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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
09 January 2020 (09.01.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/006606 A1

(51) International Patent Classification:
*A61K 31/7088* (2006.01) *A61K 31/519* (2006.01)
*A61K 31/55* (2006.01) *A61P 15/00* (2006.01)
*A61K 31/4985* (2006.01)

(21) International Application Number:
PCT/AU2019/050710

(22) International Filing Date:
05 July 2019 (05.07.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2018902444 05 July 2018 (05.07.2018) AU

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(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, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, 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, 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 2020/006606 A1

(54) Title: A PHARMACEUTICAL COMPOSITION AND METHOD OF USE OF SAME

(57) Abstract: The present disclosure relates to a pharmaceutical composition in a pharmaceutically acceptable vehicle. The pharmaceutical composition includes a physiologically effective, non-priapismic, dose of a penile-erection-inducing agent or a pharmaceutically acceptable addition salt thereof and a physiologically effective dose of an orgasm-delaying agent or a pharmaceutically acceptable addition salt thereof. The disclosed pharmaceutical composition may be useful in the treatment of erectile dysfunction and premature ejaculation.

# A PHARMACEUTICAL COMPOSITION AND METHOD OF USE OF SAME

## FIELD

The present disclosure relates to a pharmaceutical composition for inducing a non-priapismic penile erection and extending a sexual reproduction cycle of a human male. The present disclosure also relates to a method of using the pharmaceutical composition to induce a non-priapismic penile erection and to extend a sexual reproduction cycle of a human male.

## BACKGROUND

Erectile dysfunction (also known as impotence) is known to affect between 1-10% of male humans under 40 years of age and to increase in prevalence with increasing age. Erectile dysfunction is typically associated with an inability of a human male to achieve and/or maintain a penile erection during a sexual activity, in particular a shared sexual activity. The aetiology of erectile dysfunction is varied and usually considered to be multifactorial. Factors known to induce erectile dysfunction include biological/physiological factors and psychosocial factors. As will be appreciated, erectile dysfunction can impact on the mental wellbeing of the person with erectile dysfunction as well as his sexual relationships with others and his self-image.

Likewise, premature ejaculation, i.e., sexual activity accompanied by a short ejaculatory latency, is a common human male sexual experience. Premature ejaculation is typically associated with a human male having an ejaculatory latency that does not extend beyond 1-2 minutes. The aetiology of premature ejaculation is also varied and usually considered to be multifactorial. Factors known to induce premature ejaculation also include biological/physiological factors and psychosocial factors. As will also be appreciated, premature ejaculation can have a negative impact on the mental wellbeing of the person with a short ejaculatory latency as well as his sexual relationships with others and his self-image.

Accordingly, it will be readily appreciated that an effective treatment that can address erectile dysfunction and premature ejaculation will benefit those afflicted with erectile dysfunction and premature ejaculation.

## SUMMARY

The following is a broad summary of various exemplary embodiments of a composition for inducing a non-priapismic penile erection and extending a sexual reproduction cycle, the composition formulated for administration to a human male. The present disclosure also relates to a method of using the composition to induce a

non-priapismic penile erection and to extend a period of the male sexual reproduction cycle.

According to an embodiment of the invention, there is provided a pharmaceutical composition in a pharmaceutically acceptable vehicle, the pharmaceutical composition comprising a physiologically effective, non-priapismic, dose of a penile-erection-inducing agent or a pharmaceutically acceptable addition salt thereof and a physiologically effective dose of an orgasm-delaying agent or a pharmaceutically acceptable addition salt thereof.

In another embodiment, the penile-erection-inducing agent may be a phosphodiesterase type 5 inhibitor.

In another embodiment, the phosphodiesterase type 5 inhibitor may be selected from the group consisting of: avanafil, iodenafil, mirodenafil, sildenafil, tadalafil, vardenafil, udenafil, zaprinast, icariin, benzamidenafil, and dasantafil.

In another embodiment, the orgasm-delaying agent may be selected from the group consisting of: anaesthetics, analgesics, antidepressants, sedatives, and stimulants.

In another embodiment, the anaesthetic may be selected from the group consisting of: benzocaine, butamben, dibucaine, lidocaine, oxybuprocaine, pramoxine, proparacaine, proxymetacaine, and tetracaine.

