Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-097546- -00002-0000
Fecha: 2016-02-01 15:38:21 Dep: 2020 DIR NUEVASCR
Tra: 2 PATENTES Eve: 1 REGDEPOSITO
Act: 400 OPOS OBSERVTER Folios: 95

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

X Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
☐ Esquema de Trazado de Circuitos Integrados

Número de expediente: **14-097546**

Solicitante:

Apoderado: **DAVID FELIPE CAICEDO PINTO**

Título de la Nueva Creación: **COMPOSICIONES FARMACEUTICAS PARA EL TRATAMIENTO DE LA EYACULACIÓN PRECOZ, PROCESO DE FABRICACIÓN Y METODOS DE TRATAMIENTO.**

Gaceta: **744 DEL 10/NOV/2015 PUBLICACION 266**

2. Datos del Opositor

☐ Persona Natural X Persona Jurídica

LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.
Nombre o denominación /Razón social completa

TITO NOE PARRA MURILLO
Nombre del representante legal

Documento de identificación: C.C. ☐ C.E ☐ . NIT X Otr ☐ Cuál _____

Número 890.301.463-8

Dirección: **Cra. 1 # 46-84** Ciudad: **Cali - Valle**

Teléfono: **052 6877700** Fax: Correc electrónico tparra@lafrancol.com

☐ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

PARRA MURILLO TITO NOE	79.579.680	71168 C.S J.
Apellidos y Nombre	Documento de identificación	Tarjeta profesional

Dirección del representante		
CALLE 108 # 51-45		
Dirección electrónica	No. Fax	Número telefónico
tparra@lafrancol.com	7424092	7422525

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general _____

4. Fundamentos de la oposición

Causal: **VER ANEXO**

Justificación: **VER ANEXO**

Prórroga: **SI** X **NO** ☐

5. Anexos

Comprobante de pago de la tasa para la presentación de la oposición No. **16-007869** de **29/ENE/16**
Poder, si fuere el caso con el que se acredita la representación .
Anexo indicativo de las clases contra las cuales presenta oposición
☐ Pruebas como sustento de la oposición
☐ Copias para el traslado de la oposición. Se anexan **9** folios (Obligatorio indicar cuántos)
☐ Comprobante de pago de tasa por solicitud de prórroga
Comprobante de pago por invocación de notoriedad
Copia de la solicitud y sus anexos en medio magnético.

6. Firma **TITO NOE PARRA MURILLO**	
Nombre del Firmante **79.579.680 DE BOGOTA**	Firma **71168 C.S.J.**
C.C	Tarjeta Profesional

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 16 - 008602

Bogotá D.C., Febrero 01 de 2016 - 15:36:32

RECIBIDO DE : LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S. - LAFRANCOL S.A. NI 890.301.463 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
RECIBO DE CA	SIC ** RECIBO **	999999999	7869	29/01/2016	414.000.00
RECIBO DE CA	SIC ** RECIBO **	999999999	7870	29/01/2016	414.000.00
RECIBO DE CA	SIC ** RECIBO **	999999999	7872	29/01/2016	414.000.00
RECIBO DE CA	SIC ** RECIBO **	999999999	7873	29/01/2016	414.000.00
RECIBO DE CA	SIC ** RECIBO **	999999999	8587	01/02/2016	366.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	1632 OPOSICION NUEVA CRACION / PRESENTACION	430.000.00	430.000.00
				$430.000.00

SON: **CUATROCIENTOS TREINTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-097546- -00002-0000
Fecha 2016-02-01 15:38:21 Dep: 2020 DIR NUEVASCR
Tra: 2 PATENTES Eve: 1 REGDEPOSITO
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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E.S.D.

REF:	**Expediente: 14-097546**
TÍTULO SOLICITADO:	**COMPOSICIONES FARMACÉUTICAS PARA EL TRATAMIENTO DE LA EYACULACIÓN PRECOZ, PROCESO DE FABRICACIÓN Y METODOS DE TRATAMIENTO**
PUBLICACIÓN:	**GACETA 744 del 10 de noviembre de 2015, Nº de publicación 266.**
SOLICITANTE:	**DAVID FELIPE CAICEDO PINTO**
TRÁMITE:	**PRESENTACIÓN DE OPOSICIÓN**

TITO NOÉ PARRA MURILLO, mayor de edad y vecino de Bogotá, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 71168 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO COLOMBIANO S.A.S. LAFRANCOL S.A.S.,** sociedad constituida y vigente de conformidad con las leyes colombianas, con domicilio en Cali, Valle, en los términos y para los efectos del poder y del certificado de existencia y representación legal adjuntos, y estando dentro del plazo establecido por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito presentar oposición contra la solicitud de patente de invención indicada en el epígrafe.

I. PETICIÓN

Sírvase, señor Superintendente, proceder a negar el beneficio patentario a la solicitud contenida en el Expediente 14-097546, por incumplir los requisitos materiales de patentabilidad establecidos en el Título II, Capítulo I de la Decisión 486 de 2000 de la Comisión de la Comunidad Andina. Lo anterior con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LABORATORIO FRANCO COLOMBIANO S.A.S. LAFRANCOL S.A.S.,** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría, en forma contraria al Régimen Común Andino de Propiedad

Industrial, el empleo de ciertas sustancias y composiciones farmacéuticas, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS TÉCNICOS DE LA OPOSICIÓN[1]

La solicitud de la referencia incumple los requisitos materiales de patentabilidad establecidos en el Titulo II, Capítulo I de la Decisión 486 de 2000 de la Comisión de la Comunidad Andina, estos son: Novedad, Nivel Inventivo y Aplicación Industrial. Vale recordar que por Novedad se entiende aquella invención que no se encuentra comprendida dentro del estado de la técnica, siendo ésta última la que comprende todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de la patente. Con respecto al Nivel Inventivo, cabe señalar que dicho requisito se cumple cuando a una persona del oficic normalmente versada en la materia técnica correspondiente, no se le hubiese resultado dicha invención obvia o derivada de manera evidente del estado de la técnica. Por último, se entiende que una aplicación es susceptible de aplicación industrial cuando su objeto puede ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva.

a. Antecedentes Generales de la Solicitud de Patente

La solicitud de patente relativa al **Expediente Nº 14-097546**, no declara prioridad y señala la siguiente fecha de solicitud en Colombia: **07/05/2014.**

Esta solicitud de patente pretende proteger en Colombia, una **composición de clomipramina o sus sales farmacéuticamente aceptables**, en un soporte farmacéutico acuoso que comprende EDTA disódico.

Se indica que **la clomipramina se encuentra en su forma clorhidrato**, y que dicha composición contiene además **sacarina sódica y sabor a menta**, y que puede tener preservativos como metil, propil y butilparabeno.

La solicitud también señala que su forma final es un **spray de aplicación oral**, **un gel o un semisólido en crema o ungüento**.

Se desea proteger también el **proceso de preparación de la composición** caracterizada porque tiene las etapas de: mezclar los preservativos los cuales son preferiblemente parabenos en agua esteral; adicionar una sal de sulfito, EDTA di sódico y una sal inorgánica en su forma de cloruro; adicionar la clomipramina en

[1] Informe Técnico elaborado por Q.F. Natalia Soto T., Departamento de Propiedad Industrial – CFR

su forma cloruro; adicionar la sacarina sódica y sabor menta; filtrar por membrana 5 micras e iniciar envase del producto; mantener el producto en envase ámbar a temperatura ambiente; envasar en frio o liofilizar el producto o adecuar en una base gel, crema o ungüento.

Asimismo, se desea proteger un **método de tratamiento para la eyaculación precoz masculina**, caracterizado porque comprende administrar una cantidad farmacológicamente activa de cualquiera de las composiciones antes mencionadas, y el uso de dichas composiciones farmacéuticas de las para la elaboración de medicamentos o sistemas terapéuticos de administración.

Todo lo publicado antes del **07/05/2014** es parte del estado de la técnica.

b. **Antecedentes que respaldan nuestra oposición a la Solicitud de patente relativa al Expediente N° 14-097546.**

1. WO9513072 del 18/05/1995.

"The use of alfuzosin or terazosin in the treatment of premature ejaculation".

Prioridad: IT1993MI02412 del **12/11/1993.**

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger el uso de alfuzosina y las sales farmacéuticamente aceptables de los mismos para la **preparación de un medicamento para el tratamiento de la eyaculación precoz** psicógena. Se señala que la alfuzosina **puede estar en combinación** con uno o más compuestos seleccionados de los antiandrógenos, metoclopramida, **clomipramina**, fenoxibenzamina, prazosina y lorazepam.

En su memoria descriptiva, la solicitud afirma que existen medicamentos farmacológicos eficaces para el tratamiento de la eyaculación precoz, pero adolecen de graves efectos secundarios, por ejemplo **clomipramina** y la fenoxibenzamina.

