Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3094016 C 2023/10/10

(11)(21) 3 094 016

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2019/03/22
(87) Date publication PCT/PCT Publication Date: 2019/09/26
(45) Date de délivrance/Issue Date: 2023/10/10
(85) Entrée phase nationale/National Entry: 2020/09/15
(86) N° demande PCT/PCT Application No.: EP 2019/057267
(87) N° publication PCT/PCT Publication No.: 2019/180217
(30) Priorités/Priorities: 2018/03/23 (EP18305328.9); 2018/03/23 (US62/763,129)

(51) Cl.Int./Int.Cl. *A61K 31/4045* (2006.01), *A61K 45/06* (2006.01), *A61K 9/22* (2006.01), *A61K 9/50* (2006.01), *A61P 15/16* (2006.01)

(72) Inventeurs/Inventors:
EL GLAOUI, GUILLAUME, FR;
EL GLAOUI, MEHDI, FR;
PERRIN, PHILIPPE, FR;
DROUPY, STEPHANE, FR;
AGATHON-MERIAU, VERONIQUE, FR

(73) Propriétaire/Owner:
PHARMAJOR INTERNATIONAL, LU

(74) Agent: BORDEN LADNER GERVAIS LLP

(54) Titre : COMPOSITIONS NON HORMONALES ET PROCEDES DE CONTRACEPTION MASCULINE
(54) Title: NON-HORMONAL COMPOSITIONS AND METHODS FOR MALE CONTRACEPTION

(57) Abrégé/Abstract:
The present invention relates to the use of a composition in a non-hormonal contraception method for a male subject, comprising administering an alpha-1-adrenoreceptor antagonist; wherein the contraception method includes a once daily administration of said composition at about the same time each day, triggering a continuous reversible aspermia, azoospermia, or severe oligozoospermia in the male subject, and wherein after an initial period of at least two consecutive days, the contraception is not impaired by a delay of the subsequent once daily intake. This invention also relates to the packaging comprising 7, 14, 28, 56, 84, or 168 to 365 unit doses; or 10, 20, 30, 60, 90, or 180 to 360 single doses of the composition to be implemented according to the present invention.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 September 2019 (26.09.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/180217 A1

(51) International Patent Classification:
A61K 31/4045 (2006.01) *A61K 9/50* (2006.01)
A61K 45/06 (2006.01) *A61P 15/16* (2006.01)
A61K 9/22 (2006.01)

(21) International Application Number:
PCT/EP2019/057267

(22) International Filing Date:
22 March 2019 (22.03.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
18305328.9 23 March 2018 (23.03.2018) EP
62/763,129 23 March 2018 (23.03.2018) US

(71) Applicant: **LABORATOIRES MAJOR** [FR/FR]; 12 rue de Berri, 75008 Paris (FR).

(72) Inventors: **EL GLAOUI, Guillaume**; c/o LABORATOIRES MAJOR, 12 rue de Berri, 75008 Paris (FR). **EL GLAOUI, Mehdi**; c/o LABORATOIRES MAJOR, 12 rue de Berri, 75008 Paris (FR). **PERRIN, Philippe**; 10 rue du Docteur Roux, 75015 Paris (FR). **DROUPY, Stéphane**; 68 route Sauve, 30900 Nîmes (FR). **AGATHON-MERIAU, Véronique**; 31 rue Raymond Queneau, 92500 Rueil-Malmaison (FR).

(74) Agent: **ICOSA**; 83 avenue Denfert-Rochereau, 75014 Paris (FR).

(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).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

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

WO 2019/180217 A1

(54) Title: NON-HORMONAL COMPOSITIONS AND METHODS FOR MALE CONTRACEPTION

(57) Abstract: The present invention relates to the use of a composition in a non-hormonal contraception method for a male subject, comprising administering an alpha-1-adrenoreceptor antagonist; wherein the contraception method includes a once daily administration of said composition at about the same time each day, triggering a continuous reversible aspermia, azoospermia, or severe oligozoospermia in the male subject, and wherein after an initial period of at least two consecutive days, the contraception is not impaired by a delay of the subsequent once daily intake. This invention also relates to the packaging comprising 7, 14, 28, 56, 84, or 168 to 365 unit doses; or 10, 20, 30, 60, 90, or 180 to 360 single doses of the composition to be implemented according to the present invention.

NON-HORMONAL COMPOSITIONS AND METHODS FOR MALE CONTRACEPTION

FIELD OF INVENTION

The present invention relates to non-hormonal compositions and methods for male contraception. More specifically, this invention relates to a method of inducing a reversible condition of aspermia, azoospermia or severe oligozoospermia in a male subject, sufficient for a continuous contraceptive effect.

BACKGROUND OF INVENTION

Although pharmaceutical compositions and methods for female contraception have been well known in the art for decades, the same cannot be said for male contraception. The high demand for such a product is based upon the individual needs of each male subject, and may include, for example, the desire or need to reduce the burden of oral hormonal contraception on any female partner, or to minimize the possibility of failures associated with female contraception. Notwithstanding this demand, development of contraceptive pharmaceutical compositions and methods for men has proven to be a major medical challenge.

Currently, the majority of available contraception methods are female contraceptives. Only few options exist for men wishing to assume the birth control responsibility, which amount mainly to the use of prophylactics, such as condoms. The numerous drawbacks of condoms are well-known in the field, and include both potential for failure (i.e., breaking or improper use) as well as a decrease in sexual sensation. Another contraceptive option available to men is the surgical option of having a vasectomy, a procedure in which the male vas deferens are severed and then tied or sealed in a manner so as to prevent sperm from entering into the urethra. A vasectomy is typically considered to be a permanent method of sterilization, and is not easily reversed, and so is not a viable option for any male subject who wishes to have children at any point in the future.

In light of this, efforts have been made to find a safe, effective, hormone-based, or chemical-based reversible contraceptive for males. Historically, most therapeutic targets have been hormonal and therefore likely to have intolerable sexual, behavioral, physiological, and psychological side effects, such as loss of sexual desire, loss of virility (e.g. erectile dysfunction, breast tenderness and growth of breast tissue, shrinkage of testicles and penis or loss of muscle mass), depression, possible suicidal thoughts, decreased mental sharpness, weight gain, fatigue or hot flashes.

Hormonal contraceptive methods have other drawbacks as well, including, for example, the requirement of high dosage amounts (Guerin et al, INTERNATIONAL JOURNAL OF ANDROLOGY, 1988, 11 (3), 187–199) or frequent injection schedules (World Health Organization Task Force on Methods for the Regulation of Male Fertility, FERTIL. STERIL., 1996, 65(4), 821-829).

The male urinary smooth muscles contain high densities of alpha-1-adrenoceptors and several alpha-1-adrenoceptor subtypes have been identified, namely alpha-1a, alpha-1b and alpha-1d-adrenoceptor subtypes. The alpha-1a-adrenoceptor subtype has been described to be predominant in the human prostate and is present in the male reproductive tract tissues (testis, epididymis, seminal vesicle and prostate) (Patrão et al, MHR-BASIC SCIENCE OF REPRODUCTIVE MEDECINE, 2008, 14 (2), 85-96).

Alpha-1-adrenoreceptor antagonists (also known as alpha-1 blockers or alpha-1-adrenergic blocking agents) make up a class of drugs that blocks alpha1-adrenergic receptors in arteries, smooth muscles, and central nervous system tissues. When administered in humans, they prevent the hormone norepinephrine from tightening the muscles in the walls of smaller arteries and veins, which causes the vessels to remain open and relaxed. This improves blood flow and lowers blood pressure. Because alpha blockers also relax other muscles throughout the body, these medications can help improve urine flow in older men with prostate problems such as Benign Prostatic Hyperplasia (“BPH”).

However, the administration of alpha-1 adrenoceptor antagonists may induce negative side effects such as hypotension, blepharoptosis, rhinorrhea, fatigue, headaches or diarrhea.

The alpha-1-adrenoreceptor antagonist tamsulosin is sold commercially as tamsulosin hydrochloride, ((-)-(*R*)-5-[2-[[2-(o-Ethoxyphenoxy) ethyl]amino]propyl]-2- methoxy-benzenesulfonamide, monohydrochloride) under the trade name, e.g., Flomax® for the treatment of BPH. Wang et al. reported a dose dependent decrease in the volume of semen after a single dose of 0.4 or 0.8 mg of Tamsulosin (Wang J et al., Assessment of Tamsulosin as a Potential Male Contraceptive in Healthy Volunteers. UROLOGY (2012) 80: 614–617). The volume of semen was evaluated 4 to 6 hours after dosing. Complete anejaculation was reached with the 0.8-mg dose, and the authors reported that "functional sperm count was significantly reduced" with the 0.4 mg. Libido and orgasm were normal in all volunteers. Side effects including discomfort on ejaculation as well as alpha-1-adrenoreceptor antagonist side effects, such as blepharoptosis, fatigue and rhinorrhea, were reported by some subjects.

Silodosin, also known as (-)-(*R*)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide, is a highly selective alpha-1a-adrenoreceptor antagonist that is also currently known and used in the treatment of BPH. Currently, it is marketed and sold as a BPH treatment under the brand name Urorec® or Rapaflo®. In vitro studies in humans have proved the uroselectivity of silodosin, a drug which reduces the contraction of the prostatic smooth muscle (Moriyama N, Akiyama K, Murata S, et al., KMD-3213, a novel alpha1A-adrenoceptor antagonist, potently inhibits the functional alpha1-adrenoceptor in human prostate. EUR J PHARMACOL. 1997;331(1):39–42) (Akiyama K, Tatemichi S, Katayama S, et al. Relationship between prostatic alpha(1)-adrenoceptor binding and reduction in intraurethral pressure following continuous infusion of KMD-3213 in rats. PHARMACOLOGY. 2002;64(3):140–147), to be greater than that of other alpha-1 blockers, such as tamsulosin and naftopidil (Tatemichi S, Tomiyama Y, Maruyama I, et al. Uroselectivity in male dogs of silodosin (KMD-3213), a novel drug for the obstructive

component of benign prostatic hyperplasia. NEUROUROL URODYN. 2006;25(7):792–799. discussion 800–801).