In another embodiment, the analgesic may be selected from the group consisting of: acetaminophen, aspirin, buprenorphine, celecoxib, codeine, dihydromorphine, etoricoxib, hydrocodone, ibuprofen, naproxen, oxycodone, pethidine, rofecoxib, and valdecoxib.

In another embodiment, the antidepressant may be selected from the group consisting of: a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a serotonin antagonist, a serotonin reuptake inhibitor, a serotonin modulator, a serotonin stimulator, a serotonin–norepinephrine reuptake inhibitor, a tetracyclic antidepressant; and a tricyclic antidepressant.

In another embodiment, the selective serotonin reuptake inhibitor may be selected from the group consisting of: alaproclate, centropazine, cericlamine, citalopram, dapoxetine, desvenlafaxine, duloxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, indalpine, levomilnacipran, minacipran, omiloxetine, panuramine, paroxetine, seproxetine, sertraline, venlafaxine, and zimelidine.

In another embodiment, the sedative may be selected from the group consisting of: afloqualone, alfentanil, alprazolam, amobarbital, benzylbutylbarbiturate, brompheniramine, butalbital, carfentanil, chlordiazepoxide, chlorpheniramine, clobazam, clonazepam, clorazepate, cloroqualone, codeine, diazepam, dimenhydrinate, diphenhydramine, diproqualone, doxylamine, estazolam, eszopiclone, etaqualone, etizolam, fentanyl, flunitrazepam, hydrocodone, hydromorphone, hydroxyzine, lorazepam, mebroqualone, mecloqualone, meperidine, methadone, methaqualone, methylmethaqualone, midazolam, morphine, nitrazepam, nitromethaqualone, opium, oxazepam, oxycodone, oxymorphone, pentobarbital, phenobarbital, promethazine, propoxyphene, remifentanil, secobarbital, sodium thiopental, sufentanil, suvorexant, tapentadol, temazepam, tramadol, triazolam, zaleplon, zolpidem, and zopiclone.

In another embodiment, the stimulant may be selected from the group consisting of: 3,4-methylenedioxymethamphetamine, amphetamine, caffeine, ephedrine, mephedrone, methylenedioxypyrovalerone, methylphenidate, nicotine, *N*-methyl-alpha-methylphenethylamine, phenylpropanolamine, propylhexedrine, and pseudoephedrine.

According to an embodiment of the invention, there is provided a method for extending a sexual response cycle, the method comprising administering to a human male in need thereof a pharmaceutical composition in a pharmaceutically acceptable vehicle, the pharmaceutical composition comprising a physiologically effective, non-priapismic, dose of a penile-erection-inducing agent or a pharmaceutically acceptable addition salt thereof and a physiologically effective dose of an orgasm-delaying agent or a pharmaceutically acceptable addition salt thereof, the pharmaceutical composition administered to induce and maintain a penile erection sufficient to extend the sexual response cycle and attain sexual satisfaction during a sexual activity of the human male.

In another embodiment of the method, the penile-erection-inducing agent may be a phosphodiesterase type 5 inhibitor.

In another embodiment of the method, the phosphodiesterase type 5 inhibitor may be selected from the group consisting of: avanafil, iodenafil, mirodenafil, sildenafil, tadalafil, vardenafil, udenafil, zaprinast, icariin, benzamidenafil, and dasantafil.

In another embodiment of the method, the orgasm-delaying agent may be selected from the group consisting of: anaesthetics, analgesics, antidepressants, sedatives, and stimulants.

In another embodiment of the method, the anaesthetic may be selected from the group consisting of: benzocaine, butamben, dibucaine, lidocaine, oxybuprocaine, pramoxine, proparacaine, proxymetacaine, and tetracaine.

In another embodiment of the method, the analgesic may be selected from the group consisting of: acetaminophen, aspirin, buprenorphine, celecoxib, codeine, dihydromorphine, etoricoxib, hydrocodone, ibuprofen, naproxen, oxycodone, pethidine, rofecoxib, and valdecoxib.