Este antecedente **le resta nivel inventivo** a la solicitud con **Expediente N° 14-097546.**

2. WO0241883 del 30/05/2002

"As-needed administration of tricyclic and other non-sri antidepressant drugs to treat premature ejaculation"

Prioridad: US20000721412 del **21/11/2000.**

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger un **método para el tratamiento de la eyaculación precoz**, que comprende

administrar a un individuo masculino en necesidad de tal tratamiento, sobre una base según se necesite, una cantidad terapéuticamente eficaz de un **fármaco antidepresivo** seleccionado de entre el grupo que consiste de los antidepresivos tricíclicos, antidepresivos tetracíclicos, monoamina oxidasa inhibidores, antidepresivos azaspirone y antidepresivos no SRI atípicos.

Se señala que el fármaco antidepresivo está contenida dentro de una formulación farmacéutica, en donde el agente activo **se administra por vía oral**. Se indica además que la formulación farmacéutica se selecciona entre el grupo que consiste en comprimidos, cápsulas, comprimidos oblongos, **soluciones, suspensiones**, jarabes gránulos, perlas, polvos y gránulos.

La solicitud también señala que **el agente activo se administra por vía sublingual, bucal,** intranasal, por inhalación, entre varias otras

En su memoria descriptiva, la solicitud señala que esta invención se refiere en general a métodos y composiciones farmacéuticas para el tratamiento de la eyaculación precoz. Más particularmente, la invención se refiere al uso de tricíclicos, tetracíclicos, y otros fármacos antidepresivos en tales métodos y composiciones. Se indica que ejemplos de antidepresivos tricíclicos y tetracíclicos incluyen, sin limitación, amitriptilina, amoxapina, butriptilina, **clomipramina**, demexiptilina, desipramina, entre varios otros y las sales farmacológicamente aceptables de los mismos.

Se indica que **la clomipramina** (3-cloro-10,11-dihidro-N, N-dimetil-5Hdibenz [b, fJazepine-5-propanamina) y sus sales farmacológicamente aceptables de adición de ácido de los mismos, por ejemplo **clorhidrato de clomipramina**, **son particularmente preferidos.**

La solicitud señala entre sus ejemplos, que se exponen a fin de proporcionar a los expertos ordinarios en la técnica una exposición y descripción completas de cómo hacer y utilizar los compuestos de la invención, el siguiente:

EJEMPLO 5. **Una solución para usar en un spray sublingual** o inhalador pulmonar, la cual se prepara según lo siguiente: **Clomipramina clorhidrato 2,5** g; cloruro de benzalconio 0,100 g; agua destilada c.s.p. 100 mL.

Este antecedente **le resta nivel inventivo** a la solicitud con **Expediente Nº 14-097546.**

3. WO 2007/000764 del 04/01/2007

"Compositions and methods for enhancement of sexual function"

Prioridad: US20050693798P del **27/06/2005.**

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una **composición farmacéutica** que comprende una cantidad farmacéuticamente eficaz de **un agente para mejorar la erección** y una cantidad farmacéuticamente eficaz de un agente que retarda la eyaculación, siendo la composición tal que la eficacia de ambos agentes se superponen sustancialmente.

Se señala que dicha composición farmacéutica comprende **clomipramina como un agente retardante de la eyaculación**, y un inhibidor de PDE5 como un agente potenciador de la erección.

Asimismo, la solicitud reivindica un **método de tratamiento de la disfunción eréctil,** que comprende coadministrar a un sujeto que lo necesite una cantidad farmacéuticamente eficaz de un inhibidor de la fosfodiesterasa tipo 5, como un agente para mejorar la erección y **una cantidad farmacéuticamente eficaz de clomipramina, como un agente de retardante de la eyaculación**, tratando así la disfunción eréctil.

En su memoria descriptiva, la solicitud señala que **se ha demostrado que la clomipramina bloquea la eyaculación sin suprimir el orgasmo.** La clomipramina tiene un efecto sobre la fase excretora de la eyaculación, mediante la inhibición de la contracción de las fibras longitudinales de los conductos deferentes responsables de la progresión de los espermatozoides, sin afectar a la actividad contráctil de sus fibras circulares que actúan como una abrazadera, que bloquea el paso del semen.

Este antecedente **le resta nivel inventivo** a la solicitud con **Expediente Nº 14-097546.**

4. WO 2008/106738 del 12/09/2008

"Compositions for the treatment of sexual dysfunction"

Prioridad: AU20070901213 del **08/03/2007.**

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger un **método para tratar la disfunción sexual** a un sujeto en necesidad del mismo que comprende **administrar al sujeto una cantidad eficaz de un antidepresivo tricíclico** y un agente colinérgico/ muscarínico a una membrana mucosa. Se señala que la disfunción sexual es **eyaculación precoz**, y que **el antidepresivo tricíclico es clomipramina**.

Se desea proteger también un método para prolongar la relación sexual en un varón, el método incluye la etapa de administrar a la membrana mucosa del macho antes del coito una cantidad de un antidepresivo tricíclico eficaz para retrasar la eyaculación y un agente colinérgico/muscarínico.

La solicitud indica en su memoria descriptiva que **el inventor ha encontrado que la clomipramina es bastante satisfactoria en el tratamiento de la disfunción sexual. Sin embargo, cuando se utiliza durante largos períodos de tiempo, o en grandes dosis, se han observado efectos secundarios.** Estos incluyen el secado de la mucosa, en particular la mucosa nasal, especialmente cuando se entrega directamente a las membranas mucosas.

Este antecedente **le resta nivel inventivo** a la solicitud con **Expediente Nº 14-097546.**

5. WO 2009/142428 del 26/11/2009

"Pharmaceutical composition for the treatment of premature ejaculation"

Prioridad: KR20080046199 del **19/05/2008.**

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una **composición farmacéutica para el tratamiento de la eyaculación precoz**, que comprende **clomipramina o una sal farmacéuticamente aceptable de la misma**, sertralina o una sal farmacéuticamente aceptable de la misma y fluoxetina o una sal farmacéuticamente aceptable de la misma como ingredientes activos.

Se indica que **la sal farmacéuticamente aceptable es un hidrocloruro**, y que la composición de la comprende además un vehículo farmacéuticamente aceptable, el cual se selecciona del grupo que consiste de excipientes, disgregantes, aglutinantes, lubricantes, emulsionantes, agentes de suspensión, estabilizantes, **edulcorantes**, agentes aromatizantes y una combinación de los mismos.

Se desea proteger también una forma de **dosificación unitaria oral para el tratamiento de la eyaculación precoz**, que comprende la composición antes descrita y un vehículo farmacéuticamente aceptable. Se señala que dicha forma de dosificación unitaria oral se selecciona entre el grupo que consiste en comprimido, cápsula, suspensión, gránulo, **gel**, pastilla, tintura, decocción, **infusión**, alcohol, extracto fluido, elixir, extracto, jarabe, polvo, agua aromática y limonada.

Este antecedente **le resta nivel inventivo** a la solicitud con **Expediente Nº 14-097546.**

c. Conclusiones

Por todos los antecedentes expuestos (se adjunta una copia de todos los documentos citados en este informe), es evidente que **la solicitud del Expediente N° 14-097546 carece de nivel inventivo**, considerando que las composiciones farmacéuticas para el tratamiento de la eyaculación precoz proceso de fabricación y metodos de tratamiento, **se desprenden del arte previo.**

Siendo, las composiciones farmacéuticas para el tratamiento de la eyaculación precoz, proceso de fabricación y metodos de tratamiento, según lo indicado en la solicitud relativa al Expediente Nº 14-097546, algo que se desprende del estado del arte, se reafirma el fundamento de la carencia de nivel inventivo, pues **el objeto de la invención y los elementos que la componen son conocidos y forman parte del arte previo.**

Por consiguiente, podemos afirmar en forma categórica, que esta solicitud de patente **debe ser denegada**, debido a que **no presenta nivel inventivo** para gozar de un privilegio industrial en Colombia, ya que las composiciones farmacéuticas para el tratamiento de la eyaculación precoz, proceso de fabricación y metodos de tratamiento, según lo indicado en esta solicitud de patente, **se desprenden del estado de la técnica.**

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho los artículos 16, 18 y 20 de la Decisión 486 de 2000.

V. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Poder para actuar.
2. Certificado de existencia y representación legal de LAFRANCOL S.A.S.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. Los antecedentes mencionados en los fundamentos técnicos.

VI. NOTIFICACIONES

Mi representada y el suscrito las recibiremos en la Secretaría de su Despacho, o en la sede de LAFRANCOL ubicada en la Calle 108 No. 51-45 de Bogotá D.C.

Señor Superintendente,

Atentamente,

TITO NOÉ PARRA MURILLO
C.C. 79.579.680 DE BOGOTÁ.
T.P. 71168 C.S.J.

