared with an equivalent untreated control, such reduction or degree of prevention is at least 5%, 10%, 20%, 40%, 50%, 60%, 80%, 90%, 95%, or 100% as measured by any standard technique.

[0035] Any compositions or methods disclosed herein can be combined with one or more of any of the other compositions and methods provided herein.

[0036] Isotopically-labeled compounds are also within the scope of the present disclosure. As used herein, an "isotopically-labeled compound" refers to a presently disclosed compound including pharmaceutical salts thereof, each as described herein, in which one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into

compounds presently disclosed include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

[0037] By isotopically-labeling the presently disclosed compounds, the compounds may be useful in drug and/or substrate tissue distribution assays. Tritiated (^{3}H) and carbon-14 (^{14}C) labeled compounds are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (^{2}H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds presently disclosed, including pharmaceutical salts, esters, and prodrugs thereof, can be prepared by any means known in the art.

[0038] Further, substitution of normally abundant hydrogen (^{1}H) with heavier isotopes such as deuterium can afford certain therapeutic advantages, *e.g.*, resulting from improved absorption, distribution, metabolism and/or excretion (ADME) properties, creating drugs with improved efficacy, safety, and/or tolerability. Benefits may also be obtained from replacement of normally abundant ^{12}C with ^{13}C. (See, WO 2007/005643, WO 2007/005644, WO 2007/016361, and WO 2007/016431.)

[0039] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 95% ("substantially pure"), which is then used or formulated as described herein. In certain embodiments, the compounds of the present invention are more than 99% pure.

[0040] Solvates and polymorphs of the compounds of the invention are also contemplated herein. Solvates of the compounds of the present invention include, for example, hydrates.

[0041] Any appropriate route of administration can be employed, for example, parenteral, intravenous, subcutaneous, intramuscular, intraventricular, intracorporeal, intraperitoneal, rectal, or oral administration. Most suitable means of administration for a particular patient will depend on the nature and severity of the disease or condition being treated or the nature of the therapy being used and on the nature of the active compound.

[0042] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds described herein or derivatives thereof are admixed with at least one inert customary excipient (or carrier) such as sodium citrate or

dicalcium phosphate or (i) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (ii) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (iii) humectants, as for example, glycerol, (iv) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (v) solution retarders, as for example, paraffin, (vi) absorption accelerators, as for example, quaternary ammonium compounds, (vii) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (viii) adsorbents, as for example, kaolin and bentonite, and (ix) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard- filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like. Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others known in the art.

[0043] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers, such as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan, or mixtures of these substances, and the like. Besides such inert diluents, the composition can also include additional agents, such as wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents.

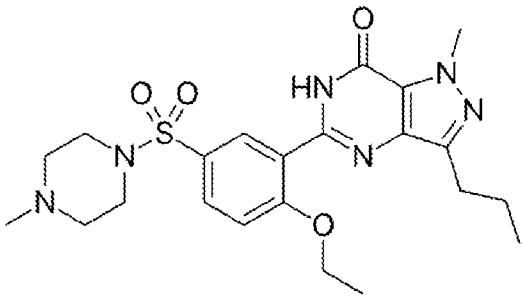
[0044] Materials, compositions, and components disclosed herein can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed methods and compositions. It is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutations of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a method is disclosed and

discussed and a number of modifications that can be made to a number of molecules including in the method are discussed, each and every combination and permutation of the method, and the modifications that are possible are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed. This concept applies to all aspects of this disclosure including, but not limited to, steps in methods using the disclosed compositions. Thus, if there are a variety of additional steps that can be performed, it is understood that each of these additional steps can be performed with any specific method steps or combination of method steps of the disclosed methods, and that each such combination or subset of combinations is specifically contemplated and should be considered disclosed.

Detailed Description of the Invention

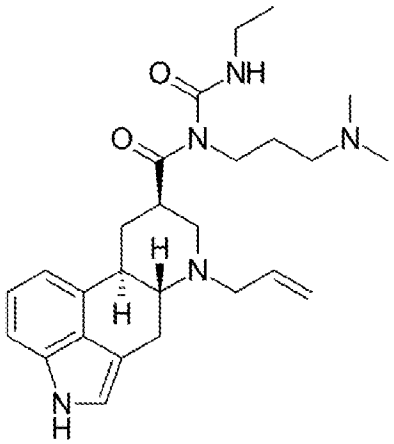
[0045] The invention provides a novel approach to treatment of ED and/or male hypogonadism. The therapeutic methods and pharmaceutical compositions disclosed herein can benefit patients in terms of additional treatment options, improved treatment outcome, and/or fewer or less severe side effects.