In another embodiment of the method, the antidepressant may be selected from the group consisting of: a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a serotonin antagonist, a serotonin reuptake inhibitor, a serotonin modulator, a serotonin stimulator, a serotonin–norepinephrine reuptake inhibitor, a tetracyclic antidepressant; and a tricyclic antidepressant.

In another embodiment of the method, the selective serotonin reuptake inhibitor may be selected from the group consisting of: alaproclate, centropazine, ericlamine, citalopram, dapoxetine, desvenlafaxine, duloxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, indalpine, levomilnacipran, minacipran, omiloxetine, panuramine, paroxetine, seproxetine, sertraline, venlafaxine, and zimelidine.

In another embodiment of the method, the sedative may be selected from the group consisting of: afloqualone, alfentanil, alprazolam, amobarbital, benzylbutylbarbiturate, brompheniramine, butalbital, carfentanil, chlordiazepoxide, chlorpheniramine, clobazam, clonazepam, clorazepate, cloroqualone, codeine, diazepam, dimenhydrinate, diphenhydramine, diproqualone, doxylamine, estazolam, eszopiclone, etaqualone, etizolam, fentanyl, flunitrazepam, hydrocodone, hydromorphone, hydroxyzine, lorazepam, mebroqualone, mecloqualone, meperidine, methadone, methaqualone, methylmethaqualone, midazolam, morphine, nitrazepam, nitromethaqualone, opium, oxazepam, oxycodone, oxymorphone, pentobarbital, phenobarbital, promethazine, propoxyphene, remifentanil, secobarbital, sodium thiopental, sufentanil, suvorexant, tapentadol, temazepam, tramadol, triazolam, zaleplon, zolpidem, and zopiclone.

In another embodiment of the method, the stimulant may be selected from the group consisting of: 3,4-methylenedioxymethamphetamine, amphetamine, caffeine, ephedrine, mephedrone, methylenedioxypyrovalerone, methylphenidate, nicotine, *N*-methyl-alpha-methylphenethylamine, phenylpropanolamine, propylhexedrine, and pseudoephedrine.

In another embodiment of the method, wherein at least one period of the sexual response cycle is extended.

In another embodiment of the method, wherein the at least one period is an excitement phase.

In another embodiment of the method, wherein the at least one period is a plateau excitement phase.

In another embodiment of the method, wherein the at least one period is an orgasm phase.

Embodiments of the invention are now described, by way of example.

## DETAILED DESCRIPTION

The present disclosure is directed, at least in part, to a pharmaceutical composition for inducing a non-priapismic penile erection and extending a sexual reproduction cycle formulated for administration to a human male. The present disclosure also relates to a method of using the pharmaceutical composition to induce a non-priapismic penile erection and to extend a period of the male sexual reproduction cycle.

Erectile dysfunction should be understood to include the inability of a human male to achieve and/or maintain a penile erection that allows sexual activity, in particular a shared sexual activity. Erectile dysfunction should be understood not to be disease *per se* but is a symptom of an underlying problem that may be biological/physiological, psychosocial, or a combination of both biological/physiological and psychosocial causes. Such causes of erectile dysfunction may include, for example, biological/physiological causes such as acromegaly; ageing; alcohol and drug abuse; Alzheimer's disease; atherosclerosis; cardiovascular disease; cigarette smoking; cortisone excess; diabetes mellitus; diabetic neuropathy; drug side effects; high cholesterol; hormonal insufficiencies; hypertension; hypogonadism; lower urinary tract symptoms; medicines used to treat: hypertension, high cholesterol, depression and psychiatric disorders; prostate cancer; multiple sclerosis; neurological problems; obesity; Parkinson's disease; pelvic surgery

(prostate and bowel); pelvic trauma; Peyronie's disease; sleep apnoea; spinal cord; physical trauma; thyroid disease; and several common lifestyle factors, such as obesity, limited or an absence of physical exercise. Psychosocial causes may include, for example, depression, employment pressures, financial pressures, performance anxiety, psychiatric disorders, relationship problems, and sexual attitudes and upbringing.