One side effect of silodosin, when administered in amounts to treat BPH, is retrograde ejaculation (RE), also known as a decrease or absence of semen during ejaculation. For example, Sakata K. et al. demonstrated that the administration of silodosin at 4 mg twice a day induced ejaculatory disorder at a high incidence (K. Sakata et al., BMC Urology 2012, 12:29). Kobayashi et al. reported that 4 mg of silodosin given twice a day for 3 days, induced a complete lack of seminal emission on healthy volunteers (Kobayashi et al., International Journal of Impotence Research 2009, 21, 306-310). Kobayashi et al. also show a 100% rate of discomfort upon ejaculation for male subjects treated with silodosin (Kobayashi K, et al. Inhibition of seminal emission is the main cause of anejaculation induced by a new highly selective α1A-blocker in normal volunteers. J. SEX MED (2008) 5:2185–2190), while Shimizu et al. report a decrease in quality of orgasm (Shimizu F, et al. Impact of dry ejaculation caused by highly selective alpha1a-blocker: randomized, double-blind, placebo-controlled crossover pilot study in healthy volunteer men. J. SEX MED. (2010) 7(3):1277-83). Other studies still show decrease in erectile function (Bozkurt O, et al. Silodosin causes impaired ejaculation and enlargement of seminal vesicles in sexually active men treated for lower urinary tract symptoms suggestive of benign prostatic hyperplasia. UROLOGY (2015) 85(5):1085-9) and sexual desire (Capogrosso P, et al. Effects of silodosin on sexual function – realistic picture from the everyday clinical practice. ANDROLOGY (2015) 3:1076–1081).

Additionally, the effect of the alpha-1, especially alpha-1a blockers on the ejaculatory function as well as their side effects is known to be dose-dependent (see e.g., Hisasue SI, et al. Ejaculatory disorder caused by alpha-1 adrenoceptor antagonists is not retrograde ejaculation but a loss of seminal emission. INTERNATIONAL JOURNAL OF UROLOGY (2006) 13:1311–1316).

In the prior art, Bhat et al (INDIAN JOURNAL OF UROLOGY (2018) 34(5): S7) reported a study aiming at evaluating the efficacy of silodosine 8 mg as on-demand, reversible, male oral contraceptive. The study was carried out in several parts. In a first part, participants received silodosine 8mg for 7 days and were evaluated 2 hours after

intake (the results were: no spermatozoa in the semen and post-analysis urine). In a second part, Day 8 to 15, they received placebo (the result was: no information in the first two days, normal semen analysis from day 2 of placebo). In a third part, during 6 months, they had on demand silodosine 8 mg, sporadically, prior to the sexual intercourse. At that time, they were not evaluated and the study states that no unintended pregnancy was reported.

Bhat et al Bhat et al reports an on-demand male contraception.

However, Bhat et al does not fulfill the needs of the subjects who ask for a safe contraceptive method ensuring a continuous contraceptive effect, where they are confident that they are not exposed to a fertility risk.

The present invention aims at bringing a solution to those subjects. Especially, the present invention aims at providing compositions and methods would not impact the erectile function, sexual desire, ejaculation, and quality of orgasm, of the male subject nor induce undesirable side effects that would discourage male subjects from using it.

SUMMARY

This invention aims at providing a male contraceptive method, where side effects are highly limited, administration is simple, effect is reversible, and as in female contraception, when a delay occurs, compared to the recommended administration scheme, such delay does not impair the effectiveness. For the purposes of establishing familiarity and compliance in male subjects, such a treatment method shall resemble to female hormonal contraceptive methods where a once-a-day pill is to be administered at the same time every day and a subject's delay in taking one pill for as long as twenty-four-hours does not impact the contraceptive effect.

Even though some pieces of prior art reported a pharmacological effect, i.e. an aspermia when alpha-adrenergic antagonists were administered, to the knowledge of the Applicant, none of the prior art documents ever described or suggested that alpha-1 adrenoceptor antagonists, especially alpha-1a adrenoceptor antagonists, could meet all the

requirements and criteria of a continuous male contraceptive method that would be suitable for a large population without much restrictions, altogether.

Up to the present invention, no administration profiles for male contraception comprising a once daily administration and with a regular duration of action were ever proposed. Surprisingly, the Applicant found out that a male contraceptive method could be envisaged, and that a daily alpha-1 adrenoceptor antagonist administration could, under certain conditions, fulfill all the criteria set forth hereabove. The use of the compositions according to the invention further ensures convenience and reversibility.

Furthermore, to the Applicants surprise, it was found that the pharmacokinetic profile of this male contraception method may not be influenced in a clinically meaningful manner by concomitant food consumption, which is a significant improvement in terms of benefit vs. risk assessment of the invention and subject compliance to the treatment.

Also surprisingly, the Applicant shows that, in a subject implementing the method of the invention, the quality of orgasm and the erectile function are preserved, as shown by the unchanged numerical rating scale (NRS) score for subjective quality of orgasms and unchanged international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction.

This invention relates to the use of a composition in a non-hormonal contraception method for a male subject, wherein said composition is an extended release formulation comprising:

- an alpha-1-adrenoreceptor antagonist; and
- at least one pharmaceutically acceptable carrier,

wherein the contraception method includes a once daily administration of said composition at about the same time each day, triggering a continuous reversible aspermia, azoospermia, or severe oligozoospermia in the male subject, and wherein after an initial period of at least two consecutive days, the contraception is not impaired by a delay of the subsequent once daily intake.

According to one embodiment, the composition is administered orally. According to another embodiment, after the initial period of consecutive days, the intake of a next dose

can be delayed from 6 to 18 hours after the last regular daily dose time, and the condition of aspermia, azoospermia or severe oligozoospermia is maintained in the male subject.

According to another embodiment, after the initial period of consecutive days, failure to intake one daily dose does not affect the continuous state of aspermia, azoospermia or severe oligozoospermia supporting the contraception method for 36 to 48 hours as of the last intake time.

According to another embodiment, the contraception method is carried on for at least eight days. According to another embodiment, the alpha-1-adrenoreceptor antagonist is in an amount ranging from about 0.1 to about 30 mg, preferably from about 0.2 to about 20 mg. According to another embodiment, the alpha-1-adrenoreceptor antagonist is (R)-silodosin. According to another embodiment, (R)-silodosin is in a polymorphic or amorphous form. According to another embodiment, the composition is formulated in an extended release formulation. According to another embodiment, the composition includes or consists of at least one particle, preferably at least one coated particle, and the average particle diameter is in the range of 0.01 to 5 mm, preferably 0.1 to 2 mm. According to another embodiment, the particles are encompassed into a capsule, each capsule being filled by particles in a number sufficient to reach the daily dose. According to another embodiment, the contraception is achieved independently from the food consumption by the male subject. According to another embodiment, the daily administration contraception method further comprises a simultaneous or sequential administration of an additional composition suitable for treating erectile dysfunction; preferably the additional composition comprises a phosphodiesterase-5 inhibitor.

This invention also relates to a packaging comprising at least 7, 14, 28, 56, 84, or 168 to 365 unitary doses; or 10, 20, 30, 60, 90, or 180 to 360 unitary doses of the composition of the invention, each unitary dose being a daily dose. According to one embodiment, the composition includes an alpha-1-adrenoreceptor antagonist in an amount ranging from about 0.1 to about 30 mg, preferably from about 0.2 to about 20 mg, preferably the alpha-1-adrenoreceptor antagonist is (R)-silodosin in an amount of 8 to 12 mg.

This invention also relates to a method of inducing a reversible condition of aspermia, azoospermia or severe oligozoospermia in a male subject sufficient for contraceptive effect, the method comprising administering once daily doses of a composition comprising:

- an extended release formulation of alpha-1-adrenoreceptor antagonist in an amount effective, when administered on a once daily dosing regimen, to induce a reversible condition of aspermia, azoospermia or severe oligozoospermia sufficient for contraceptive effect in the male subject; and
- a pharmaceutically acceptable carrier,

wherein the failure to administer one daily dose after an initial period of two consecutive days does not affect the continuous state of aspermia, azoospermia or severe oligozoospermia sufficient for contraceptive effect in the male subject.

According to one embodiment, the initial period of consecutive days is at least two consecutive days, with administration at about the same time each day. According to one embodiment, the initial period of consecutive days is at least 5 days. According to one embodiment, the method is suitable for short term, at least 8 days, to long term treatment. According to one embodiment, successive daily doses may be missed or omitted such that no dose is administered for more than about 48 hours.

According to one embodiment, two successive daily doses can be missed or omitted without affecting contraceptive effect in the male subject.

According to one embodiment, the amount of alpha-1-adrenoreceptor antagonist in the composition administered once daily is about 4 to about 12 mg. According to one embodiment, the alpha-1-adrenoreceptor antagonist is (R)-silodosin. According to one embodiment, the amount of (R)-silodosin in the composition administered once daily is about 4 to about 12 mg. According to one embodiment, the amount of (R)-silodosin in the composition administered once daily is about 8 mg.

According to one embodiment, the composition is administered orally. According to one embodiment, the composition is simultaneously or sequentially co-administered with a composition suitable for treating erectile dysfunction; preferably the additional

composition comprises a phosphodiesterase-5 (PDE5) inhibitor. According to one embodiment, the male subject suffers from benign prostatic hyperplasia (BPH). According to one embodiment, the male subject suffers from BPH and erectile dysfunction. According to one embodiment, the composition is administered with food. According to one embodiment, the composition is administered without food.

According to one embodiment, the extended release formulation comprises a microgranule form. According to one embodiment, the microgranules are less than 2 millimeters in diameter. According to one embodiment, the microgranules have a density greater than or equal to about 1.

This invention also relates to a method for reversible continuous non-hormonal contraception in a male subject, the method comprising administering once daily doses of a composition comprising:

- an extended release formulation of alpha-1-adrenoreceptor antagonist in an amount effective, when administered on a once daily dosing regimen, to induce a reversible condition of aspermia, azoospermia or severe oligozoospermia sufficient for contraceptive effect in the male subject; and
- a pharmaceutically acceptable carrier,

wherein the failure to administer one daily dose after an initial period of two consecutive days does not affect the continuous state of aspermia, azoospermia or severe oligozoospermia sufficient for contraceptive effect in the male subject.