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

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WO 02/41883 A2

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(30) Priority Data:
09/721,412 21 November 2000 (21.11.2000) US

(71) Applicant: **VIVUS, INC.** [US/US]; 1172 Castro Street, Mountain View, CA 94040 (US).

(72) Inventors: **TAM, Peter**; 404 Wembley Court, Redwood City, CA 94061 (US). **GESUNDHEIT, Neil**; 250 Portola Court, Los Altos, CA 94002 (US). **WILSON, Leland, F.**; 164 East Creek Drive, Menlo Park, CA 94025 (US).

(74) Agents: **REED, Dianne, E.** et al.; Reed & Associates, Suite 210, 800 Menlo Avenue, Menlo Park, CA 94025 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/41883 A2

(54) Title: AS-NEEDED ADMINISTRATION OF TRICYCLIC AND OTHER NON-SRI ANTIDEPRESSANT DRUGS TO TREAT PREMATURE EJACULATION

(57) Abstract: A method is provided for treatment of premature ejaculation by administration of an antidepressant drug selected from tricyclic antidepressants, tetracyclic antidepressants, MAO inhibitors, azaspirone antidepressants, and atypical non-SRI antidepressants. In a preferred embodiment, administration is on as "as-needed" basis, i.e., the drug is administered immediately or at most several hours prior to sexual activity. Pharmaceutical formulations and packaged kits are also provided.

AS-NEEDED ADMINISTRATION OF TRICYCLIC AND OTHER NON-SRI ANTIDEPRESSANT DRUGS TO TREAT PREMATURE EJACULATION

TECHNICAL FIELD

This invention relates generally to methods and pharmaceutical compositions for the treatment of premature ejaculation. More particularly, the invention relates to the use of tricyclic, tetracyclic, and other antidepressant drugs in such methods and compositions.

BACKGROUND

Premature ejaculation is a debilitating yet common sexual dysfunction, and has been estimated to affect at least 30 to 40 percent of men at some point in their lives (Derogatis (1980) *Med. Aspects Hum. Sexuality* 14:1168-76; Frank et al. (1978) *New Engl. J. Med.* 299:111-115; Schein et al. (1985) *Fam. Pract. Res. J.* 7(3):122-134). The condition can lead to an inability to enter into or sustain relationships, can cause psychological damage to sufferers, and can also impair reproductive success.

The Diagnostics and Statistical Manual of Mental Disorders (DSM-IV) (Washington, D.C.: American Psychiatric Association, 1994) delineates three criteria for a diagnosis of premature ejaculation: (1) "persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wishes it," which is (2) associated with "marked distress or interpersonal difficulty," and (3) not due exclusively to the "direct" effects of a "substance" (with withdrawal from opioids cited as an example). The disorder is usually primary, but can also be secondary. "Primary" premature ejaculation refers to a lifelong, typically congenital condition, while "secondary" premature ejaculation refers to a late onset condition, acquired after a period of normal functioning. Sexual dysfunctions such as premature ejaculation may also be further characterized as being generalized or limited to certain situations, and with respect to degree or frequency of the disturbance.

Premature ejaculation has historically been treated by psychosexual counseling in combination with "behavioral" therapies such as the so-called "pause" and "pause-squeeze" techniques. See St. Lawrence et al. (1992), "Evaluation and Treatment of Premature Ejaculation: A Critical Review," *Int. J. Psychiatry in Medicine* 22(1):77-97; Semans, "Premature Ejaculation: A New Approach," *Southern Medical Journal* 49:353-

357, regarding the "pause" technique; and Masters and Johnson, *Human Sexual Inadequacy*, Little, Brown & Company, Boston, MA, 1970, regarding the "pause-squeeze' technique. Any improvement resulting from the aforementioned techniques is short-lived, however, and the cooperation of a man's sexual partner is required. Typically, psychosexual counseling also requires the cooperation of the partner. Furthermore, many men may demand a quicker solution to the problem or are unwilling to attend counseling sessions. In addition, psychosexual counseling requires specialized therapists who may not be available to all patients, particularly in remote locations. Finally, counseling benefits only a subset of patients, i.e., those for whom the condition is psychogenic. Psychological therapies cannot alleviate premature ejaculation resulting from non-psychological causes.

Topical anesthetic agents and intracavernosal injection of medicaments have also been employed to treat patients suffering from premature ejaculation. However, anesthetic agents are problematic insofar as they necessarily decrease tissue sensitivity and thereby diminish sexual pleasure. Also, topical anesthetics can be transferred to sexual partners and thereby decrease their sensitivity and pleasure as well. Intracavernosal injection is associated with pain and discomfort, and is not a preferred mode of drug administration. Various devices have also been proposed to delay ejaculation; however, such devices can be awkward, inconvenient and embarrassing to use.

Methods for treating premature ejaculation by systemic administration of serotonin reuptake inhibitors (SRIs), including selective serotonin reuptake inhibitors (SSRIs), have been described (U.S. Patent Nos. 4,507,323, 4,940,731, 5,151,448, and 5,276,042; PCT Publication No. W095/13072). For example, administration of the antidepressant fluoxetine (commercially available under the tradename Prozac® from Eli Lilly & Company), an SSRI, has been claimed to treat premature ejaculation; see U.S. Patent No. 5,151,448. However, the administration of fluoxetine has many undesired aspects. Patients with hepatic or renal impairments may not be able to use fluoxetine due to its metabolism in the liver and excretion via the kidney. Systemic events during fluoxetine treatment involving the lungs, kidneys or liver have occurred, and death has occurred from overdoses. In addition, numerous side effects are associated with oral fluoxetine administration include hair loss, nausea, vomiting, dyspepsia, diarrhea, anorexia, anxiety, nervousness, insomnia, drowsiness, fatigue, headache, tremor, dizziness, convulsions,

sweating, pruritis, and skin rashes. Fluoxetine interacts with a range of drugs, often by impairing their metabolism by the liver.

U.S. Patent No. 4,940,731 describes the oral or parenteral administration of another SSRI, sertraline (commercially available under the tradename Zoloft® from Pfizer), for treating premature ejaculation. It has been recognized that sertraline shares many of the same problems as fluoxetine; see Martindale, *The Extra Pharmacopoeia*, 31st edition, at p. 333 (London: The Royal Pharmaceutical Society, 1996). Sertraline is metabolized in the liver, and is excreted in the urine and feces. Thus, patients with cirrhosis must take lower doses, and caution must be exercised when administering sertraline to patients with renal impairment. Individuals taking monoamine oxidase inhibitors cannot take sertraline due to the risk of toxicity. Side effects resulting from oral sertraline administration include nausea, diarrhea, dyspepsia, insomnia, somnolence, sweating, dry mouth, tremor and mania. Rare instances of coma, convulsions, fecal incontinence and gynecomastia have occurred in patients undergoing sertraline therapy.

U.S. Patent No. 5,276,042 describes the administration of paroxetine (commercially available under the tradename Paxil® from SmithKline Beecham), an additional SSRI, for the treatment of premature ejaculation. Paroxetine is predominantly excreted in the urine, and decreased doses are recommended in patients with hepatic and renal impairments. Like sertraline, paroxetine cannot be given to patients undergoing treatment with a monoamine oxidase inhibitor. Side effects from oral administration of paroxetine include hyponatremia, asthenia, sweating, nausea, decreased appetite, oropharynx disorder, somnolence, dizziness, insomnia, tremor, anxiety, impaired micturition, weakness and paresthesia.

All of the known methods to treat premature ejaculation are thus problematic in one or more respects. An ideal method would not require ongoing ("chronic") drug therapy or use of active agents with numerous and/or serious side effects. An ideal method would be useful in the treatment of individuals with secondary, acquired premature ejaculation as well as those suffering from a primary, lifelong condition. The method would not involve application of anesthetic agents, intracavernosal drug administration, or use of devices, and would not require ongoing counseling sessions.

Thus there is a need for methods and dosage forms for treating premature ejaculation that requires no specialized psychological therapy, can be used conveniently

and without embarrassment, and avoids the disadvantages associated with prior therapeutic methods and dosage forms.

Accordingly, the present invention is addressed to the limitations of the prior art, and provides a novel treatment for individuals suffering from either primary or secondary premature ejaculation, wherein drug administration may be on an "as-needed" basis rather than necessarily involving chronic pharmacotherapy, and does not involve use of anesthetic agents, intracavernosal drug administration, or use of devices. To the best of applicants' knowledge, the present method of treating premature ejaculation is novel and completely unsuggested by the prior art.

SUMMARY OF THE INVENTION

It is a primary object of the invention to address the above-described need in the art by providing a novel method for the treatment of premature ejaculation by administering an effective amount of an antidepressant drug selected from tricyclic, tetracyclic, and other non-SRI antidepressant agents to an individual in need of such therapy, on an "as-needed" basis. That is, the method does not involve chronic pharmacotherapy; rather, administration is on an "as-needed" basis, wherein "as-needed" administration involves administration shortly before anticipated sexual activity. The term "antidepressant agent" includes such agents *per se* as well pharmaceutically acceptable, pharmacologically active salts, esters, amides, prodrugs, active metabolites, conjugates, and other analogs thereof. Administration of the drug may be carried out using any systemic mode of administration.