[0046] Sildenafil, sold under the brand name Viagra® among others, is an agent used to treat erectile dysfunction and pulmonary arterial hypertension. Sildenafil acts by blocking phosphodiesterase 5 (PDE5), an enzyme that promotes breakdown of cGMP, which regulates blood flow in the penis.



Sildenafil

[0047] Cabergoline, sold under the brand name Dostinex® among others, is a dopaminergic agent used in the treatment of high prolactin levels, prolactinomas, Parkinson's disease, and other indications. Cabergoline is a potent dopamine D_2 receptor agonist.



Cabergoline

[0048] In one aspect, the invention generally relates to a method for treating erectile dysfunction, or a related disease or condition, comprising administering to a male subject in need thereof (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof.

[0049] In another aspect, the invention generally relates to a method for treating male hypogonadism, or a related disease or condition, comprising administering to a male subject in need thereof (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof.

[0050] In yet another aspect, the invention generally relates to a method for treating erectile dysfunction and male hypogonadism, or a related disease or condition, comprising administering to a male subject in need thereof (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof.

[0051] Any pharmaceutically acceptable sildenafil may be used. In certain embodiments, (a) is sildenafil salt. In certain embodiments, (a) is sildenafil citrate.

[0052] Any pharmaceutically acceptable cabergoline may be used. In certain embodiments, (b) is cabergoline in its free form.

[0053] In certain embodiments, the subject is administered a daily dose of about 25 mg to about 100 mg (*e.g.*, about 25 mg to about 75 mg, about 50 mg to about 100 mg) of sildenafil, or a pharmaceutically acceptable form thereof, and about 0.125 mg to about 1 mg (*e.g.*, about 0.125 mg to about 0.5 mg, about 0.5 mg to about 1 mg) of cabergoline, or a therapeutically acceptable form thereof.

[0054] In certain embodiments, the subject is administered a daily dose of about 50 mg of sildenafil and about 0.25 mg of cabergoline.

[0055] In certain embodiments, (a) and (b) are together in a single oral dosage form. In certain embodiments, the single oral dosage form is a tablet. In certain embodiments, the single oral dosage form is a capsule. In certain embodiments, the single oral dosage form is a liquid solution or suspension.

[0056] In certain embodiments, (a) and (b) are in two separate oral dosage forms.

[0057] In certain embodiments, (a) and (b) are administered twice weekly for a time period of about 1 week to about 2 years (*e.g.*, about 1 week to about 6 months, about 6 months to about 1 year).

[0058] In certain embodiments, the method further comprises administering to the subject a further therapy or a further therapeutic agent (*e.g.*, testosterone or clomiphene).

[0059] In yet another aspect, the invention generally relates to a pharmaceutical composition comprising (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof, and a pharmaceutically acceptable excipient, carrier, or diluent.

[0060] In certain embodiments of the pharmaceutical composition, (a) is sildenafil citrate salt.

[0061] In certain embodiments of the pharmaceutical composition, (b) is cabergoline in its free form.

[0062] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition according to invention.

[0063] In certain embodiments of the unit dosage form, the pharmaceutical composition is suitable for oral administration.

[0064] In certain embodiments, the unit dosage form is a tablet or capsule.

[0065] In certain embodiments, the unit dosage form is a liquid solution or suspension.

[0066] In yet another aspect, the invention generally relates to a kit comprising a unit dosage form of the invention and optionally a unit form of a further therapeutic agent and instructions for administration thereof.

[0067] In yet another aspect, the invention generally relates to use of (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof, for the manufacture of a medicament for the treatment of erectile dysfunction and/or male hypogonadism, or a related disease or condition.

[0068] In yet another aspect, the invention generally relates to use of (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof, for treating erectile dysfunction and male hypogonadism.

[0069] **Table 1** lists ingredients for an exemplary formulation according to the invention.