This invention also relates to a method for birth control, the method comprising administering to a male subject once daily doses of a composition comprising:

- an extended release formulation of alpha-1-adrenoreceptor antagonist in an amount effective, when administered on a once daily dosing regimen, to induce a reversible condition of aspermia, azoospermia or severe oligozoospermia sufficient for contraceptive effect in the male subject; and
- a pharmaceutically acceptable carrier,

wherein the failure to administer one daily dose after an initial period of two consecutive days does not affect the continuous state of aspermia, azoospermia or severe oligozoospermia sufficient for contraceptive effect in the male subject.

DESCRIPTION

Use of an alpha-1-adrenoreceptor antagonist comprising composition

This invention relates to the use of a composition in a non-hormonal contraception method for a male subject, the composition comprising an alpha-1-adrenoreceptor antagonist, preferably an alpha-1a-adrenoreceptor antagonist, more preferably silodosin; and a pharmaceutically acceptable carrier. The non-hormonal contraception method includes a once-a-day administration of the composition according to the present invention. In order to maintain an effective exposure to the male subject, the contraception method is carried out for at least two days.

This once-a-day administration induces a contraceptive effect resulting from triggering aspermia, azoospermia, or severe oligozoospermia in the male subject for at least 24 hours.

Advantageously, the contraceptive effect obtained by the once-a-day administration of the composition of the invention is not affected by a delay of the consecutive once-a-day administration, supposed to occur 24 hours after the former administration, said delay not exceeding 6 hours after first administration, and said delay not exceeding 24 hours after further administration. Thus, the contraceptive effect obtained by the once-a-day administration of the composition of the invention is not reversed by a delay of the consecutive once-a-day administration, said delay not exceeding 6 hours after first administration, and said delay not exceeding 24 hours after further administration.

In a particular embodiment, the daily administration of the alpha-1-adrenoreceptor antagonist is made at about the same time on each day. In this particular embodiment, about means two hours before or after the same time.

A regular timetable in the administration has the benefit of assisting with patient compliance with the daily administration schedule. Further, as discussed in more detail below, for contraceptive products, it is usually recommended to take the drug at approximately the same time each day in order to maintain an effective exposure of the patient to the drug all along the dosing interval. According to one embodiment, the daily administration contraception method is a single daily administration contraception method.

Dose

In one embodiment, the use of the composition as previously described, comprises a biologically effective amount of alpha-1-adrenoreceptor antagonist. The biologically effective amount of alpha-1 adrenoreceptor antagonist can be determined by a person skilled in the art based on his general knowledge, the pharmacokinetic parameters of the alpha-1 adrenoreceptor antagonist, the subject's age, health condition etc.

In one embodiment, the alpha-1-adrenoreceptor antagonist is comprised in the composition in the amount from about 0.1 to about 30 mg. In one particular embodiment, the alpha-1-adrenoreceptor antagonist is comprised in the amount from about 0.2 to about 30 mg, preferably from about 4 to about 20 mg.

In one embodiment, the therapeutic dose of the alpha-1-adrenoreceptor antagonist (alpha blocker) used in any of the dosage forms described or referred to herein may be or include, by way of example only, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.8 mg, about 1 mg, about 2 mg, about 4 mg, about 6 mg, about 8 mg, about 10 mg, about 12 mg, about 16 mg, about 20 mg. about 24 mg, about 26 mg, or about 30 mg.

Formulations per os

Embodiments of the compositions' formulation administrated in the invention's use may be, include, or resemble a variety of dosage forms that are well known in the art. For example, this may include capsules, tablets, caplets, soft shell capsules, gel caplets (gel-caps), liquid compositions, powders, concentrated powders, concentrated powders

admixed with liquids, chewable forms, swallowable forms, water soluble films, granulated forms, pellet forms, and oral liquid suspensions.

The composition can be into a single day oral dosage forms selected from the group consisting of: soft-gels, caplets, pills, tablets, microtablets, capsules, hydromatrix tablets, and osmotic tablets.

All pharmaceutical preparations described herein are well known to those of ordinary skill in the art, and determination of workable methods for preparing orally dissolvable compositions in any particular instance will generally be within the capability of the person skilled in the art.

Details concerning any of excipients may be found in WADE & WELLER, HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (2nd ed. 1994). All active ingredients, fillers and excipients are commercially available from companies such as Aldrich Chemical Co., FMC Corp, Bayer, BASF, Alexi Fres, Witco, Mallinckrodt, Rhodia, ISP, and others. The excipients used in the orally dissolvable compositions fall into several functional categories and may include, by way of example, plasticizers, emulsifiers, taste enhancers, sweeteners, and flavoring agents. Additionally, or alternatively, excipients may be of the type used in other FDA-approved oral contraceptive products.

In one embodiment, the non-hormonal contraceptive compositions comprise one or more inactive ingredients. The inactive ingredients may comprise one or more of the following: sugar, corn starch, water, gelatin, citric acid, lactic acid, one or more glazing agents (e.g., vegetable oil, beeswax, carnauba wax), one or more natural flavors (e.g., plum, apple, mixed berry, cherry), one or more natural colors (e.g., black carrot), and one or more masking flavors (e.g., tartaric acid, menthol). In some embodiments, the non-hormonal contraceptive compositions may comprise one or more inactive ingredients that include but are not limited to water, buffers (including, by way of example and without limitation, phosphate buffers, citrate buffers, lactic acid, and others known to those of ordinary skill in the art), stabilizing agents (including, by way of example and without limitation, antioxidants (e.g., ascorbic acid, propionic acid, sodium bisulfite, sodium sulfite, and the

like), chelating agents (e.g., fumaric acid, sodium edetate, and the like), and others known to those of ordinary skill in the art), surfactants (including, by way of example and without limitation, wetting agents (e.g., sorbitan monolaurate, etc.), antifoaming agents (e.g., sorbitan trioleate, etc.), detergents (e.g., sucrose stearate, etc.), solubilizing agents (e.g., polyethylene glycol 400 monostearate, etc.), and others known to those of ordinary skill in the art), processing aids (e.g., substances used to assist processing, including, by way of example and without limitation, lubricating agents, antioxidants, and others known to those of ordinary skill in the art), lubricating agents (including, by way of example and without limitation, stearic acid, calcium stearate, magnesium stearate, zinc stearate, talc, mineral and vegetable oils, benzoic acid, poly (ethylene glycol), glyceryl behenate, stearyl futmarate, and others known to those of ordinary skill in the art), emulsifiers (including, by way of example and without limitation, synthetic (e.g., sodium lauryl sulfate, potassium laurate, etc.), natural (e.g., gelatin, lecithin, etc.), and finely divided solid emulsifiers (e.g., bentonite, magnesium hydroxide, etc.), and others known to those of ordinary skill in the art), suspending agents (including, by way of example and without limitation, cellulose derivatives (e.g., carboxymethylcellulose, methylcellulose, ethyl cellulose, etc.), natural polymers (e.g., alginates, xanthan gum, guar gum, etc.), synthetic polymers (e.g., carbomers, polyvinyl pyrrolidone, etc.), clays (e.g., magnesium aluminum silicate, hectorite, etc.), and others known to those of ordinary skill in the art), preservatives (including, by way of example and without limitation, benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetrimide, glycerin, propylene glycol, benzoic acid and sodium benzoate, potassium sorbate and sorbic acid, and others known to those of ordinary skill in the art), opaquing agents (including, by way of example and without limitation, titanium dioxide, and others known to those of ordinary skill in the art), glidants (including, by way of example and without limitation, silicon dioxide, colloidal or fumed silica, magnesium stearate, calcium stearate, stearic acid, cornstarch, talc and others known to those of ordinary skill in the art), diluents (including, by way of example and without limitation, corn syrup, lactose, sodium chloride, sucrose (sugar), and others known to those of ordinary skill in the art), colorants or coloring agents (including, by way of example and without limitation, FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, FD&C Orange No. 5, D&C Red No. 8, caramel, ferric oxide red, pigments, dyes, tints, titanium dioxide, natural

coloring agents, such as grape skin extract, red beet powder, beta carotene, annato, carmine, turmeric, paprika, black carrot juice, and others known to those of ordinary skill in the art), sweeteners or sweetening agents (including, by way of example and without limitation, sucrose, fructose, , high fructose corn syrup, dextrose, saccharin sodium, maltodextrin, aspartame, potassium acesulfame, neohesperidin dihydrochalcone, sucralose, monoammonium glycyrrhizinate, and others known to those of ordinary skill in the art), perfuming agents (including, by way of example and without limitation, natural flavor oil, natural vanilla extract, a synthetic flavor oil, and others known to those of ordinary skill in the art), glazing agents (including, by way of example and without limitation, vegetable oil, beeswax, carnauba wax, and others known to those of ordinary skill in the art), flavoring agents or flavorants (including, by way of example and without limitation, natural flavor oil, synthetic flavor oil, and other masking flavors known to those of ordinary skill in the art), and cooling agents (including, by way of example, N-substituted p-menthane-3-carboxamides, such as N-ethyl p-menthane-3-carboxamide ("WS-3") (Millennium Specialty Chemicals, Jacksonville, FL). Additional examples of other inactive ingredients are well known in the art. See, e.g., REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (21st ed. 2005).

Current formulations of alpha-1-adrenoreceptor antagonist for the treatment of benign prostate hyperplasia (BPH), such as the commercial products Rapaflo® or Urorec®, release the active ingredient immediately upon swallowing, and thus are "immediate release" (or "IR") formulations. For a contraceptive product, however, embodiments of the invention comprising a formulation of the non-hormonal contraceptive compositions in which the therapeutic effect is capable of withstanding a delay in intake may be particularly desirable. Such formulations may be referred to as an "extended release" (or "ER") formulations. In such embodiments, a male subject's delay in intake, or failure to intake, of one (or more) dose(s) would not nullify the contraceptive effect of the treatment regimen, and would also allow a day-to-day adjustment to a more convenient intake time.

According to a first embodiment, the daily administration of the alpha-1-adrenoceptor antagonist can be delayed as of the third day of two consecutive daily intakes with no impact on the contraceptive effect on the male subject, such delay not exceeding 2, 4, 6,

8, 10 12, 16, 20 or 24 hours from the day-before uptake time, preferably not exceeding 2, 4, 6 hours from the day-before uptake time.