It is another object of the invention to provide such a method wherein the antidepressant drug is administered orally.

It is another object of the invention to provide such a method wherein the antidepressant drug is administered parenterally, transdermally, sublingually, buccally, nasally, transrectally, transurethrally, or via inhalation, or by other routes.

It is still another object of the invention to provide such a method wherein the antidepressant drug is a tricyclic antidepressant.

It is still another object of the invention to provide such a method wherein the antidepressant drug is a tetracyclic antidepressant.

It is still another object of the invention to provide such a method wherein the antidepressant drug is a monoamine oxidase inhibitor (MAOI).

It is still another object of the invention to provide such a method wherein the antidepressant drug is a non-SRI antidepressant drug not encompassed by the foregoing groups.

It is another object of the invention to provide a dosage form for delaying the onset of ejaculation in a male individual, comprising a rapid-release formulation for systemic absorption containing an active agent selected from the group consisting of tricyclic, tetracyclic, and other non-SRI antidepressants, in an amount effective to delay the onset of ejaculation by the individual during sexual activity.

Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

In a first aspect of the invention, a method is provided for the treatment of an individual prone to or suffering from premature ejaculation, the method comprising systemically administering to an individual in need of such treatment a therapeutically effective amount of an antidepressant drug selected from the group consisting of tricyclic antidepressants, tetracyclic antidepressants, azaspirone antidepressants, MAOIs, and other non-SRI antidepressants. In contrast to serotonin reuptake inhibitors such as paroxetine, sertraline, and fluoxetine, the present agents do not exhibit any significant side effects and do not require chronic administration for effectiveness. By contrast, administration of the active agents disclosed herein is an "as-needed" basis. By "as-needed" dosing, also known as *pro re nata* dosing, is meant the administration of a single dose of the active agent at some time prior to anticipated sexual activity. Administration can be immediately prior to sexual activity, or up to about 2 or 3 hours prior to anticipated sexual activity. Drug delivery may be accomplished through any mode of administration, including, but not limited to, the oral route.

In a further aspect of the invention, pharmaceutical formulations are provided for carrying out the method of the invention. The pharmaceutical formulations comprise a therapeutically effective amount of an active agent as provided herein, and a pharmacologically acceptable carrier or vehicle. Other types of components may be incorporated into the formulation as well, e.g., excipients, surfactants, preservatives (e.g., antioxidants), stabilizers, chelating agents, and the like, as will be appreciated by those

skilled in the art of pharmaceutical formulation preparation and drug delivery. The pharmaceutical dosage form may be any dosage form suitable for systemic absorption and may be, but is not limited to, rapidly disintegrating tablets, effervescent tablets, sublingual tablets, buccal dosage forms, sublingual sprays, gum formulations or inhalers. Preferably, the dosage form is an immediate release oral formulation.

In another aspect of the invention, a packaged kit is provided for a patient to use in the treatment of premature ejaculation. The kit includes a pharmaceutical formulation of an antidepressant agent as provided herein, a container housing the pharmaceutical formulation during storage and prior to administration, and instructions, e.g., written instructions on a package insert or label, for carrying out drug administration in a manner effective to treat premature ejaculation. The pharmaceutical formulation may be any formulation described herein, e.g., an oral dosage form containing a unit dosage of the active agent, the unit dosage being a therapeutically effective dosage for treatment of premature ejaculation.

DETAILED DESCRIPTION OF THE INVENTION

I. DEFINITIONS AND OVERVIEW:

Before describing the present invention in detail, it is to be understood that this invention is not limited to specific active agents, dosage forms, dosing regimens, or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" or "a pharmacologically active agent" includes a single active agent as well a mixture or combination of two or more different active agents, reference to "a carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The terms "active agent," "pharmacologically active agent" and "drug" are used interchangeably herein to refer to a chemical compound that induces a desired

pharmacological, physiological effect, i.e., in this case, treatment of premature ejaculation. The primary active agents herein are antidepressant agents that do not act as serotonin reuptake inhibitors, and are thus termed "non-SRI" antidepressants. The terms also encompass pharmaceutically acceptable, pharmacologically active derivatives of those active agents specifically mentioned herein, including, but not limited to, salts, esters, amides, prodrugs, active metabolites, conjugates, analogs, and the like. When the terms "active agent," "pharmacologically active agent" and "drug" are used, then, or when an active agent such as a tricyclic or tetracyclic antidepressant is specifically identified, it is to be understood that applicants intend to include the active agent *per se* as well as pharmaceutically acceptable, pharmacologically active salts, esters, amides, prodrugs, metabolites, conjugates, analogs, etc.

By "pharmaceutically acceptable," such as in the recitation of a 'pharmaceutically acceptable carrier,' or a 'pharmaceutically acceptable acid addition salt," is meant a material that is not biologically or otherwise undesirable, i.e , the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. "Pharmacologically active" (or simply "active") as in a "pharmacologically active " derivative or metabolite, refers to a derivative or metabolite having the same type of pharmacological activity as the parent compound and approximately equivalent in degree. When the term "pharmaceutically acceptable" is used to refer to a derivative (e.g., a salt) of an active agent, it is to be understood that the compound is pharmacologically active as well, i.e., therapeutically effective in the treatment of premature ejaculation.

"Carriers" or "vehicles" as used herein refer to conventional pharmaceutically acceptable carrier materials suitable for drug administration, and include any such materials known in the art that are nontoxic and do not interact with other components of a pharmaceutical composition or drug delivery system in a deleterious manner.

The terms "treating" and "treatment" as used herein refer to the ability to increase an individual's ejaculatory latency (i.e., delay ejaculation) during sexual activity, particularly sexual intercourse, relative to that individual's ejaculatory latency in the absence of pharmacotherapy as provided herein. Preferably, upon treatment according to

the present invention, an individual's ejaculatory latency is increased by at least a factor of two, more preferably a factor of four and most preferably a factor of at least ten.

By an "effective" amount or a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect, i.e., of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect, i.e., an increase in ejaculatory latency as explained above. The amount that is "effective," however, will vary from subject to subject, depending on the age and general condition of the individual, the particular active agent or agents, and the like. Thus, it is not always possible to specify an exact "effective amount." However, an appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

By "as-needed" dosing, also referred to as "*pro re nata*" dosing, "prn" dosing, and "on-demand" dosing or administration, is meant the administration of an active agent at a time just prior to the time at which drug efficacy is wanted, e.g., just prior to anticipated sexual activity, and within a time interval sufficient to provide for the desired therapeutic effect, i.e., enhancement in sexual desire and in sexual responsiveness during sexual activity. "As-needed" administration herein does not involve priming doses or chronic administration, "chronic" meaning administration at regular time intervals on an ongoing basis. As-needed administration may involve administration immediately prior to sexual activity, but will generally be about 0.25 to 3.5 hours, preferably about 0.5 to 3 hours, and most preferably about 1 to 2.5 hours prior to anticipated sexual activity. "As-needed" administration may or may not involve administration of a sustained release formulation in advance of anticipated sexual activity, with drug release taking place throughout an extended drug delivery period typically in the range of about 4 to 72 hours.

By the term "transdermal" drug delivery is meant delivery by passage of a drug through the skin or mucosal tissue and into the bloodstream. "Transdermal" delivery is also intended to encompass passage through scrotal skin.

By "transmucosal" drug delivery is meant administration of a drug to the mucosal surface of an individual so that the drug passes through the mucosal tissue and into the individual's blood stream. Transmucosal drug delivery may be "buccal" or "transbuccal," referring to delivery of a drug by passage through an individual's buccal mucosa and into

the bloodstream. Another form of transmucosal drug delivery herein is "sublingual" drug delivery, which refers to delivery of a drug by passage of a drug through an individual's sublingual mucosa and into the bloodstream. An additional form of transmucosal drug delivery herein is "rectal" or 'transrectal" drug delivery, referring to delivery of a drug by passage of a drug through an individual's rectal mucosa and into the bloodstream. Another form of transmucosal drug delivery is 'urethral" or "transurethral" delivery, referring to delivery of the drug into the urethra such that the drug contacts and passes through the wall of the urethra.

"Rapidly disintegrating' as in a "rapidly disintegrating tablet" as used herein refers to a tablet that dissolves or disperses in manner that allows for the absorption of the active agent such that "as-needed" administration of the active agent is possible. Thus, many rapidly disintegrating tablets often, but not necessarily, include a disintegrant in the tablet formulation or are otherwise specially designed to quickly disintegrate upon administration.