Table 1. Exemplary Formulation

Ingredients	**Function**	**Unit Prescription (mg/Tab)**		**Theoretical Batch Size (g)**
		25 mg/0.25 mg	**50 mg/0.5 mg**	
Interior				
Sildenafil Citrate	Active Ingredient	35.12	70.24	526.80
Cabergoline	Active Ingredient	0.25	0.50	3.75
Microcrystalline cellulose 112	Filler	65.03	130.06	975.45
Anhydrous calcium hydrogen phosphate	Filler	27.00	54.00	405.00
Croscarmellose Sodium	Disintegrant	8.00	16.00	120.00
Anhydrous Lactose	Filler	58.40	116.80	876.00
Leucine	Stabilizer	2.20	4.40	33.00
Magnesium stearate	Filler	2.00	4.00	30.00
Exterior				

Magnesium stearate	Lubricant	2.00	4.00	30.00
Coating Materials				
Gastric soluble film coating premix 00K605000-CN Blue	Coating Agent	6.00	12.00	90.00
Purified Water	Coating Solvent	44.00	88.00	660.00

Batch Size：3000.00 g;
25 mg/0.25 mg: 5000 tables;
50 mg/0.5 mg：5000 tables.

[0070] **Table 2** shows exemplary analytical data from test of exemplary tables.

Table 2. Test Report for Analysis

Version No.: 01	Batch Size: 2000EA
Product Name: CR-067 Tablets 25 mg/ 0.25 mg	Batch Number: CR-067-240926-01C1P
Manufacturing Date: 26-Sep-2024	Expiry data：25-Sep-2026

Testing Items	Acceptance Criteria	Result	
Appearance	Blue film-coated tablets, which becomes white or off-white after removing the coating	Blue film-coated tablets, which becomes off-white after removing the coating	
Identification	The retention time of main peak in chromatogram of sample is consistent with that in the chromatogram of reference standard in Assay item	The retention time of main peak in chromatogram of sample is consistent with that in the chromatogram of reference standard in Assay item	
	The characteristic absorption wavelength in sample solution should be consistent with that in standard solution in Assay item	The characteristic absorption wavelength in sample solution should be consistent with that in standard solution in Assay item	
Content Uniformity	Complies with USP <905> Complies with ChP <0941>	Cabergoline	Conforms AV: 7.6 A+2.2S: 8.3
		Sildenafil	Conforms AV: 2.1 A+2.2S: 3.4
Assay	90%~110% of the labeled amount	Cabergoline	98.5%
		Sildenafil	102.9%

Testing Items	Acceptance Criteria	Result	
Related Substances 1	Sildenafil N-oxide: ≤ 0.2% Any unspecified impurity：≤ 0.2% Total impurities: ≤ 0.5%	Sildenafil N-oxide: N.D. Any unspecified impurity：N.D. Total impurities: N.D.	
Related Substances 2	impurity A≤ 1.0% impurity D≤ 1.0% impurity：≤ 0.5% Total impurities: ≤ 2%	impurity A：N.D. impurity D：N.D. Any unspecified impurity：＜0.1% Total impurities: ＜0.1%	
Dissolution	Conforms to ChP general chapter<0931>, 30 minutes, Q=80% Conforms to USP general chapter <711>, 30 minutes, Q=75%	Cabergoline	97%（30min）
		Sildenafil	101%（30min）
Water Content	Report result	2.1%	

N.D.: Not detected

[0071] Applicant's disclosure is described herein in preferred embodiments with reference to the Figures, in which like numbers represent the same or similar elements. Reference throughout this specification to "one embodiment," "an embodiment," or similar language means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, appearances of the phrases "in one embodiment," "in an embodiment," and similar language throughout this specification may, but do not necessarily, all refer to the same embodiment.

[0072] The described features, structures, or characteristics of Applicant's disclosure may be combined in any suitable manner in one or more embodiments. In the description, herein, numerous specific details are recited to provide a thorough understanding of embodiments of the invention. One skilled in the relevant art will recognize, however, that Applicant's composition and/or method may be practiced without one or more of the specific details, or with other methods, components, materials, and so forth. In other instances, well-known structures, materials, or operations are not shown or described in detail to avoid obscuring aspects of the disclosure.

[0073] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Although any methods and

materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Methods recited herein may be carried out in any order that is logically possible, in addition to a particular order disclosed.

Incorporation by Reference

[0074] References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, have been made in this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes. Any material, or portion thereof, that is said to be incorporated by reference herein, but which conflicts with existing definitions, statements, or other disclosure material explicitly set forth herein is only incorporated to the extent that no conflict arises between that incorporated material and the present disclosure material. In the event of a conflict, the conflict is to be resolved in favor of the present disclosure as the preferred disclosure.