The aetiology underlying a need to extend a latency period of the male sexual reproduction cycle that may be due to premature ejaculation can be classified as primary premature ejaculation or secondary premature ejaculation. Primary premature ejaculation, also known as lifelong premature ejaculation, may occur across all or nearly all sexual activities across the sexual lifespan of a human male. Secondary premature ejaculation, also known as acquired premature ejaculation, may arise, i.e., be acquired, after previous sexual activities where premature ejaculation was not experienced as a problem.

Premature ejaculation may be defined as always or nearly always ejaculating within a very short time of penetration and an inability to delay ejaculation during sexual activities all or nearly all the time. Premature ejaculation is known to be associated with a feeling of distress and frustration and consequent tendency to avoid a shared sexual and intimate experience as a result.

As mentioned above, men tend to experience a high level of discomfiture when premature ejaculation occurs during a sexual experience, in particular a shared sexual experience. Premature ejaculation is a common and treatable condition, known to be affected by several factors that play a role in the development and continued experience thereof. Such factors are known to include a complex interaction of psychosocial factors and physiological/biological factors.

Psychosocial factors that play a role in the development and continued experience of premature ejaculation include: depression, early sexual experiences, erectile dysfunction, guilty feelings that increase a tendency to hasten sexual experiences, poor body image, sexual abuse which occurred in childhood, and an ongoing concern about experiencing premature ejaculation.

The present disclosure contemplates a pharmaceutical composition in a pharmaceutically acceptable vehicle, the pharmaceutical composition comprising a physiologically effective, non-priapismic, dose of a penile-erection-inducing agent or a pharmaceutically acceptable addition salt thereof and a physiologically effective dose

of an orgasm-delaying agent or a pharmaceutically acceptable addition salt thereof. The formulation of the pharmaceutical composition such that it will be suitable to administration to a human male will be known to a person skilled in the art. Such formulation may include a formulation suitable for oral administration or parenteral administration. Routes of administration may include, for example, buccal, epicutaneous, epidural, insufflation, intra-arterial, intracavernous injection, intradermal, intraperitoneal, intravenous, nasal, oral, subcutaneous, sublabial, sublingual, transdermal, and transmucosal.

The present disclosure contemplates embodiments of the pharmaceutical composition that include a phosphodiesterase type 5 inhibitor as a penile-erection-inducing agent for treatment and/or amelioration of erectile dysfunction. In preferred embodiments, the phosphodiesterase type 5 inhibitor is selected from the group consisting of: avanafil, iodenafil, mirodenafil, sildenafil, tadalafil, vardenafil, udenafil, zaprinast, icariin, benzamidenafil, and dasantafil.

The present disclosure contemplates embodiments that include an orgasm-delaying agent is selected from the group consisting of: anaesthetics, analgesics, antidepressants, sedatives, and stimulants for the treatment and/or amelioration of premature ejaculation.

The present disclosure also contemplates that in some embodiments of the composition, the anaesthetic is selected from the group consisting of: benzocaine, butamben, dibucaine, lidocaine, oxybuprocaine, pramoxine, proparacaine, proxymetacaine, and tetracaine.

The present disclosure also contemplates that in some embodiments of the composition, the analgesic is selected from the group consisting of: acetaminophen, aspirin, buprenorphine, celecoxib, codeine, dihydromorphine, etoricoxib, hydrocodone, ibuprofen, naproxen, oxycodone, pethidine, rofecoxib, and valdecoxib.

The present disclosure also contemplates that in some embodiments of the pharmaceutical composition, the antidepressant is selected from the group consisting of: a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a serotonin antagonist, a serotonin reuptake inhibitor, a serotonin modulator, a serotonin stimulator, a serotonin-norepinephrine reuptake inhibitor, a tetracyclic antidepressant; and a tricyclic antidepressant.

The present disclosure also contemplates that in some embodiments of the pharmaceutical composition, the selective serotonin reuptake inhibitor is selected from

the group consisting of: alaproclate, centropazine, cericlamine, citalopram, dapoxetine, desvenlafaxine, duloxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, indalpine, levomilnacipran, minacipran, omiloxetine, panuramine, paroxetine, seproxetine, sertraline, venlafaxine, and zimelidine.