According to second embodiment, the daily administration of the alpha-1-adrenoceptor antagonist can be delayed as of the fourth day of three consecutive daily intakes with no impact on the contraceptive effect on the male subject, such delay not exceeding 2, 4, 6, 8, 10 12, 16, 20 or 24 hours from the day-before uptake time.

According to a third embodiment, the daily administration of the alpha-1-adrenoceptor antagonist can be delayed as of the fifth day of four consecutive daily intakes with no impact on the contraceptive effect on the male subject, such delay not exceeding 2, 4, 6, 8, 10 12, 16, 20 or 24 hours from the day-before uptake time.

According to a fourth embodiment, the daily administration of the alpha-1-adrenoceptor antagonist can be delayed as of the sixth day of five consecutive daily intakes with no impact on the contraceptive effect on the male subject, such delay not exceeding 2, 4, 6, 8, 10 12, 16, 20 or 24 hours from the day-before uptake time.

According to a fifth embodiment, the daily administration of the alpha-1-adrenoceptor antagonist can be delayed as of the seventh day of six consecutive daily intakes with no impact on the contraceptive effect on the male subject, such delay not exceeding 2, 4, 6, 8, 10 12, 16, 20 or 24 hours from the day-before uptake time.

In one embodiment, the once-a-day administration contraception method is carried out for at least two days. In one embodiment, the once-a-day administration contraception method is carried out for at least three days. In one embodiment, the once-a-day administration contraception method is carried out for at least for at least four days. In one embodiment, the once-a-day administration contraception method is carried out for at least for at least five. In one embodiment, the once-a-day administration contraception method is carried out for at least six days.

According to the aforementioned embodiments the delay of a subsequent daily administration does not exceed 2, 4, 6, 8, 10 12, 16, 20 or 24 hours from the day-before uptake time. In one embodiment, the delay does not exceed 2, 4, 6, 8, 10 12, 16, 20 or 24

hours from the day-before uptake time. In one embodiment, the delay does not exceed 2 hours from the day-before uptake time. In one embodiment, the delay does not exceed 4 hours from the day-before uptake time. In one embodiment, the delay does not exceed 6 hours from the day-before uptake time. In one embodiment, the delay does not exceed 8 hours from the day-before uptake time. In one embodiment, the delay does not exceed 10 hours from the day-before uptake time. In one embodiment, the delay does not exceed 12 hours from the day-before uptake time. In one embodiment, the delay does not exceed 16 hours from the day-before uptake time. In one embodiment, the delay does not exceed 20 hours from the day-before uptake time. In one embodiment, the delay does not exceed 24 hours from the day-before uptake time.

By way of example only, the contraceptive effect may be designed to withstand a delayed intake of 6 hours (e.g., contraceptive effect maintained up to 24 hours, and an additional six hour-delay, for a total of 30 hours post-dose).

In embodiments of the invention, this duration of action is longer, and the daily administration of the alpha-1- adrenoceptor antagonist can be delayed as of the first, second, third, fourth, fifth or sixth daily administration.

It should be noted the typical or conventional means of achieving a lengthening of the duration of action — an increase of the therapeutic dose — is not a viable option in the case of alpha-1-adrenoreceptor antagonists, as it may expose the patient to an increase in the risk of orthostatic hypotension.

In one embodiment, the dosage form is self-administered.

The dosage form may be enteral, particularly oral, buccal or sublingual. Oral, buccal, sublingual or transdermal administration may be discretely carried out without need for any external device. In a particular embodiment of the invention, the dosage form may comprise granules in a hard capsule containing a biologically effective amount of an alpha-1-adrenoreceptor antagonist to guarantee the contraception during a targeted duration. In such an embodiment, the granules may comprise (i) an inert core, (ii) a drug layer applied to the inert core, comprising the alpha-1-adrenoreceptor antagonist and a binder, and (iii) a controlled release coating surrounding the drug layer. Further

embodiments of the invention may also comprise, optionally, a surfactant in combination with item (ii).

Additionally or alternatively, the granules may be matrix granules of an alpha-1-adrenoreceptor antagonist surrounded by controlled release coating and filled in a capsule, such as for example a hard capsule. Alternatively, the granules can be compressed into a tablet. The compositions described in this paragraph, including methods for preparing them, are well known in the pharmaceutical arts. WADE & WELLER, HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (2nd ed. 1994); REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (21st ed. 2005).

In such an embodiment, formulations to be used in the methods of the invention may further be, include, or resemble tablets or microtablets in a hard capsule, a coated tablet, a hydromatrix tablet, or an osmotic tablet containing a biologically effective amount of the alpha-1-adrenoreceptor antagonist to guarantee the contraception during a targeted duration. Embodiments of the invention may therefore comprise tablets, specifically, matrix tablets of the alpha-1-adrenoreceptor antagonist surrounded by controlled release coating, and filled in a hard capsule. The tablets can optionally be coated by a controlled release coating prior to their formulation into a tablet. The obtained tablet may further be coated by a controlled release coating. A coated tablet may be or comprise a matrix tablet of the alpha-1-adrenoreceptor antagonist surrounded by controlled release coating.

In such embodiment, the compositions administrated in the use according to the present invention are formulated in forms comprising granules or tablets. The granules or tablets may optionally be coated by a controlled release coating.

The granules or tablets, as previously described, can be further filled into a capsule that optionally comprises a controlled release coating.

In one embodiment, the composition is in a multiparticulate form. In such embodiment, a capsule may then be filled with the previously described particles or granules. The sufficient number of these particles or granules within the capsule is determined by a person skilled in the art in view of reaching to daily dose of the alpha-1-adrenoreceptor antagonist.

In one embodiment, the contraceptive effect resulting from triggering aspermia, azoospermia, or severe oligozoospermia and the absence of undesired side effects in the male subject is achieved independently from the food consumption by the male subject.

In one embodiment, contraceptive effect resulting from triggering aspermia, azoospermia, or severe oligozoospermia in the male subject has the same efficacy and/or safety profile independently from the food consumption by the male subject.

In one embodiment, the composition comprising the alpha-1-adrenoreceptor antagonist includes or consists of at least one particle, preferably at least one coated particle, and the average particle diameter is in the range of 0.01 to 5 mm, preferably 0.1 to 2 mm.

As described above, embodiments of the invention may comprise unitary dosage forms such as granules or tablets in a capsule that are released in the stomach. With sufficiently small size (for instance, *e.g.*, with a diameter $\leq$ 5 mm, preferably $\leq$ 2 mm) to progress to the intestine in the flow of the digestive fluids, the granules or tablets are not retained in the stomach with the food. Thus, the usual food effect seen for silodosine—which relies upon a delayed voiding of the stomach in the presence of food—does not impact such formulations. In such embodiment, the average diameter of the particles ranges from 0.01 to 5 mm, preferably from 0.1 to 2 mm.

In one embodiment, the particles as previously described are encompassed into a capsule, each capsule being filled by particles in a number sufficient to reach the daily dose.

In embodiments of the invention, the granules or tablets may also be designed with a specific density in order to avoid the food effect. If the density of the granules or tablets is too low, they will float at the top of the gastric fluids contained in the stomach during a fasting state, delaying transit to the intestine. Accordingly, in embodiments of the invention, the target density of the granules or tablets may be designed to avoid the floating phenomenon. In embodiments of the invention, a density ranging from about 1 to about 1.6 may be desirable. However, those skilled in the art will appreciate that other densities may be appropriate or ideal.

In embodiments of the invention, a hydromatrix tablet may also be used as a dosage form, particularly, e.g., a single or multiple-layer tablet comprising an alpha-1-adrenoreceptor antagonist and a hydrophilic excipient. The compositions described in this paragraph, including methods for preparing them, are well known in the pharmaceutical arts. (Peter Timmins,Samuel R. Pygall,Colin D. Melia. Hydrophilic Matrix Tablets for Oral Controlled Release (2014), Rumondor ACF et al. Minitablets: Manufacturing, Characterization Methods, and Future Opportunities. July 30, 2016. Nokhodchi A. The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems. BioImpacts (2012) 2(4):175-187).

alpha-1-adrenoreceptor antagonist

The present invention can be implemented with any alpha-1-adrenoreceptor antagonist. A person skilled in the art can adapt the composition using his general knowledge on the pharmacodynamic and pharmacokinetic properties of the said alpha-1-adrenoreceptor antagonist. In one embodiment, the alpha-1-adrenoreceptor antagonist is selected from the group comprising silodosin, terazosin, doxazosin, tamsulosin and fiduxosin.

In a preferred embodiment, the composition implemented in the present invention comprises silodosin as an alpha-1-adrenoreceptor antagonist. In another embodiment, the composition comprises tamsulosine as an alpha-1-adrenoreceptor antagonist.

In a preferred embodiment, the alpha-1-adrenoreceptor antagonist is (*R*)-Silodosin. In one embodiment, the alpha-1-adrenoreceptor antagonist is (*R*)-Silodosin in a polymorphic or amorphous form.

(R)-Silodosin may be particularly advantageous because it is a known antagonist of the alpha-1-adrenoreceptors, and particularly, has high affinity and selectivity toward human alpha-1a-adrenoreceptors (pKi = 10.4 ± 0.07) (CDER, NDA 22-206, PHARMACOLOGY REVIEWS. Sep 2008).

In embodiments of the formulation described herein, the non-hormonal compositions may also allow for consumption with or without food. Typically, as discussed herein, alpha-1 blockers may be administered with food in order to decrease the peak of their plasma

concentration and consequently limit the occurrence of the cardiovascular side effects. A so-called "food effect" is known to impact the pharmacokinetic profile of traditional formulations of (R)-Silodosin, leading to a delayed T_{max} and lower C_{max}. (EMA/793234/2009. CHMP assessment report for Urorec. Procedure No. EMEA/H/C/001092. 10 Jan 2010.) It is assumed that these effects are due to the delayed voiding of the stomach in the presence of food. Consequently, the use of the composition according to the invention is of very particular interest, as it can be used by the general population, and no specific warning is necessary about the taking of meals or food before, at the time of after the administration.

In embodiments of the invention, the use of the composition offers an effective exposure for about 30 hours allowing maintenance of the contraceptive effect

In a particular embodiment, the single daily oral dosage form comprises about 12 mg of alpha-1-adrenoreceptor antagonist; and said composition provides a pharmacokinetic profile of alpha-1-adrenoreceptor antagonist having:

i) a T_{max} ranging from about 3 hours to about 8 hours; and

ii) a mean C_{max} which is less than about 70 ng/mL.