Equivalents

[0075] The representative examples are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples and the references to the scientific and patent literature included herein. The examples contain important additional information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

What is claimed is:

CLAIMS

1. A method for treating erectile dysfunction, or a related disease or condition, comprising administering to a male subject in need thereof (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof.
2. A method for treating male hypogonadism, or a related disease or condition, comprising administering to a male subject in need thereof (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof.
3. A method for treating erectile dysfunction and male hypogonadism, or a related disease or condition, comprising administering to a male subject in need thereof (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof.
4. The method of any one of claims 1-3, wherein (a) is sildenafil citrate salt.
5. The method of any one of claims 1-4, wherein (b) is cabergoline in its free form.
6. The method of any one of claims 1-5, wherein the subject is administered a daily dose of about 25 mg to about 100 mg of sildenafil, or a pharmaceutically acceptable form thereof, and about 0.125 mg to about 1.0 mg of cabergoline, or a therapeutically acceptable form thereof.
7. The method of claim 6, wherein the subject is administered a daily dose of about 50 mg of sildenafil and about 0.25 mg of cabergoline.
8. The method of any one of claims 1-7, wherein (a) and (b) are together in a single oral dosage form.
9. The method of claim 8, wherein the single oral dosage form is a tablet.
10. The method of claim 8, wherein the single oral dosage form is a capsule.
11. The method of claim 8, wherein the single oral dosage form is a liquid solution or suspension.

12. The method of any one of claims 1-7, wherein (a) and (b) are in two separate oral dosage forms.
13. The method of any one of claims 1-12, wherein (a) and (b) are administered twice weekly.
14. The method of claim 13, wherein (a) and (b) are administered for a time period of about 1 week to about 2 years.
15. The method of any one of claims 1-14, further comprising administering to the subject a further therapy.
16. The method of any one of claims 1-14, further comprising administering to the subject a further therapeutic agent.
17. The method of claim 15 or 16, wherein the further therapy or a further therapeutic agent is selected from testosterone and clomiphene.
18. A pharmaceutical composition comprising (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof, and a pharmaceutically acceptable excipient, carrier, or diluent.
19. The pharmaceutical composition of claim 18, wherein (a) is sildenafil citrate salt.
20. The pharmaceutical composition of claim 18 or 19, wherein (b) is cabergoline in its free form.
21. A unit dosage form comprising a pharmaceutical composition according to any one of claims 18-20.
22. The unit dosage form of claim 21, wherein the pharmaceutical composition is suitable for oral administration.
23. The unit dosage form of claim 21, being in the form of a tablet.
24. The unit dosage form of claim 21, being in the form of a capsule.
25. The unit dosage form of claim 21, being in the form of a liquid solution.
26. The unit dosage form of claim 21, being in the form of a liquid suspension.
27. A kit comprising a unit dosage form of any one of claims 21-26 and optionally a unit form of a further therapeutic agent and instructions for administration thereof.
28. Use of (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a

therapeutically acceptable form thereof, for the manufacture of a medicament for the treatment of erectile dysfunction and/or male hypogonadism, or a related disease or condition.

29. Use of (a) a therapeutically effective amount of sildenafil, or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of cabergoline, or a therapeutically acceptable form thereof, for treating erectile dysfunction and male hypogonadism.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/055651

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 31/395*** (2024.01); ***A61K 31/18*** (2024.01); ***A61K 31/505*** (2024.01); *A61K 31/33* (2024.01)

CPC: ***A61K 31/395; A61K 31/18; A61K 31/505;*** *A61K 31/33*

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2023/0285283 A1 (Kydes Pharmaceutical, LLC) 14 September 2023 (14.09.2023) para [0002], [0003], [0009], [0025], [0027], [0038]	1-4, 18-20, 28-29
A	US 2015/0018324 A1 (Chickmath et al) 15 January 2015 (15.01.2015) entire document	1-4, 18-20, 28-29
A	US 2021/0221793 A1 (Cyclerion Therapeutics, Inc) 22 July 2021 (22.07.2021) entire document	1-4, 18-20, 28-29
A	US 2011/0182997 A1 (Lewis et al) 28 July 2011 (28.07.2011) entire document	1-4, 18-20, 28-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 December 2024 (26.12.2024)	**13 January 2025 (13.01.2025)**

Name and mailing address of the ISA/US	Authorized officer
COMMISSIONER FOR PATENTS **MAIL STOP PCT, ATTN: ISA/US** **P.O. Box 1450** **Alexandria, VA 22313-1450** **UNITED STATES OF AMERICA**	**KARI RODRIQUEZ**
Facsimile No. **571-273-8300**	Telephone No. **PCT Help Desk: 571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/055651

Box No. II 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:

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.: **5-17, 21-27**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).