The present disclosure also contemplates that in some embodiments of the pharmaceutical composition, the sedative is selected from the group consisting of: afloqualone, alfentanil, alprazolam, amobarbital, benzylbutylbarbiturate, brompheniramine, butalbital, carfentanil, chlordiazepoxide, chlorpheniramine, clobazam, clonazepam, clorazepate, cloroqualone, codeine, diazepam, dimenhydrinate, diphenhydramine, diproqualone, doxylamine, estazolam, eszopiclone, etaqualone, etizolam, fentanyl, flunitrazepam, hydrocodone, hydromorphone, hydroxyzine, lorazepam, mebroqualone, mecloqualone, meperidine, methadone, methaqualone, methylmethaqualone, midazolam, morphine, nitrazepam, nitromethaqualone, opium, oxazepam, oxycodone, oxymorphone, pentobarbital, phenobarbital, promethazine, propoxyphene, remifentanil, secobarbital, sodium thiopental, sufentanil, suvorexant, tapentadol, temazepam, tramadol, triazolam, zaleplon, zolpidem, and zopiclone.

The present disclosure also contemplates that in some embodiments of the pharmaceutical composition, the stimulant is selected from the group consisting of: 3,4-methylenedioxymethamphetamine, amphetamine, caffeine, ephedrine, mephedrone, methylenedioxypyrovalerone, methylphenidate, nicotine, *N*-methyl-alpha-methylphenethylamine, phenylpropanolamine, propylhexedrine, and pseudoephedrine.

The present disclosure also contemplates a method for extending a sexual response cycle, the method comprising administering to a human male in need thereof a pharmaceutical composition in a pharmaceutically acceptable vehicle, the pharmaceutical composition comprising a physiologically effective, non-priapismic, dose of a penile-erection-inducing agent or a pharmaceutically acceptable addition salt thereof and a physiologically effective dose of an orgasm-delaying agent or a pharmaceutically acceptable addition salt thereof, the pharmaceutical composition administered to induce and maintain a penile erection sufficient to extend the sexual response cycle and attain sexual satisfaction during a sexual activity of the human male.

The present disclosure also contemplates that in some embodiments of the method, the penile-erection-inducing agent is a phosphodiesterase type 5 inhibitor.

The present disclosure also contemplates that in some embodiments of the method, the phosphodiesterase type 5 inhibitor is selected from the group consisting of: avanafil, iodenafil, mirodenafil, sildenafil, tadalafil, vardenafil, udenafil, zaprinast, icariin, benzamidenafil, and dasantafil.

The present disclosure also contemplates that in some embodiments of the method, the orgasm-delaying agent is selected from the group consisting of: anaesthetics, analgesics, antidepressants, sedatives, and stimulants.

The present disclosure also contemplates that in some embodiments of the method, the anaesthetic is selected from the group consisting of: benzocaine, butamben, dibucaine, lidocaine, oxybuprocaine, pramoxine, proparacaine, proxymetacaine, and tetracaine.

The present disclosure also contemplates that in some embodiments of the method, the analgesic is selected from the group consisting of: acetaminophen, aspirin, buprenorphine, celecoxib, codeine, dihydromorphine, etoricoxib, hydrocodone, ibuprofen, naproxen, oxycodone, pethidine, rofecoxib, and valdecoxib.

The present disclosure also contemplates that in some embodiments of the method, the antidepressant is selected from the group consisting of: a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a serotonin antagonist, a serotonin reuptake inhibitor, a serotonin modulator, a serotonin stimulator, a serotonin-norepinephrine reuptake inhibitor, a tetracyclic antidepressant; and a tricyclic antidepressant.

The present disclosure also contemplates that in some embodiments of the method, the selective serotonin reuptake inhibitor is selected from the group consisting of: alaproclate, centropazine, ericlamine, citalopram, dapoxetine, desvenlafaxine, duloxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, indalpine, levomilnacipran, minacipran, omiloxetine, panuramine, paroxetine, seproxetine, sertraline, venlafaxine, and zimelidine.