In another particular embodiment, the single daily oral dosage form comprises about 8 mg of alpha-1-adrenoreceptor antagonist; said composition provides a pharmacokinetic profile of alpha-1-adrenoreceptor antagonist having:

i) a T_{max} ranging from about 3 hours to about 8 hours; and

ii) a mean C_{max} which is less than about 50 ng/mL.

In embodiments of the invention, a dose of a consecutive day administration may be delayed within twenty-four hours (for, by way of example only, about 1, about 2, about 3, about 4, about 6, about 8, about 10, about 12, about 15, about 18, or about 21 hours) without impacting or altering the contraceptive effect of the composition. In embodiments of the invention, a dose may be missed or omitted such that no dose is administered for more than about 24 hours (for, by way of example only, about 24, about 36, about 48, about 60, about 72, about 84, or about 96 hours).

Embodiments of the invention therefore include methods and compositions of administering an alpha-1-adrenoreceptor antagonist, or more in particular silodosin, which do not, or not significantly, impair the quality of orgasm for the male subject (often measured by the Numerical Rating Scale, NRS, for the quality of orgasm). Other potential side effects which the claimed invention would avoid or maintain at a minimum, include discomfort upon ejaculation, decreased sexual desire, feelings of reduced virility, ejaculation distress, decreased satisfaction, undesirable decrease or increase in intravaginal ejaculation latency time, or premature ejaculation.

In embodiments of the invention, the alpha-1-adrenoreceptor antagonist or silodosin in particular, is present either alone, or in association with another active agent, or in combination with another active agent.

Co-administration

In an embodiment of the invention, the alpha-1-adrenoreceptor antagonist as previously described may be included or used in the non-hormonal contraceptive compositions in any specific form just described. In another embodiment, the non-hormonal contraceptive compositions may include or use a combination of an alpha-1-adrenoreceptor antagonists as previously described or other components in the ranges or amounts as generally known in the art.

In one embodiment, the use of the composition in the daily administration contraception method further comprises a simultaneous or sequential administration of an additional composition. In one embodiment, the additional composition is related or not related to the sexual health of the male subject. In one embodiment, the additional composition does not affect the cardiovascular system of the male subject. In one other embodiment, the additional composition affects the cardiovascular system of the male subject. More in particular, the additional composition may induce the lowering of the male subject arterial pressure.

Advantageously, the safety profile of the present inventions male contraceptive method allows the simultaneous or sequential administration of an additional composition that may lower the patient's arterial pressure, with no risk of a hypotensive crisis.

Phosphodiesterase type 5 (PDE5) inhibitors, for example, are a class of drugs used in the treatment of erectile dysfunction having as an adverse effect the lowering of the subjects blood pressure. Embodiments of the invention may comprise the co-administration of PDE5 inhibitors and (*R*)-Silodosin in male patients suffering from erectile dysfunction and wanting to follow a male contraception method.

In one embodiment, use of the composition in the daily administration contraception method further comprises a simultaneous or sequential administration of an additional composition suitable for treating erectile dysfunction; preferably the additional composition comprises a phosphodiesterase-5 inhibitor.

PDE5 inhibitors are mild vasodilators associated with small decreases in blood pressure. (Huang S; and Lie J. Phosphodiesterase-5 (PDE5) Inhibitors In the Management of Erectile Dysfunction. PT (2013) 38(7): 407, 414-419.) Alpha-blockers are also well known vasoactive compounds. Thus, the co-administration of PDE5 inhibitors and alpha-blockers may, under some circumstances, result in additive vasodilatory effect, particularly within patient populations likely to be prescribed PDE5 inhibitors in clinical practice. (Schwartz B, Kloner R. Drug Interactions With Phosphodiesterase-5 Inhibitors Used for the Treatment of Erectile Dysfunction or Pulmonary Hypertension. CIRCULATION (2010) 122:88-95) (CDER, NDA 22-206, Medical Reviews, Sep 2008.) However, the embodiments of the invention described herein include an ER (R)-Silodosin formulation with a decreased alpha blocker C_{max}. Because the cardiovascular side effects of alpha blockers are related to their C_{max}, an ER (R)-Silodosin formulation would likely minimize the potential for additive side effects during co-administration with PDE5 inhibitors.

Another typical way to limit the risk of side effects of co-administration of an alpha blocker and PDE5 inhibitor is to separate the intake of each drug by several hours, as reported by Schwartz et al. The median T_{max} (time when the peak of plasma concentrations are reached) of the 4 currently marketed PDE-5 inhibitors (sildenafil, vardenafil, tadalafil, avanafil) ranges from 0.5 to 2 hours (Sharon A. Huang; and Janette D. Lie. Phosphodiesterase-5 (PDE5) Inhibitors In the Management of Erectile Dysfunction. P&T (2013) 38 (7):407-419). The median T_{max} of (R)-Silodosin L is about

2 hours (CDER, NDA 22-206, CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEWS. Jul 2008). When the alpha blocker and the PDE-5 inhibitor are taken several hours apart, the C_{max} of each compound is not reached in the same time so that the cumulative effect is lower. However, as described herein, in embodiments of the present invention, such as an ER formulation of (*R*)-Silodosin, the C_{max} is lower than in traditional/IR formulations of (*R*)-Silodosin and the T_{max} is delayed further apart from the T_{max} of its associated PDE5 inhibitor. Thus, it is possible to co-administer an alpha blocker composition as described herein as well as the PDE-5 inhibitor in the same time for the patient convenience and a better observance.

Advantageously, alpha-adrenoreceptor antagonist extended release formulations allow the simultaneous or sequential administration of an additional composition that may lower the patient's arterial pressure, with no risk of a hypotensive crisis. In one embodiment, the alpha-adrenoreceptor antagonist is an alpha-1-adrenoreceptor antagonist, preferably (*R*)-Silodosin. In one embodiment, the extended release formulations are adapted according to the general knowledge of the skilled artisan. In one embodiment the extended release formulations are the extended release formulations according to the present invention.

Since the prevalence of erectile dysfunction and of benign prostatic hyperplasia increases in aging men, embodiments of the invention may comprise the co-administration of PDE5 inhibitors and (*R*)-Silodosin in extended release formulations for the treatment of male patients suffering from both pathologies.

Packaging

In a specific embodiment, various active ingredients may be incorporated into multiple compositions as a kit. In some embodiments, the non-hormonal contraceptive compositions disclosed herein may be packaged as kits using materials known to those of ordinary skill in the art.

The packaging of the present invention may comprise or use a combination of compositions, including but not limited to PDE5 inhibitors. Additionally or alternatively, kits may further include, by way of example, one or more back-up methods of birth

control provided in the event that it is needed. For instance, embodiments of the invention may comprise a composition formulated to maintain a contraceptive effect in a male subject for about 30 hours.

In embodiments of the invention, the packaging may be packaged in a sachet or package. In such embodiments, a packaging may comprise one or more individual dosage forms. In some embodiments, each packaging may comprise two individual dosage forms. In some embodiments, each packaging may comprise three individual dosage forms.

Additionally or alternatively, in embodiments of the invention a unit dosage form may be individually wrapped, packaged as multiple units on paper strips, preferably blisters, or in vials of any size, without limitation. In one embodiment, the unitary doses are individually removable oral dosage units comprising the composition to be implemented according to the invention. The orally dissolvable compositions of the invention may be packaged in unit dose, rolls, bulk bottles, and combinations thereof, without limitation.

Therefore, the invention also relates to a packaging of unitary doses of the composition of the invention. The composition, as previously described, includes alpha-1-adrenoreceptor antagonist in an amount ranging from about 0.1 to about 30 mg, preferably from about 0.2 to about 20 mg, preferably the alpha-1-adrenoreceptor antagonist is (*R*)-silodosin in an amount of 8 to 12 mg.

In one embodiment the male contraceptive packaging comprises at least one packaging unit; wherein said packaging unit comprises from about 7 to about 30 separately packaged unitary doses of the composition as described in the present invention.

In one embodiment, the male contraceptive packaging comprises from about 7 to about 28 unitary doses. The male contraceptive packaging may comprise 7, 14, 28, 56 or 84 unitary doses. The male contraceptive packaging may be suitable for longer periods of the non-hormonal male contraception method of the present invention. In such embodiments, the male contraceptive packaging comprises 7, 14, 28, 56, 84 or 168 to 365 unitary doses of the composition as described in the present invention.

According to another embodiment the male contraceptive packaging comprises from about 10 to about 30 unitary doses. The male contraceptive packaging may comprise 10, 20, 30, 60 or 90 unitary doses. The male contraceptive packaging may be suitable for longer periods of the non-hormonal male contraception method of the present invention. In such embodiments, the male contraceptive packaging comprises 10, 20, 30, 60, 90 or 180 to 360 unitary doses of the composition as described in the present invention.

In one embodiment the unitary doses are placed in at least one blister. The male contraceptive packaging is adequately labeled and may further comprise instructions for the male contraception method according to the present invention.

Parenteral formulations

The present invention, however, is not limited to oral administration of, e.g., capsules, tablets, and the like. Embodiments of the invention may be or comprise other dosage forms or methods, such as injection, transdermal patch, or subdermal implant. These are also well known in the arts and in embodiments of the invention may be similar to comparable female contraceptive products, such as, for example, Depo-Provera®, Ortho Evra®, and Nexplanon®, respectively.

Methods

In one aspect, the invention relates to a method for male contraception. This method comprises the administration of a composition comprising an alpha-1-adrenoreceptor antagonist; and a pharmaceutically acceptable carrier, wherein the composition has a contraceptive effect by inducing aspermia, azoospermia or severe oligozoospermia making the male subject unable to conceive.

In another aspect, the invention relates to a method for inducing a continuous state of aspermia, azoospermia, or severe oligozoospermia in a male subject. This method comprises the administration of a composition comprising an alpha-1-adrenoreceptor antagonist; and a pharmaceutically acceptable carrier. In such aspects, the alpha-1-adrenoreceptor antagonist, compositions and formulations thereof, as well as the frequency of the administration can be as previously described.