In order to carry out the method of the invention, a selected non-SRI antidepressant drug is administered to a male individual suffering from or prone to premature ejaculation, either chronic, lifelong ("primary") premature ejaculation or acquired ("secondary") premature ejaculation. The active agent may be administered orally, transmucosally (including buccally, sublingually, transurethrally, and rectally), transdermally, by inhalation, or using any other route of administration. Oral administration, because of its convenience, is preferred for those active agents that have sufficient oral bioavailability.

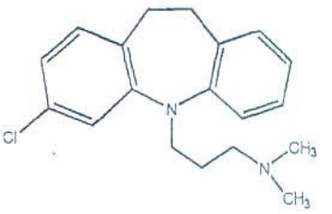
II. Active Agents:

The active agent administered using the method of the invention is a non-SRI antidepressant drug. The drug may be a tricyclic antidepressant, a tetracyclic antidepressant, an MAO inhibitor, an azaspirone antidepressant, or a non-SRI antidepressant not encompassed by the aforementioned groups.

Any non-SRI antidepressant drug may be used so long as the drug is effective in delaying the onset of ejaculation.

Tricyclic antidepressants are conventionally identified by their characteristic "tricyclic," e.g., iminodibenzyl, dibenzyocycloheptadiene, and dibenzyloxepinylidene, cores. Tetracyclic antidepressants generally have a similar tricyclic core wherein two

central carbons are connected through a lower alkylene bridge, thereby forming a fourth ring. Examples of tricyclic and tetracyclic antidepressants include, without limitation, amitryptiline, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, imipramine, iprindole, lofepramine, maprotiline, melitracen, metapramine, mianserin, mirtazapine, nortryptiline, propizepine, protriptyline, quinupramine, setiptiline, tianeptine, trimipramine, and pharmacologically acceptable salts thereof. Clomipramine (3-chloro-10,11-dihydro-N,N-dimethyl-5H-dibenz[b,f]azepine-5-propanamine) and its pharmacologically acceptable acid addition salts thereof, e.g., clomipramine hydrochloride, are particularly preferred herein.



CLOMIPRAMINE

Monoamine oxidase inhibitors represent another class of antidepressant drugs suitable for use in accordance with the present invention. Representative monoamine oxidase inhibitors include amiflamine, brofaromine, clorgyline, α-ethyltryptamine, iproclozide, iproniazid, isocarboxazid, mebanazine, moclobemide, nialamide, pargyline, phenelzine, pheniprazine, pirlindole, safrazine, selegiline, toloxatone, tranylcypromine, and pharmacologically acceptable salts thereof.

Another class of suitable antidepressant drugs for use in conjunction with the present method are the azaspirones, including, without limitation, buspirone, gepirone, ipsapirone, tandospirone, tiaspirone, and pharmacologically acceptable salts thereof.

Other, "atypical," non-SRI antidepressants suitable for use herein include, by way of example, example, amesergide, amineptine, benactyzine, bupropion, fezolamine, levoprotiline, medifoxamine, mianserin, minaprine, oxaflozane, oxitriptan, rolipram, teniloxazine, tofenacin, trazadone, tryptophan, viloxazine, and pharmacologically acceptable salts thereof.

A single antidepressant agent may be administered, or a combination of antidepressants agents may be administered, in either a single formulation, or in separate

formulations, and in the latter case, either simultaneously or sequentially. Additionally, one or more additional active agents can be administered with the antidepressant agent, either simultaneously or sequentially. The additional active agent will generally although not necessarily be one that is effective in treating premature ejaculation, and/or an agent that potentiates the effect of the antidepressant agent. Such agents include, for example, phosphodiesterase inhibitors, including Type III phosphodiesterase inhibitors (e.g., bipyridines such as milrinone, amrinone and olprinone; imidazolones such as piroximone and enoximone, imidazolines such as imazodan and 5-methyl-imazodan; imidazo-quinoxalines; and dihydropyridazinones such as indolidan and LY181512 (5-(6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-1,3-dihydro-indol-2-one); dihydroquinolinone compounds such as cilostamide, cilostazol, and vesnarinone), Type IV phosphodiesterase inhibitors (e.g., quinazolinediones such as nitraquazone and nitraquazone analogs; xanthine derivatives such as denbufylline and arofylline; tetrahydropyrimidones such as atizoram; and oxime carbamates such as filaminast), and Type V phosphodiesterase inhibitors (e.g., sildenafil, zaprinast, dipyridamole, and the compounds described in WO 01/19802 to Aoyama, particularly (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine, 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]-pyrimidine, and (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]-pyrimidine), and nonspecific phosphodiesterase inhibitors such as theophylline, theobromine, IBMX, pentoxifylline and papaverine.

Other additional active agents that may be co-administered with the antidepressant agent include vasoactive agents such as: nitrates and like compounds such as nitroglycerin, isosorbide dinitrate, erythrityl tetranitrate, amyl nitrate, sodium nitroprusside, molsidomine, linsidomine chlorhydrate ("SIN-1"), S-nitroso-N-acetyl-d,l-penicillamine ("SNAP"), S-nitroso-N-cysteine and S-nitroso-N-glutathione ("SNO-GLU") and diazenium diolates ("NONOates"); long and short acting α-blockers such as phenoxybenzamine, dibenamine, doxazosin, terazosin, phentolamine, tolazoline, prazosin, trimazosin, alfuzosin, tamsulosin and indoramin; ergot alkaloids such as ergotamine and ergotamine analogs, e.g., acetergamine, brazergoline, bromerguride, cianergoline, delorgotrile, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotrile,

lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, proterguride and terguride; antihypertensive agents such as diazoxide, hydralazine and minoxidil; vasodilators such as nimodepine, pinacidil, cyclandelate, dipyridamole and isoxsuprine; chlorpromazine; haloperidol; yohimbine; Rec15/2739; trazodone; naturally occurring prostaglandins such as PGE_0, PGE_1, PGA_1, PGB_1, $PGF_{1\alpha}$, 19-hydroxy-PGA_1, 19-hydroxy-PGB_1, PGE_2, PGA_2, PGB_2, 19-hydroxy-PGA_2, 19-hydroxy-PGB_2, PGE_3, $PGF_{3\alpha}$; semisynthetic or synthetic derivatives of natural prostaglandins, including carboprost tromethamine, dinoprost tromethamine, dinoprostone, lipoprost, gemeprost, metenoprost, sulprostone and tiaprost; and vasoactive intestinal peptide.

Still other additional active agents that may be co-administered with the non-SRI antidepressant drug include: adrenergic agonists including methoxamine, methpentermine, metaraminol, mitodrine, clonidine, apraclonidine, guanfacine, guanabenz, methyldopa, amphetamine, methamphetamine, epinephrine, norepinephrine, ethylnorepinephrine, phenylephrine, ephedrine, pseudoephedrine, methylphenidate, pemoline, naphazoline, tetrahydrozoline, oxymetazoline, xylometazoline, phenylpropanolamine, phenylethylamine, dopamine, dobutamine, colterol, isoproterenol, isotharine, metaproterenol, terbutaline, metaraminol, tyramine, hydroxyamphetamine, ritodrine, prenalterol, albuterol, isoetharine, pirbuterol, bitolterol, fenoterol, formoterol, procaterol, salmeterol, mephenterine and propylhexedrine; adrenergic antagonists including phenoxybenzamine, phentolamine, tolazoline, prazosin, terazosin, doxazosin, trimazosin, yohimbine, ergot alkaloids, labetalol, ketanserin, urapidil, alfuzosin, bunazosin, tamsulosin, chlorpromazine, haloperidol, phenothiazines, butyrophenones, propranolol, nadolol, timolol, pindolol, metoprolol, atenolol, esmolol, acebutolol, bopindolol, carteolol, oxprenolol, penbutolol, carvedilol, medroxalol, naftopidil, bucindolol, levobunolol, metipranolol, bisoprolol, nebivolol, betaxolol, carteolol, celiprolol, sotalol, propafenone and indoramin; adrenergic neurone blockers including bethanidine, debrisoquine, guabenxan, guanadrel, guanazodine, guanethidine, guanoclor and guanoxan; benzodiazepines including alprazolam, brotizolam, chlordiazepoxide, clobazepam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazapam, oxazepam, prazepam, quazepam, temazepam and triazolam; selective serotonin reuptake inhibitors (using a reduced dose) such as cianopramine, citalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine,

milnacipran, nomifensine, oxaprotiline, paroxetine, sertraline, sibutramine, venlafaxine, viqualine, and zimeldine; and other active agents such as clovoxamine, etoperidone, nefazodone, and opipramol.