The present disclosure also contemplates that in some embodiments of the method, the sedative is selected from the group consisting of: afloqualone, alfentanil, alprazolam, amobarbital, benzylbutylbarbiturate, brompheniramine, butalbital, carfentanil, chlordiazepoxide, chlorpheniramine, clobazam, clonazepam, clorazepate, cloroqualone, codeine, diazepam, dimenhydrinate, diphenhydramine, diproqualone,

doxylamine, estazolam, eszopiclone, etaqualone, etizolam, fentanyl, flunitrazepam, hydrocodone, hydromorphone, hydroxyzine, lorazepam, mebroqualone, mecloqualone, meperidine, methadone, methaqualone, methylmethaqualone, midazolam, morphine, nitrazepam, nitromethaqualone, opium, oxazepam, oxycodone, oxymorphone, pentobarbital, phenobarbital, promethazine, propoxyphene, remifentanil, secobarbital, sodium thiopental, sufentanil, suvorexant, tapentadol, temazepam, tramadol, triazolam, zaleplon, zolpidem, and zopiclone.

The present disclosure also contemplates that in some embodiments of the method, the stimulant is selected from the group consisting of: 3,4-methylenedioxymethamphetamine, amphetamine, caffeine, ephedrine, mephedrone, methylenedioxypyrovalerone, methylphenidate, nicotine, *N*-methyl-alpha-methylphenethylamine, phenylpropanolamine, propylhexedrine, and pseudoephedrine.

The present disclosure also contemplates that in some embodiments of the method, a period between a first phase of the sexual response cycle (excitement) and a third phase of the sexual response cycle (orgasm) is extended.

The following prophetic examples are made:

Example 1

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, avanafil and dapoxetine.

Example 2

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, sildenafil and dapoxetine.

Example 3

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, tadalafil and dapoxetine.

Example 4

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, vardenafil and dapoxetine.

Example 5

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, udenafil and dapoxetine.

Example 6

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, avanafil and paroxetine.

Example 7

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, sildenafil and paroxetine.

Example 8

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, tadalafil and paroxetine.

Example 9

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, vardenafil and paroxetine.

Example 10

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is

prepared. The composition comprises, each in a physiologically effective dose, udenafil and paroxetine.

Example 11

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, avanafil and clomipramine.

Example 12

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, sildenafil and clomipramine.

Example 13

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, tadalafil and clomipramine.

Example 14

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, vardenafil and clomipramine.

Example 15

A pharmaceutical composition formulated for oral administration to a human male comprising a penile-erection-inducing agent and an orgasm-delaying agent is prepared. The composition comprises, each in a physiologically effective dose, udenafil and clomipramine.

Example 16

A 48-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 1. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 17

A 58-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 2. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 18

A 60-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 3. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 19

A 38-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 4. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 20

A 35-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 5. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 21

A 39-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 6. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 22

A 49-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 7. Tumescence

of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 23

A 59-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 8. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 24

A 69-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 9. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 25

A 29-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 10. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 26

A 31-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 11. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 27

A 43-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 12. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 28

A 55-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 13. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 29

A 19-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 14. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

Example 30

A 24-year-old male human subject having both erectile dysfunction and premature ejaculation participates in a treatment regime comprising the oral consumption of the pharmaceutical composition as set out in Example 15. Tumescence of the penis is experienced with full erection and delayed ejaculation relative to previously experienced sexual activity, i.e., an untreated condition.

A person skilled in the art will appreciate that the composition of the above prophetic examples may be formulated to accommodate other physiologically acceptable routes of administration.

It is to be understood that the terminology employed above is for the purpose of description and should not be regarded as limiting. The described embodiments are intended to be illustrative of the invention, without limiting the scope thereof. The invention is capable of being practised with various modifications and additions as will readily occur to those skilled in the art.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition in a pharmaceutically acceptable vehicle, the pharmaceutical composition comprising a physiologically effective, non-priapismic, dose of a penile-erection-inducing agent or a pharmaceutically acceptable addition salt thereof and a physiologically effective dose of an orgasm-delaying agent or a pharmaceutically acceptable addition salt thereof.

2. The composition of claim 1, wherein the penile-erection-inducing agent is a phosphodiesterase type 5 inhibitor.

3. The composition of claim 2, wherein the phosphodiesterase type 5 inhibitor is selected from the group consisting of: avanafil, iodenafil, mirodenafil, sildenafil, tadalafil, vardenafil, udenafil, zaprinast, icariin, benzamidenafil, and dasantafil.