Other objectives, features and advantages of the present invention will become apparent from the following specific examples. The specific examples, while indicating specific embodiments of the invention, are provided by way of illustration only. Accordingly, the present invention also includes those various changes and modifications within the spirit and scope of the invention that may become apparent to those skilled in the art from this detailed description. The invention will be further illustrated by the following non-limiting examples.

DEFINITIONS

In the present invention, the following terms have the following meanings:

- "**About**" is used herein to mean approximately, roughly, around, or in the region of. When the term "about" is preceding a figure means plus or less 20% of the value of said figure. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth by 20 %.
- "**Aspermia**" refers to failure to produce semen.
- "**Azoospermia**" refers to the absence of sperm in the semen.
- "**Contraceptive method**" means a method which is defined by an administration scheme and a rule of oblivion (possibility to accept a delay in the uptake, without down effect), which sustain the contraceptive effect of the drug and make it efficient and suitable for regular and wide use by a general population. In other words, in a contraceptive method in the meaning of this invention, failure to administer one daily dose during the daily dosing regimen to the male subject may not affect the continuous state of aspermia, azoospermia, or severe oligozoospermia especially if the failure occurs after a continuous administration of at least 2, preferably at least 5 preceding days.
- "**Dosage form**" may be the form in which the dose is to be administered to the subject or patient. The drug or supplement is generally administered as part of a formulation that includes nonmedical agents. The dosage form has unique physical and

pharmaceutical characteristics. Dosage forms, for example, may be solid, liquid or gaseous. "Dosage forms," may include for example, a capsule, tablet, caplet, a soft-shell capsule, such as a gel caplet (gel-cap), syrup, a liquid composition, a powder, a concentrated powder, a concentrated powder admixed with a liquid, a swallowable form, a granulated form, a pellet form, and an oral liquid solution. Dosage forms may also include a subdermal implant, transdermal patch, injectable form, nasal spray, adhesive tablets, or transmucosally delivered solutions.

- "**Excipient**" refers to any compound that is an inactive ingredient of a described composition. The definition of "inactive ingredient" as used herein follows that of the U.S. Food and Drug Administration, as defined in 21 C.F.R. § 201.3(b)(8), which is any component of a drug product other than the active ingredient. As used herein, the term "inert," refer to any compound that is an inactive ingredient of a described composition. The term "active ingredient," in the meaning of the invention includes any compound intended to furnish a pharmacological activity and a pharmaceutical profile as needed for a male contraception method.

- "**Male subject contraception**" a method used on male to prevent pregnancy of their female sexual partners; may refer to inducing one of the condition(s) of aspermia, azoospermia, and/or severe oligozoospermia in such a manner that makes the male subject unable to conceive.

- "**Multiparticulate**" means comprise more than one particle, term particle meaning a sphere, a microsphere, a tablet, a microtablet, a capsule or a microcapsule. The term multiparticulate may include clustered, pelletized, compressed or loose particles.

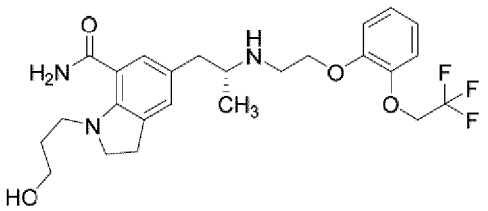
- "**Once-a-day administration**" means about the same time i.e. more or less 2 hours.

- "**Pharmaceutically acceptable**" refers to compounds, materials, compositions and/or dosage forms which are, within the scope of sound pharmaceutical/medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Thus, the phrase "pharmaceutically acceptable carriers," as used herein, refers to such suitable compounds and materials defined above that may be added to the dosage form to

assist in satisfactory processing of the dosage form or provide desirable physical characteristics to the dosage form. For example, "pharmaceutically acceptable carriers" may include, but is not limited to, binders, diluents, lubricants, glidants, colorants, emulsifiers, disintegrants, starches, water, oils, alcohols, preservatives, and sugars.

- "**Severe oligozoospermia**" refers to semen with a low total number or low concentration of sperm, typically about less than or equal to $1x10^6$ sperms per ejaculate.

- "**Silodosin**" refers to the compound 1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide.
The molecular formula is $C_{25}H_{32}F_3N_3O_4$, and it has a molecular weight of 495.53. In a preferred embodiment, the (R) stereoisomer of Silodosin, "***(R)*-Silodosin**", is used. *(R)*-Silodosin formally known as (-)-(*R*)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide having the following formula:



"*(R)*-Silodosin" is powder that appears white or pale yellow/white. It melts at approximately 105 to 109°C. It is very soluble in acetic acid, freely soluble in alcohol, and very slightly soluble in water.

- "**Subject**" as used herein, comprises any and all organisms and includes the term "patient." "Subject" may refer to a human or any other animal. Subjects may be referred to as "male subject(s)" or "female subject(s)" depending on their respective sex. In one embodiment, the "subject" is a healthy male human subject. In a second embodiment, the subject is a male human suffering from erectile dysfunction. In a third embodiment, the subject is a male human suffering from benign prostatic

hyperplasia (BPH). In a fourth embodiment, the subject is a male human suffering from both benign prostatic hyperplasia (BPH) and erectile dysfunction.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph illustrating the dissolution rate of the extended release (ER) formulation A of *(R)*-Silodosin, in comparison with the dissolution rate of an immediate release (IR) formulation of *(R)*-Silodosin.

Figure 2 is a graph illustrating plasma concentration-versus-time profiles for *(R)*-Silodosin after multiple daily oral administrations of extended release formulations of 12 or 8 mg of *(R)*-Silodosin. The plasma concentration obtained 24 h after a single administration of 8 mg of *(R)*-Silodosin in an immediate release formulation (C24) is also presented in the graph.

Figure 3 is a graph illustrating plasma concentration-versus-time profile for *(R)*-Silodosin after multiple daily oral administrations of 12 or 8 mg of *(R)*-Silodosin extended release formulation (ER) and a 6-hour delayed 6^{th} intake. The plasma concentration obtained 24 h after a single administration of 8 mg of *(R)*-Silodosin in an immediate release formulation (C24) is also presented in the graph.

Figure 4 is a graph illustrating plasma concentration-versus-time profile for *(R)*-Silodosin after multiple daily oral administrations of 12 or 8 mg of *(R)*-Silodosin extended release formulation (ER) and an omitted 6^{th} intake. The plasma concentration obtained 24 h after a single administration of 8 mg of *(R)*-Silodosin in an immediate release formulation (C24) is also presented in the graph.

EXAMPLES

The present invention is further illustrated but not limited by the following examples.

Example 1: *(R)*-Silodosin extended release formulation

This example relates to extended release formulations of *(R)*-Silodosin.

Controlled release granules of *(R)*-Silodosin are prepared in accordance with the present invention as follows. *(R)*-Silodosin is suspended in an aqueous solution of hydroxypropylmethyl cellulose (Opadry©) and potassium phosphate monobasic (KH_2PO_4). The composition of the *(R)*-Silodosin suspension in detailed in table 1.

	% w/w
Silodosin	9.60
HPMC (Opadry©)	10.00
KH_2PO_4	0.68
Purified water	79.72

Table 1. *(R)*-Silodosin suspension composition

Then, the suspension, under continuous stirring, is sprayed onto inert cores of cellulose spheres and the obtained granules are dried. The composition of the obtained granules is presented in table 2.

	% w/w
Silodosin	4.36
HPMC (Opadry©)	4.54
KH_2PO_4	0.31
Cellulose microspheres (Cellets®)	90.79

Table 2. *(R)*-Silodosin granules composition

An aqueous coating solution containing ethylcellulose (ECD Aquacoat®, 26.67 % w/w) and dibutylsebaccate (DBS, 2.0 % w/w) is then sprayed onto the *(R)*-Silodosin granules and dried. The composition of the protected granules is presented in table 3.

	% w/w
Silodosin	4.15
HPMC (Opadry©)	4.32
KH_2PO_4	0.30
Cellulose microspheres (Cellets ®)	86.47
Aquacoat ECD/DBS	4.76

Table 3. *(R)*-Silodosin protected granules composition

The coated granules are further coated by spraying with an aqueous extended release coating solution of ethylcellulose (ECD Aquacoat®, 25.25 % w/w), dibutylsebaccate (DBS, 1.89 % w/w) and guar gum (0.53 % w/w). The extended release granules are dried and their final composition is presented in table 4, hereafter named formulation A.

	% w/w
Silodosin	3.32
HPMC (Opadry©)	3.46
KH_2PO_4	0.23
Cellulose microspheres	69.18
Aquacoat ECD/DBS	3.81
Aquacoat ECD/guar gum/DBS	20.00

Table 4. *(R)*-Silodosin formulation A extended release granules composition

The average particle size was less than 2 mm and the average density thereof was superior to 1.

Hard capsules were filled with the adequate quantity of formulation A to a final content of 8 and 12 mg per capsule.

Example 2: *(R)*-Silodosin extended release dissolution rate

The dissolution test for comparison of the dissolution rate of *(R)*-Silodosin from the reference immediate release (Urorec®) formulation and from the experimental extended release formulation A according to example 1 was carried out at 50 rpm in 900 mL of 0.1N HCl solution in a USP type 2 apparatus at 25°C. The results of this comparative dissolution rate are presented in Figure 1.

The dissolution rate of the extended release formulation is slowed down compared to that of the reference immediate release formulations, such as for example Rapaflo® or Urorec®.

Example 3: Single administration contraceptive effect

A study is undertaken to evaluate the effectiveness of the compositions of the present invention in the treatment of male subjects. The objective of the study is to determine whether oral intake of an *(R)*-Silodosin results in a contraceptive effect.

A total of 7 subjects, aged 18 to 40 years were enrolled in an, open-label study. An initial analysis of each subject's semen, collected via masturbation after 3 days of abstinence, is carried out. Each subject receives one single dose of 12 mg *(R)*-Silodosin.

A semen analysis of each subject is conducted 24 h after the dosing. The analysis shows the results in Table 5 below.

Effect	**24h** (N=7)
Aspermia	6/7
Azoospermia	1/7
Contraceptive effect	7/7

Table 5. Contraceptive efficacy of a single dose of 12 mg of (*R*)-silodosin

As shown in Table 5, administration of the *(R)*-Silodosin formulation leads to a contraceptive effect (aspermia or azoospermia) in 100% of the male subjects.