Any of the active agents may be administered in the form of a salt, ester, amide, prodrug, active metabolite, conjugate, derivative, or the like, provided that the salt, ester, amide, prodrug, metabolite, conjugate or other derivative is suitable pharmacologically, i.e., effective in the present method. Salts, esters, amides, prodrugs, conjugates and other derivatives of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 4th Ed. (New York: Wiley-Interscience, 1992). For example, acid addition salts may be prepared from a free base (e.g., a compound containing a primary amino group) using conventional methodology involving reaction of the free base with an acid. Suitable acids for preparing acid addition salts include both organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. An acid addition salt may be reconverted to the free base by treatment with a suitable base. Conversely, preparation of basic salts of any acidic moieties that may be present may be carried out in a similar manner using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine, or the like. Preparation of esters involves reaction of a hydroxyl group with an esterification reagent such as an acid chloride, or esterification of a free carboxylic acid group. Amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid chloride by reaction with ammonia or a lower alkyl amine. Prodrugs, conjugates, and active metabolites may also be prepared using techniques known to those skilled in the art or described in the pertinent literature. Prodrugs and conjugates are typically prepared by covalent attachment of a moiety that results in a compound that is therapeutically inactive until modified by an individual's metabolic system.

In addition, many of the active agents contain chiral centers and can thus be in the form of a single isomer or a racemic mixture of isomers. Chiral active agents may be in isomerically pure form, or they may be administered as a racemic mixture of isomers.

Other derivatives and analogs of the active agents may be prepared using standard techniques known to those skilled in the art of synthetic organic chemistry, or may be deduced by reference to the pertinent literature.

III. Pharmaceutical Compositions and Dosage Forms:

The compounds of the invention may be administered orally, parenterally, rectally, buccally, sublingually, nasally, by inhalation, topically, transdermally, or via an implanted reservoir in dosage forms containing conventional non-toxic pharmaceutically acceptable carriers and excipients. The term "parenteral" as used herein is intended to include subcutaneous, intravenous, and intramuscular injection. The amount of the compound administered will, of course, be dependent on the particular active agent, the condition or disorder being treated, the severity of the condition or disorder, the subject's weight, the mode of administration and other pertinent factors known to the prescribing physician. Generally, however, dosage will be in the range of approximately 0.001 mg/kg/day to 100 mg/kg/day, more preferably in the range of about 0.1 mg/kg/day to 10 mg/kg/day.

Suitable compositions and dosage forms include tablets, capsules, caplets, gel caps, troches, dispersions, suspensions, solutions, syrups, transdermal patches, gels, powders, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, and the like.

Oral dosage forms are preferred for those therapeutic agents that are orally active, and include tablets, capsules, caplets, solutions, suspensions and/or syrups, and may also comprise a plurality of granules, beads, powders or pellets that may or may not be encapsulated. Such dosage forms are prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts, e.g., in *Remington: The Science and Practice of Pharmacy,* 20th Edition, Gennaro, A.R., Ed. (Lippincott, Williams and Wilkins, 2000). Tablets and capsules represent the most convenient oral dosage forms, in which case solid pharmaceutical carriers are employed.

Depending on the intended mode of administration, the pharmaceutical formulation may be a solid, semi-solid or liquid, such as, for example, a tablet, a capsule, caplets, a liquid, a suspension, an emulsion, a suppository, granules, pellets, beads, a powder, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. Suitable pharmaceutical compositions and dosage forms may be prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts and literature, e.g., in *Remington: The Science and Practice of Pharmacy*, 19th Ed. (Easton, Pa.: Mack Publishing Co., 1995).

Tablets may be manufactured using standard tablet processing procedures and equipment. Direct compression and granulation techniques are preferred. In addition to the active agent, tablets will generally contain inactive, pharmaceutically acceptable carrier materials such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like. Binders are used to impart cohesive qualities to a tablet, and thus ensure that the tablet remains intact. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, microcrystalline cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), and Veegum. Lubricants are used to facilitate tablet manufacture, promoting powder flow and preventing particle capping (i.e., particle breakage) when pressure is relieved. Useful lubricants are magnesium stearate, calcium stearate, and stearic acid. Disintegrants are used to facilitate disintegration of the tablet, and are generally starches, clays, celluloses, algins, gums, or crosslinked polymers. Fillers include, for example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose, and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride, and sorbitol. Stabilizers, as well known in the art, are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions.

Capsules are also preferred oral dosage forms, in which case the active agent-containing composition may be encapsulated in the form of a liquid or solid (including particulates such as granules, beads, powders or pellets). Suitable capsules may be either

hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. See, for example, *Remington: The Science and Practice of Pharmacy*, Nineteenth Edition. (1995) cited *supra*, which describes materials and methods for preparing encapsulated pharmaceuticals.

Preferred oral dosage forms are rapid-release formulations, and are therefore effective to provide rapid and systemic absorption of the active agent. Although the time necessary for systemic absorption will depend on the particular dosage form used, it is preferred that the formulation and dosage form provide systemically effective levels of and the desired biological response to the active agent less than 3.5, preferably less than 3, more preferably less than 2.5, still more preferably less than 2.0, and ideally less than 1.5 hours following administration. It is particularly preferred that the formulation and dosage form provide systemically effective levels of the drug and the desired biological response less than 1.0 hour following administration with less than 0.5 hours being most preferred.

Preparations according to this invention for parenteral administration include sterile nonaqueous solutions, suspensions, and emulsions. Examples of nonaqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Parenteral formulations may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. The formulations are rendered sterile by incorporation of a sterilizing agent, filtration through a bacteria-retaining filter, irradiation, or heat. They can also be manufactured using a sterile injectable medium.

The active agent may also be administered through the skin or mucosal tissue using conventional transdermal drug delivery systems, wherein the active agent is contained within a laminated structure that serves as a drug delivery device to be affixed to the skin. In such a structure, the drug composition is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs. In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Alternatively, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described

above, or it may be a liquid or hydrogel reservoir, or may take some other form. Transdermal drug delivery systems may in addition contain a skin permeation enhancer.

Other modes of administration are suitable as well, with, again, rapid release formulations particularly preferred.

For example, transmucosal administration may be advantageously employed. Transmucosal administration is carried out using any type of formulation or dosage unit suitable for application to mucosal tissue. For example, the selected active agent may be administered to the buccal mucosa in an adhesive tablet or patch, sublingually administered by placing a solid dosage form under the tongue, administered nasally as droplets or a nasal spray, administered by inhalation of an aerosol formulation, a non-aerosol liquid formulation, or a dry powder, placed within or near the rectum ("transrectal" formulations), or administered to the urethra as a suppository, ointment, or the like.

Preferred buccal dosage forms will typically comprise a therapeutically effective amount of the selected active agent and a bioerodible, hydrolyzable, polymeric carrier that may also serve to adhere the dosage form to the buccal mucosa. The buccal dosage unit is fabricated so as to erode fairly quickly, so as to provide for rapid release of the active agent, in turn enabling as-needed administration. The time period is preferably in the range of approximately 0.25 hours to 3.5 hours, preferably about 0.5 to 3 hours, more preferably about 1.0 to 2.5 hours. Buccal drug delivery, as will be appreciated by those skilled in the art, avoids the disadvantages encountered with oral drug administration, e.g., slow absorption, degradation of the active agent by fluids present in the gastrointestinal tract and/or first-pass inactivation in the liver. The dosage unit will generally contain from approximately 1.0 wt.% to about 50 wt.% active agent, preferably on the order of 1 wt.% to about 30 wt.% active agent. With regard to the bioerodible (hydrolyzable) polymeric carrier, it will be appreciated that virtually any such carrier can be used, so long as the desired drug release profile is not compromised, and the carrier is compatible with the active agent to be administered and any other components of the buccal dosage unit. Generally, the polymeric carrier comprises a hydrophilic (water-soluble and water-swellable) polymer that adheres to the wet surface of the buccal mucosa. Examples of polymeric carriers useful herein include acrylic acid polymers and co, e.g., those known as "carbomers" (Carbopol®, which may be obtained from B.F. Goodrich, is one such polymer).

Preferred sublingual dosage forms include sublingual tablets, creams, ointments and pastes. The tablet, cream, ointment or paste for sublingual delivery comprises a therapeutically effective amount of the selected active agent and one or more conventional nontoxic carriers suitable for sublingual drug administration. The sublingual dosage forms of the present invention can be manufactured using conventional processes. The sublingual dosage unit is fabricated to disintegrate rapidly. The time period for complete disintegration of the dosage unit is typically in the range of from about 10 seconds to about 30 minutes, and optimally is less than 5 minutes. In addition to the active agent, other components may also be incorporated into the sublingual dosage forms described herein. The additional components include, but are not limited to binders, disintegrants, wetting agents, lubricants, and the like. Examples of binders that may be used include water, ethanol, polyvinylpyrrolidone, starch solution gelatin solution, and the like. Suitable disintegrants include dry starch, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic monoglyceride, lactose, and the like. Wetting agents, if used, include glycerin, starches, and the like.