4. The composition according to any one of claims 1 to 3, wherein the orgasm-delaying agent is selected from the group consisting of: anaesthetics, analgesics, antidepressants, sedatives, and stimulants.

5. The composition according to claim 4, wherein the anaesthetic is selected from the group consisting of: benzocaine, butamben, dibucaine, lidocaine, oxybuprocaine, pramoxine, proparacaine, proxymetacaine, and tetracaine.

6. The composition according to claim 4, wherein the analgesic is selected from the group consisting of: acetaminophen, aspirin, buprenorphine, celecoxib, codeine, dihydromorphine, etoricoxib, hydrocodone, ibuprofen, naproxen, oxycodone, pethidine, rofecoxib, and valdecoxib.

7. The composition according to claim 4, wherein the antidepressant is selected from the group consisting of: a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a serotonin antagonist, a serotonin reuptake inhibitor, a serotonin modulator, a serotonin stimulator, a serotonin–norepinephrine reuptake inhibitor, a tetracyclic antidepressant; and a tricyclic antidepressant.

8. The composition according to claim 7, wherein the selective serotonin reuptake inhibitor is selected from the group consisting of: alaproclate, centropazine, cericlamine, citalopram, dapoxetine, desvenlafaxine, duloxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, indalpine, levomilnacipran, minacipran, omiloxetine, panuramine, paroxetine, seproxetine, sertraline, venlafaxine, and zimelidine.

9. The composition according to claim 4, wherein the sedative is selected from the group consisting of: afloqualone, alfentanil, alprazolam, amobarbital, benzylbutylbarbiturate, brompheniramine, butalbital, carfentanil, chlordiazepoxide, chlorpheniramine, clobazam, clonazepam, clorazepate, cloroqualone, codeine, diazepam, dimenhydrinate, diphenhydramine, diproqualone, doxylamine, estazolam, eszopiclone, etaqualone, etizolam, fentanyl, flunitrazepam, hydrocodone, hydromorphone, hydroxyzine, lorazepam, mebroqualone, mecloqualone, meperidine, methadone, methaqualone, methylmethaqualone, midazolam, morphine, nitrazepam, nitromethaqualone, opium, oxazepam, oxycodone, oxymorphone, pentobarbital, phenobarbital, promethazine, propoxyphene, remifentanil, secobarbital, sodium thiopental, sufentanil, suvorexant, tapentadol, temazepam, tramadol, triazolam, zaleplon, zolpidem, and zopiclone.

10. The composition according to claim 4, wherein the stimulant is selected from the group consisting of: 3,4-methylenedioxymethamphetamine, amphetamine, caffeine, ephedrine, mephedrone, methylenedioxypyrovalerone, methylphenidate, nicotine, *N*-methyl-alpha-methylphenethylamine, phenylpropanolamine, propylhexedrine, and pseudoephedrine.

11. A method for extending a sexual response cycle, the method comprising administering to a human male in need thereof a pharmaceutical composition in a pharmaceutically acceptable vehicle, the pharmaceutical composition comprising a physiologically effective, non-priapismic, dose of a penile-erection-inducing agent or a pharmaceutically acceptable addition salt thereof and a physiologically effective dose of an orgasm-delaying agent or a

pharmaceutically acceptable addition salt thereof, the pharmaceutical composition administered to induce and maintain a penile erection sufficient to extend the sexual response cycle and attain sexual satisfaction during a sexual activity of the human male.

12. The method of claim 11, wherein the penile-erection-inducing agent is a phosphodiesterase type 5 inhibitor.

13. The method of claim 12, wherein the phosphodiesterase type 5 inhibitor is selected from the group consisting of: avanafil, iodenafil, mirodenafil, sildenafil, tadalafil, vardenafil, udenafil, zaprinast, icariin, benzamidenafil, and dasantafil.

14. The method according to any one of claims 11 to 13, wherein the orgasm-delaying agent is selected from the group consisting of: anaesthetics, analgesics, antidepressants, sedatives, and stimulants.

15. The composition according to claim 14, wherein the anaesthetic is selected from the group consisting of: benzocaine, butamben, dibucaine, lidocaine, oxybuprocaine, pramoxine, proparacaine, proxymetacaine, and tetracaine.