The study also showed that administration of the composition did not impair the erectile function nor the quality of orgasm in any of the male subjects.

Example 4: *(R)*-Silodosin pharmacokinetic properties

The pharmacokinetic properties of *(R)*-Silodosin (SIL) is modeled based on plasma concentration-versus-time profiles obtained after a single administration of 8 mg of *(R)*-Silodosin to healthy volunteers. *(R)*-Silodosin data are described by a bi-compartment

model with a first-order input rate constant.. The pharmacokinetic properties of *(R)*-Silodosin were measured on the basis of observed plasma concentrations. The observed plasma concentrations validate the plasma concentration simulation methods for *(R)*-Silodosin.

Since the pharmacokinetic properties of *(R)*-Silodosin are linear over the dose-range 1 – 24 mg and are time-independent, the models are suitable for predicting the pharmacokinetic profiles of the compounds given at different doses under multiple dosing regimens.

A contraception is maintained up to 24 h after the administration of a 12-mg single dose of *(R)*-Silodosin. The C24 is the *(R)*-Silodosin plasma concentration 24 hours post-dose. Thus, a dosing regimen maintaining *(R)*-Silodosin plasma concentrations significantly above C24 results in a continuous contraception.

Maintaining the *(R)*-Silodosin concentration at a level at least equal to C24 should be sufficient; however, due to the variability of the pharmacokinetic properties of *(R)*-Silodosin and the individual metabolism variability, it is important to provide a significant security margin (ie., minimum *(R)*-Silodosin concentration significantly higher than C24).

Example 5: Effective exposure after repeated administrations of *(R)*-Silodosin

The model is used to simulate the pharmacokinetic properties of *(R)*-Silodosin after at least two to at least five daily administrations of 8 mg of *(R)*-Silodosin. After the administration of the *(R)*-Silodosin formulation A, the *(R)*-Silodosin plasma concentrations are constantly above C24, as presented in figure 2.

The effective exposure of *(R)*-Silodosin concentration is significantly superior to the C24 concentration as for the second administration, showing that the contraceptive efficiency is maintained.

Furthermore, the maximal plasma concentration (Cmax) is inferior to the Cmax measured past the administration of immediate release 8 mg *(R)*-Silodosin formulations where the risk of orthostatic hypotension is considered acceptable by health authorities.

Thus, the administration of *(R)*-Silodosin formulation A reduces the risk of unacceptable orthostatic hypotension.

Example 6: delayed or omitted intake does not affect contraceptive effect

The administration of 8 and 12 mg *(R)*-Silodosin extended release formulations according to formulation A allows maintaining the contraception all along the once daily treatment, including in case of delayed intake and in case of a single omission.

A 6-hour delay in the 6th intake (intake at 126 hours instead of 120 hours) does not allow the *(R)*-Silodosin concentration to drop below the C24 concentration, as illustrated in Figure 3.

Furthermore, the *(R)*-Silodosin plasma concentration is maintained above C24 even if the 6th day administration is omitted, as illustrated in Figure 4.

Thus, as confirmed by the results presented in Figures 3 and 4, the administration according to the present invention is able to maintain the contraception all along the treatment duration, including in case of delayed or omitted intake.

CLAIMS

1. Composition for use in a non-hormonal contraception for a male subject,

wherein said composition is an extended-release formulation comprising:

- an alpha-1-adrenoreceptor antagonist, and
- at least one pharmaceutically acceptable carrier,

wherein said composition is for a once daily administration at about the same time each day, triggering a continuous reversible aspermia, azoospermia, or severe oligozoospermia in the male subject,

wherein after an initial period of at least two consecutive days, the contraception is not impaired by a delay of the subsequent once daily intake, and

wherein said alpha-1-adrenoreceptor antagonist is *(R)*-silodosin.

2. Use of a composition in a non-hormonal contraception for a male subject,

wherein said composition is an extended-release formulation comprising:

- an alpha-1-adrenoreceptor antagonist, and
- at least one pharmaceutically acceptable carrier,

wherein said composition is for a once daily administration at about the same time each day, triggering a continuous reversible aspermia, azoospermia, or severe oligozoospermia in the male subject,

wherein after an initial period of at least two consecutive days, the contraception is not impaired by a delay of the subsequent once daily intake, and

wherein said alpha-1-adrenoreceptor antagonist is *(R)*-silodosin.

3. Use of a composition in the manufacture of a medicament for a non-hormonal contraception for a male subject,

wherein said composition is an extended-release formulation comprising:

- an alpha-1-adrenoreceptor antagonist, and
- at least one pharmaceutically acceptable carrier,

Date Reçue/Date Received 2023-06-19

wherein said medicament is for a once daily administration at about the same time each day, triggering a continuous reversible aspermia, azoospermia, or severe oligozoospermia in the male subject,

wherein after an initial period of at least two consecutive days, the contraception is not impaired by a delay of the subsequent once daily intake, and

wherein said alpha-1-adrenoreceptor antagonist is *(R)*-silodosin.

4. The composition for use according to claim 1 or the use according to claim 2, wherein said composition is for oral administration; or the use according to claim 3, wherein said medicament is for oral administration.

5. The composition for use or the use according to any one of claims 1 to 4, wherein, after the initial period of consecutive days, the intake of a next dose can be delayed from 6 to 18 hours after the last regular daily dose time, and the condition of aspermia, azoospermia or severe oligozoospermia is maintained in the male subject.

6. The composition for use or the use according to any one of claims 1 to 5, wherein after the initial period of consecutive days, failure to intake one daily dose does not affect the continuous state of aspermia, azoospermia or severe oligozoospermia supporting the contraception for 36 to 48 hours as of the last intake time.

7. The composition for use according to claim 1 or the use according to claim 2, wherein said composition is for a once daily administration for at least eight days; or the use according to claim 3, wherein said medicament is for a once daily administration for at least eight days.

8. The composition for use or the use according to any one of claims 1 to 7, wherein said composition includes *(R)*-silodosin in an amount ranging from about 0.1 to about 30 mg.

9. The composition for use or the use according to claim 8, wherein said composition includes *(R)*-silodosin in an amount ranging from about 4 to about 30 mg.

Date Reçue/Date Received 2023-06-19

10. The composition for use or the use according to claim 9, wherein said composition includes *(R)*-silodosin in an amount ranging from about 4 to about 20 mg.

11. The composition for use or the use according to claim 9, wherein said composition includes *(R)*-silodosin in an amount ranging from about 8 to about 30 mg.

12. The composition for use or the use according to claim 11, wherein said composition includes *(R)*-silodosin in an amount ranging from about 8 to about 20 mg.

13. The composition for use or the use according to claim 11, wherein said composition includes *(R)*-silodosin in an amount of about 8 mg.

14. The composition for use or the use according to claim 11, wherein said composition includes *(R)*-silodosin in an amount of about 10 mg.

15. The composition for use or the use according to claim 11, wherein said composition includes *(R)*-silodosin in an amount of about 12 mg.

16. The composition for use or the use according to claim 11, wherein said composition includes *(R)*-silodosin in an amount of about 16 mg.

17. The composition for use or the use according to claim 11, wherein said composition includes *(R)*-silodosin in an amount of about 20 mg.

18. The composition for use or the use according to claim 11, wherein said composition includes *(R)*-silodosin in an amount of about 24 mg.

19. The composition for use or the use according to claim 11, wherein said composition includes *(R)*-silodosin in an amount of about 26 mg.

Date Reçue/Date Received 2023-06-19

20. The composition for use or the use according to claim 11, wherein said composition includes *(R)*-silodosin is an amount of about 30 mg.

21. The composition for use or the use according to any one of claims 1 to 20, wherein *(R)*-silodosin is in a polymorphic or amorphous form.

22. The composition for use or the use according to any one of claims 1 to 21, wherein said composition includes at least one particle and the average particle diameter is in the range of 0.01 to 5 mm.

23. The composition for use or the use according to claim 22, wherein said at least one particle is a coated particle.

24. The composition for use or the use according to claim 23, wherein said coated particle comprises:

(i) an inert core,

(ii) a drug layer applied to the inert core, wherein the drug layer comprises *(R)*-silodosin and a binder, and

(iii) an extended-release coating surrounding the drug layer.

25. The composition for use or the use according to claim 22, wherein the average particle diameter is in the range of 0.1 to 2 mm.

26. The composition for use or the use according to any one of claims 22 to 25, wherein said at least one particle is encompassed into a capsule comprising a plurality of particles as defined in any one of claims 22 to 25, said capsule being filled by said particles in a number sufficient to reach the daily dose.

Date Reçue/Date Received 2023-06-19

27. The composition for use or the use according to any one of claims 1 to 26, wherein the contraception is achieved independently from the food consumption by the male subject.

28. The composition for use according to claim 1 or the use according to claim 2, wherein said composition is for a simultaneous or sequential administration of an additional composition suitable for treating erectile dysfunction; or the use according to claim 3, wherein said medicament is for a simultaneous or sequential administration of an additional composition suitable for treating erectile dysfunction.

29. The composition for use or the use according to claim 28, wherein said additional composition comprises a phosphodiesterase-5 inhibitor.

30. Packaging for use in a non-hormonal contraception for a male subject, comprising at least 7, 14, 28, 56, 84, or 168 to 365 unitary doses; or 10, 20, 30, 60, 90, or 180 to 360 unitary doses of the composition as defined in any one of claims 1 to 27, each unitary dose being a daily dose.