In addition to sublingual tablets, other rapidly disintegrating tablets are preferred. Examples of such tablets are well known in the art. Another preferred rapidly disintegrating tablet includes effervescent tablets. Effervescent tablets are described in Remington, *supra*, and examples may be found in the literature, and in, for example, U.S. Patent No. 5,211,957 to Hagemann et al. Generally, effervescent tablets contain the active agent in combination with additives such as sodium bicarbonate and an organic acid, e.g., tartaric acid or citric acid. In the presence of water, these additives react to liberate carbon dioxide thereby facilitating the disintegration of the tablet. Once the tablet is substantially disintegrated, an individual swallows the resultant solution thereby providing systemic adsorption of the active agent.

Another version of a rapidly disintegrating tablet includes "open matrix network" tablets. These tablets can disintegrate within seconds, i.e., within five to ten seconds, after being placed on the tongue of an individual. The contents of the tablet can then be swallowed with or without water. An example of such a tablet is found in U.S. Patent No. 4,371,516 to Gregory et al. As described therein, the carrier provides a low-density network, e.g., about 10 to about 200 mg/cm^3, of water-soluble or water-dispersible material. The tablet is produced by subliming a solution containing both the drug and

carrier that is subsequently directed to a mold having tablet-shaped depressions. The carrier may be any suitable material, but is preferably gelatin, with partially hydrolyzed gelatin most preferred.

Another example of a rapidly disintegrating tablet is described in U.S. Patent No. 5,466,464 to Masaki et al. As described therein, an agar solution is prepared using conventional techniques, such as adding agar powder to water followed by gentle heating. Lactose and/or mannitol along with the active agent are added to the agar solution and mixed until uniform. Excipients, e.g., sweeteners, preservatives, and so forth, are also added. Thereafter, aliquots of the mixture are placed in individual molds corresponding to the desired shape of the dosage form. Upon cooling, the mixture solidifies into a "jelly form," which is then dried using conventional techniques, e.g., by reducing the pressure to vacuum-like conditions or aerating, thereby forming a rapidly disintegrating tablet. These and other rapidly disintegrating tablets are available using technology available from Yamanouchi Pharma Technologies, Inc. (Palo Alto, CA), some dosage forms of which are marketed under the WOWTAB® trademark.

In addition to sublingual tablets, other rapidly disintegrating tablets may also be used. For example, other suitable rapidly disintegrating tablets are effervescent tablets. Effervescent tablets are described in *Remington*, *supra*, and examples may be found in the literature, and in, for example, U.S. Patent No. 5,211,957 to Hagemann et al. Generally, effervescent tablets contain the active agent in combination with additives such as sodium bicarbonate and an organic acid, e.g., tartaric acid or citric acid. In the presence of water, these additives react to liberate carbon dioxide thereby facilitating the disintegration of the tablet. Once the tablet is substantially disintegrated, an individual swallows the resultant solution thereby providing systemic adsorption of the active agent.

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mold having tablet-shaped depressions. The carrier may be any suitable material, but is preferably gelatin, with partially hydrolyzed gelatin most preferred.

Another example of a rapidly disintegrating tablet is described in U.S. Patent No. 5,466,464 to Masaki et al., which describes preparation of an agar solution using conventional techniques, such as adding agar powder to water followed by gentle heating. Lactose and/or mannitol along with the active agent are added to the agar solution and mixed until uniform. Excipients, e.g., sweeteners, preservatives, and so forth, are also added. Thereafter, aliquots of the mixture are placed in individual molds corresponding to the desired shape of the dosage form. Upon cooling, the mixture solidifies into a "jelly form," which is then dried using conventional techniques, e.g., by reducing the pressure to vacuum-like conditions or aerating, thereby forming a rapidly disintegrating tablet. These and other rapidly disintegrating tablets are available using technology available from Yamanouchi Pharma Technologies, Inc. (Palo Alto, CA), some dosage forms of which are marketed under the WOWTAB® name.

In addition, the active agent may be administered via a chewing gum formulation. Gum formulations containing a pharmacologically active agent and techniques for preparing such formulations are well known in the art. For example, a gum base (available commercially from, for example, Cafosa, Inc., Calabria, Spain) is rolled in a suitable roller at about 10 to 85 °C for about three minutes. Thereafter, all components except for the active agent, e.g., plasticizers, sugars, sweeteners, fillers, polymers and waxes, are added sequentially and rolled until a homogenous material is obtained. Then, active agent is added and rolled until the entire material is homogenous. Once homogenous, the material is removed from the roll, cooled to room temperature and processed into the desired gum shape, e.g., cubes or sticks.

For transurethral administration, the formulation comprises a urethral dosage form containing the active agent and one or more selected carriers or excipients, such as water, silicone, waxes, petroleum jelly, polyethylene glycol ("PEG"), propylene glycol ("PG"), liposomes, sugars such as mannitol and lactose, and/or a variety of other materials, with polyethylene glycol and derivatives thereof particularly preferred. Transurethral drug administration, as explained in U.S. Patent Nos. 5,242,391, 5,474,535, 5,686,093 and 5,773,020 to Place et al., can be carried out in a number of different ways using a variety of urethral dosage forms. For example, the drug can be introduced into the urethra from a

flexible tube, squeeze bottle, pump or aerosol spray. The drug may also be contained in coatings, pellets or suppositories that are absorbed, melted or bioeroded in the urethra. In certain embodiments, the drug is included in a coating on the exterior surface of a penile insert. A preferred drug delivery device for administering a drug transurethrally is described and illustrated in the aforementioned U.S. patents to Place et al.

Preferred transrectal dosage forms include rectal suppositories, creams, ointments, and liquid formulations (enemas). The suppository, cream, ointment or liquid formulation for transrectal delivery comprises a therapeutically effective amount of the selected active agent and one or more conventional nontoxic carriers suitable for transrectal drug administration. The transrectal dosage forms of the present invention can be manufactured using conventional processes. The transrectal dosage unit can be fabricated to disintegrate rapidly or over a period of several hours. The time period for complete disintegration is preferably in the range of from about 10 minutes to about 6 hours, and optimally is less than 3 hours.

The active agents may also be administered intranasally or by inhalation. Compositions for nasal administration are generally liquid formulations for administration as a spray or in the form of drops, although powder formulations for intranasal administration, e.g., insufflations, are also known.

Formulations for inhalation may be prepared as an aerosol, either a solution aerosol in which the active agent is solubilized in a carrier (e.g., propellant) or a dispersion aerosol in which the active agent is suspended or dispersed throughout a carrier and an optional solvent. Non-aerosol formulations for inhalation may take the form of a liquid, typically an aqueous suspension, although aqueous solutions may be used as well. In such a case, the carrier is typically a sodium chloride solution having a concentration such that the formulation is isotonic relative to normal body fluid. In addition to the carrier, the liquid formulations may contain water and/or excipients including an antimicrobial preservative (e.g., benzalkonium chloride, benzethonium chloride, chlorobutanol, phenylethyl alcohol, thimerosal and combinations thereof), a buffering agent (e.g., citric acid, potassium metaphosphate, potassium phosphate, sodium acetate, sodium citrate, and combinations thereof), a surfactant (e.g., polysorbate 80, sodium lauryl sulfate, sorbitan monopalmitate and combinations thereof), and/or a suspending agent (e.g., agar, bentonite, microcrystalline cellulose, sodium carboxymethylcellulose, hydroxypropyl

methylcellulose, tragacanth, veegum and combinations thereof). Non-aerosol formulations for inhalation may also comprise dry powder formulations, particularly insufflations in which the powder has an average particle size of about 0.1 μm to 50 μm, preferably 1 μm to about 25 μm.

IV. Dosage and Administration:

The present formulations are administered on an as-needed basis, as explained previously. Such flexibility in administration is desirable since the individual may administer the formulation at any convenient time within a 0.25-hour to 3-hour window prior to anticipated sexual activity. In addition, because they are all systemically acting, the formulations may be discreetly administered without need for a device.

As stated above, the amount of active agent administered, and the dosing regimen used, will, of course, be dependent on, *inter alia*, the age and general condition of the individual being treated, the degree to which the onset of ejaculation is to be delayed, and the judgment of the prescribing physician. The concentration of active agent in any given dosage form can vary a great deal, and will depend on a variety of factors, including the type of composition or dosage form, the corresponding mode of administration, the nature and activity of the specific active agent, and the intended drug release profile.

As will appreciated by those skilled in the art, the methods and dosage forms of the invention relate to systemic administration. In order to achieve systemically effective levels of a drug, a typical as-needed dose of the active agent is generally in the range of from about 0.1 mg to about 300 mg, preferably of from about 1 mg to about 200 mg with a dose in the range of from about 1 mg to about 50 mg being most preferred. Thus, unit dosage forms preferably contain the active agent in these ranges as well, i.e., from about 0.1 mg to about 300 mg, more preferably from about 1 mg to about 200 mg with about 1 mg to about 50 mg of active agent in each unit dose form. The dosing regimen can be modulated in order to achieve satisfactory control of the onset of ejaculation. These amounts are particularly preferred when the active agent is clomipramine or clomipramine hydrochloride.