16. The composition according to claim 14, wherein the analgesic is selected from the group consisting of: acetaminophen, aspirin, buprenorphine, celecoxib, codeine, dihydromorphine, etoricoxib, hydrocodone, ibuprofen, naproxen, oxycodone, pethidine, rofecoxib, and valdecoxib.

17. The composition according to claim 14, wherein the antidepressant is selected from the group consisting of: a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a serotonin antagonist, a serotonin reuptake inhibitor, a serotonin modulator, a serotonin stimulator, a serotonin–norepinephrine reuptake inhibitor, a tetracyclic antidepressant; and a tricyclic antidepressant.

18. The composition according to claim 17, wherein the selective serotonin reuptake inhibitor is selected from the group consisting of: alaproclate,

centropazine, cericlamine, citalopram, dapoxetine, desvenlafaxine, duloxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, indalpine, levomilnacipran, minacipran, omiloxetine, panuramine, paroxetine, seproxetine, sertraline, venlafaxine, and zimelidine.

19. The composition according to claim 14, wherein the sedative is selected from the group consisting of: afloqualone, alfentanil, alprazolam, amobarbital, benzylbutylbarbiturate, brompheniramine, butalbital, carfentanil, chlordiazepoxide, chlorpheniramine, clobazam, clonazepam, clorazepate, cloroqualone, codeine, diazepam, dimenhydrinate, diphenhydramine, diproqualone, doxylamine, estazolam, eszopiclone, etaqualone, etizolam, fentanyl, flunitrazepam, hydrocodone, hydromorphone, hydroxyzine, lorazepam, mebroqualone, mecloqualone, meperidine, methadone, methaqualone, methylmethaqualone, midazolam, morphine, nitrazepam, nitromethaqualone, opium, oxazepam, oxycodone, oxymorphone, pentobarbital, phenobarbital, promethazine, propoxyphene, remifentanil, secobarbital, sodium thiopental, sufentanil, suvorexant, tapentadol, temazepam, tramadol, triazolam, zaleplon, zolpidem, and zopiclone.

20. The composition according to claim 14, wherein the stimulant is selected from the group consisting of: 3,4-methylenedioxymethamphetamine, amphetamine, caffeine, ephedrine, mephedrone, methylenedioxypyrovalerone, methylphenidate, nicotine, *N*-methyl-alpha-methylphenethylamine, phenylpropanolamine, propylhexedrine, and pseudoephedrine.

21. The method of any one of claims 11 to 20, wherein at least one period of the sexual response cycle is extended.

22. The method of claim 22, wherein the at least one period is an excitement phase.

23. The method of claim 22, wherein the at least one period is a plateau excitement phase.

24. The method of claim 22, wherein the at least one period is an orgasm phase.

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/AU2019/050710**

A. CLASSIFICATION OF SUBJECT MATTER

***A61K 31/7088 (2006.01)*** ***A61K 31/55 (2006.01)*** ***A61K 31/4985 (2006.01)*** ***A61K 31/519 (2006.01)*** ***A61P 15/00 (2006.01)***

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)

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

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

EPODOC, WPIAP, PATENW, CAPLUS, MEDLINE -, keywords - avanafil, stendra, sildenafil, viagra, tadalafil, Cialis, vardenafil, lebvitra, udenafil, zydena, dapoxetine, paroxetine, clomipramine, penile, erection, orgasm, oral, anaesthetic, benzoacaine, diducaine, lidocaine, pramoxine, tetracine, erectile, NSAID, aspirin, codeine, oxycodone, ibuprofen.

Google Patents - keywords sildenafil, tadalafil, caffeine.

Applicantt/Inventor serach.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| | Documents are listed in the continuation of Box C | |

[X] Further documents are listed in the continuation of Box C [X] 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 |
|---|---|
| 18 September 2019 | 18 September 2019 |
| **Name and mailing address of the ISA/AU** | **Authorised officer** |
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| INTERNATIONAL SEARCH REPORT<br>Information on patent family members | International application No.<br>**PCT/AU2019/050710** |
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

| INTERNATIONAL SEARCH REPORT<br>Information on patent family members | International application No.<br>**PCT/AU2019/050710** |
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**End of Annex**

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.