Date Reçue/Date Received 2023-06-19

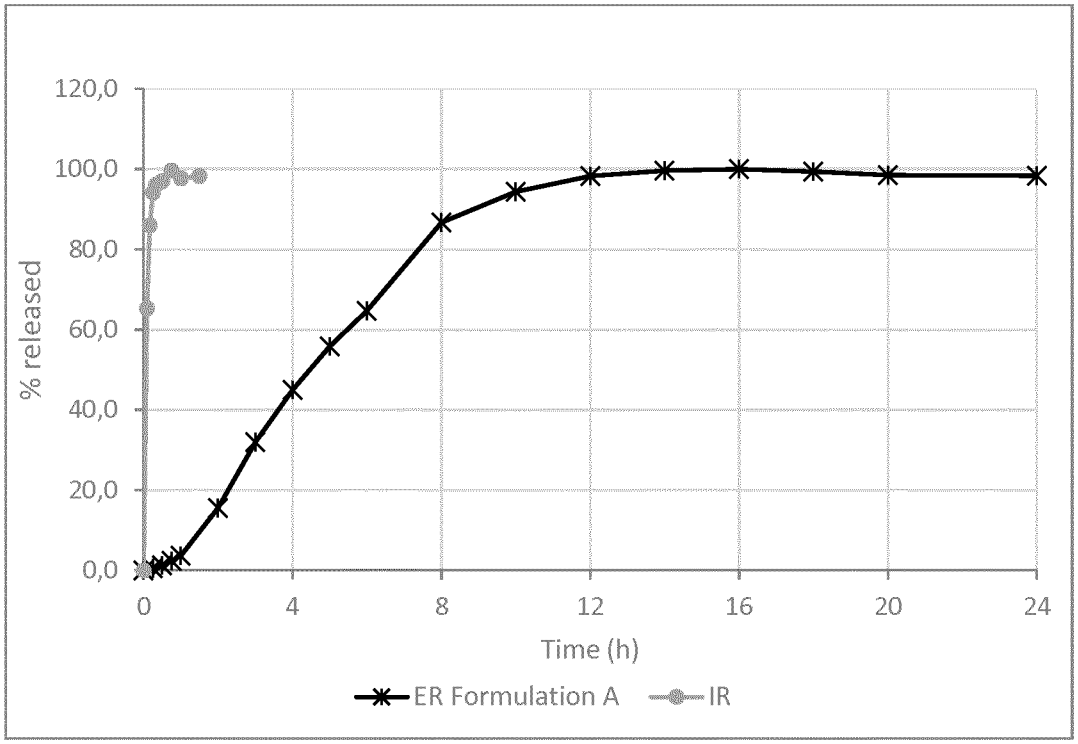

120,0
100,0
80,0
60,0
40,0
20,0
0,0
% released
0
4
8
12
16
20
24
Time (h)
ER Formulation A
IR

FIG. 1

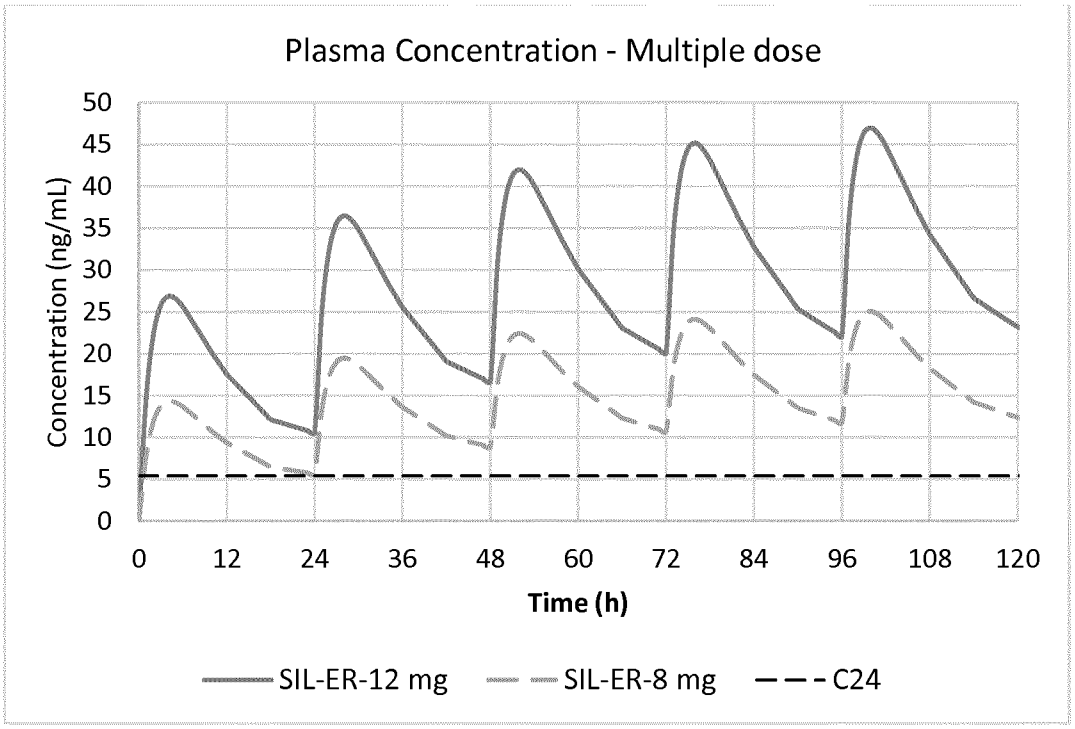

Plasma Concentration - Multiple dose
50
45
40
35
30
25
20
15
10
5
0
Concentration (ng/mL)
0
12
24
36
48
60
72
84
96
108
120
Time (h)
SIL-ER-12 mg
SIL-ER-8 mg
C24

FIG. 2

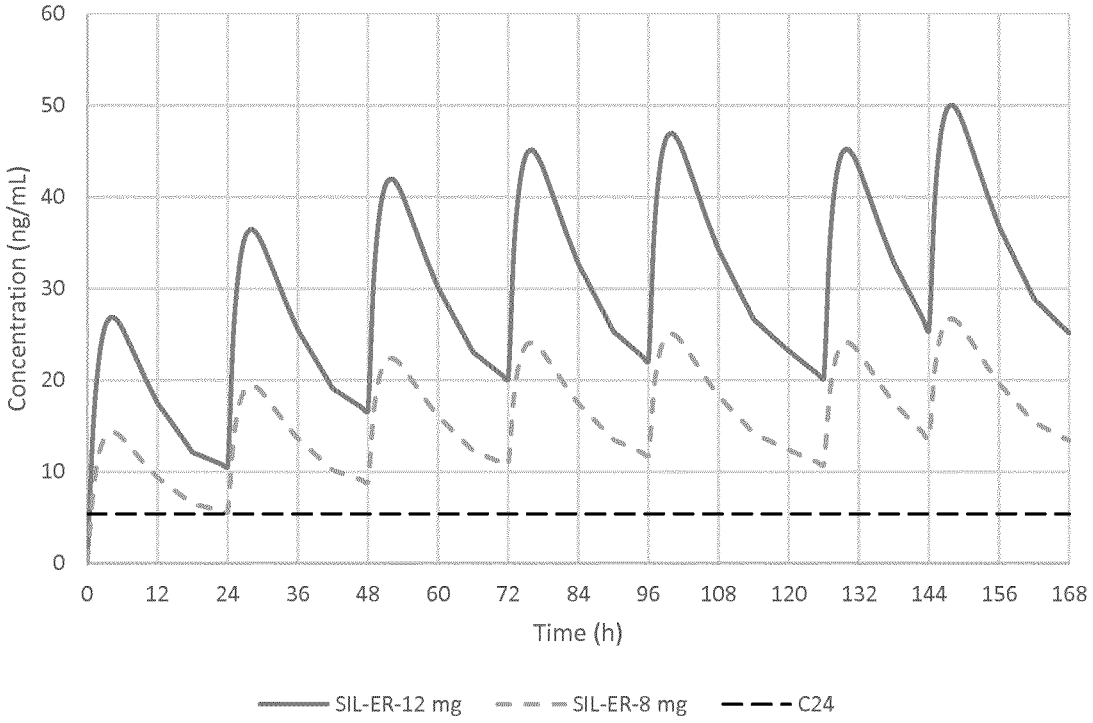

60
50
40
30
20
10
0
Concentration (ng/mL)
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168
Time (h)
SIL-ER-12 mg
SIL-ER-8 mg
C24

FIG. 3

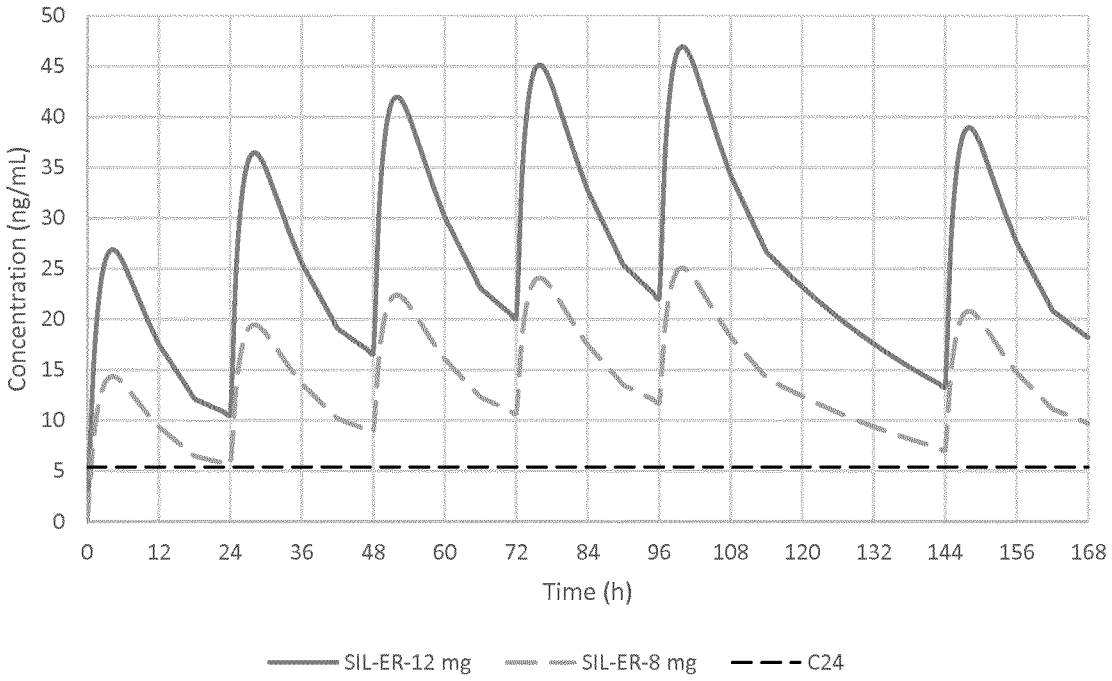

50
45
40
35
30
25
20
15
10
5
0
Concentration (ng/mL)
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168
Time (h)
SIL-ER-12 mg
SIL-ER-8 mg
C24

FIG. 4