V. PACKAGED KITS:

In another embodiment, a packaged kit is provided that contains the pharmaceutical formulation to be administered, i.e., a pharmaceutical formulation containing a non-SRI antidepressant drug for the treatment of premature ejaculation, a container, preferably sealed, for housing the formulation during storage and prior to use, and instructions for carrying out drug administration in a manner effective to treat premature ejaculation. The instructions will typically be written instructions on a package insert and/or on a label. Depending on the type of formulation and the intended mode of administration, the kit may also include a device for administering the formulation (e.g., a transurethral drug delivery device such as shown in FIG. 1). The formulation may be any suitable formulation as described herein. For example, the formulation may be an oral dosage form containing a unit dosage of the active agent. The kit may contain multiple formulations of different dosages of the same agent. The kit may also contain multiple formulations of different active agents.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications will be apparent to those skilled in the art to which the invention pertains. Furthermore, the practice of the present invention will employ, unless otherwise indicated, conventional techniques of drug formulation that are within the skill of the art. Such techniques are fully explained in the literature. See *Remington: The Science and Practice of Pharmacy*, cited *supra*, as well as Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th Ed. (New York: McGraw-Hill, 1996).

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the compounds of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C and pressure is at or near atmospheric.

EXAMPLE 1

An effervescent tablet is prepared containing the following components:

Component	Amount (per tablet)
Clomipramine hydrochloride	300 mg
Sodium bicarbonate	1985 mg
Citric acid	1000 mg

The components (i.e., clomipramine hydrochloride, sodium bicarbonate and citric acid, as set forth in the above table) are thoroughly mixed. An effervescent tablet is produced by placing the mixture in a die followed by compression with an appropriate punch. Relatively little compression force is used, e.g., about 3,000 to about 20,000 pounds of force.

EXAMPLE 2

A buccal tablet is prepared containing the following components:

Component	Amount (per tablet)
Clomipramine hydrochloride	10 mg
Gelatin	90 mg
Glycerin (concentrated)	20 mg
Lactose	10 mg
Mannitol	20 mg

Clomipramine hydrochloride (10 g) and 90 g of gelatin are mixed and pulverized in a mill. After the mixing is complete, 20 g of concentrated glycerin, 10 g of lactose and 20 g of mannitol are added and the components are mixed until uniform. 150 mg aliquot portions of the mixture are compression-molded to provide a buccal dosage unit. Each buccal unit contains 10 mg of clomipramine hydrochloride.

EXAMPLE 3

A sublingual tablet is prepared containing the following components:

Component	Amount (% by weight)
Clomipramine hydrochloride	35 %
Lactose	63.67 %
Polyethylene glycol 3350	1.0 %
Magnesium stearate	0.33 %

The components (i.e., clomipramine hydrochloride, lactose, polyethylene glycol 3350 and magnesium stearate, as set forth in the above table) are thoroughly mixed. A sublingual tablet is produced by placing the mixture in a die followed by compression with an appropriate punch. Relatively little compression force is used, e.g., about 3,000 to about 20,000 pounds of force.

EXAMPLE 4

An "open matrix network' tablet is prepared A solution containing the following components is prepared:

Component	Amount
Clomipramine hydrochloride	50 g
Partially hydrolyzed gelatin	q.s. to 1,000 ml

A metal mold containing cylindrical depressions (each depression is about 0.5 cm in diameter and about 1.0 cm deep) is cooled to about -192 °C with liquid nitrogen. The clomipramine is mixed with the partially hydrolyzed gelatin solution With continuous mixing, 0.5 ml of the solution is transferred into each depression. After the solution freezes, the mold is placed in a vacuum chamber at room temperature under a vacuum of 0.3 mm Hg for 12 hours. The dosage forms, each containing about 25 mg of the active agent, are then removed from the molds. The dosage forms disintegrate rapidly, i.e., from about five to ten seconds when administered orally.

EXAMPLE 5

A solution for use in a sublingual spray or pulmonary inhaler is prepared. The solution is prepared according to the following:

Component	Amount
Clomipramine hydrochloride	2.5 g
Benzalkonium chloride	0.100 g
Distilled water	q.s. to 100 ml

The formulation is prepared by initially forming a clomipramine hydrochloride solution by combining, under aseptic conditions, 2.5 g of clomipramine hydrochloride in 50 ml of distilled water. Sodium chloride may be added such that the final solution is isotonic. The amount of sodium chloride necessary to provide a final isotonic solution can be calculated based on equations provided in the literature or can be determined experimentally by those skilled in the art. Benzalkonium chloride is used as a preservative and is added to the solution followed by mixing.

The solution is then placed into a spray bottle, which typically comprises a collapsible container vessel, an applicator and a cap. For sublingual sprays, the applicator is shaped and sized to be received under the tongue. For pulmonary administration, the applicator is shaped and sized to facilitate tracheal inhalation by an individual. The applicator will have an opening to release a spray or mist of the solution.

The spray bottle is designed to deliver an individual dose with one to three compressions of the bottle to deliver an effective dose. For example, a single compression of the bottle may be designed to administer approximately 0.33 ml of liquid as a mist or spray. In the context of the formulation described above housed in such a bottle, one or more compressions of the bottle will provide an effective dose of clomipramine.

EXAMPLE 6

A gum formulation is prepared. The components of the gum formulation are as follows:

Component	Amount (% by weight)
Clomipramine hydrochloride	2 % to 30 %
Gum base (Cafosa TAB-3-T, available from Cafosa, Inc., Calabria, Spain)	15 % to 50 %
Sorbitol powder	10 % to 50 %

Cafosa gum base TAB-3-T is rolled in a suitable roller at about 45 °C for about three minutes. Thereafter, the sorbitol powder is added and rolled for about four minutes to obtain a homogenous mixture. Clomipramine hydrochloride is then added to and rolled with the material for another three minutes. The rolled material is removed from the rolling equipment, cooled to room temperature and processed into the small cubes. Each cube contains a therapeutically effective amount of the active agent.

EXAMPLE 7

A rapidly disintegrating tablet is prepared. The general formulation is as follows:

Component	Amount (approximately)	Preferred Amount (approximately)
Active agent (e.g., clomipramine hydrochloride)	0.001 to 50 parts	0.01 to 20 parts
Lactose and/or mannitol	50 to 99.999 parts	80 to 99.9 parts
Agar and excipients (e.g., sweetener, coloring agent, preservative, etc.)	0.12 to 1.2 parts	0.2 to 0.4 parts

An aqueous solution containing 0.3 to 2.0%, preferably 0.3 to 0.8%, of agar is prepared and the above components are added to the solution and mixed to obtain a suspension. The suspension is then filled in a suitable mold at room temperature and then dried. Suitable drying procedures include exposing the suspension for two to five hours at reduced pressure, e.g., at or near vacuum conditions, at a temperature of from about 25°C

to about 35°C. In addition, the suspension may be dried via aeration drying at a temperature of from about 3°C to about 15°C for one to six days. The tablets may have a size of about 9.5 mm in diameter and about 4.2 mm thick or about 12mm in diameter and about 5.2 mm thick.

EXAMPLE 8

A rapidly disintegrating tablet for as-needed administration of clomipramine hydrochloride to treat premature ejaculation was prepared. The tablet contains a 10 mg unit dosage of clomipramine, with the remainder of the tablet containing the following components:

COMPONENT	% SOLID (W/W)	QUANTITY PER TABLET (MG)	QUANTITY PER BATCH (G)
Clomipramine HCl	8.333	10.00	100.00
Mannitol	84.417	101.30	1013.00
Maltose	5.000	6.00	60.00
Acesulfame Potassium	0.500	0.60	6.00
Peppermint (Beta Natural)	0.250	0.30	3.00
Magnesium Stearate	0.750	9.00	9.00
Stearic Acid (Micronized)	0.750	9.00	9.00
Purified Water*	-----	-----	-----
Total	100.000	120.00	1200.0

* Purified water is removed during processing and is not part of the final formula.

EXAMPLE 9

The patients for the study are drawn from a waiting list for psychosexual therapy of a sexology outpatient department and through advertisement. The inclusion criteria are that the patients be heterosexual, be aged 18-75 years, be involved in a sexual relationship with a female partner during the previous 6 months, the partner is able to participate in the study, and the patient experiences premature ejaculation.

Patients are excluded if they used psychoactive medication, are receiving any therapy for sexual dysfunction, have inhibited male orgasm, are alcohol or substance abusers, score greater than 14 on the 24-item Hamilton Rating Scale for Depression (HAM-D) indicating clinically significant depression, and for other clinically significant medical disease or symptomology. For the duration of the study, the patients are required to abstain from alcohol.

Patients are randomly assigned to double blind treatment with any rapid-release formulation described in the previous examples or a placebo. Patients who remain in the study for at least 3 weeks are included in the statistical analysis. Patients are provided with formulations prepared in the preceding Examples for administration or matching placebo. Patients are instructed to administer the formulation at any time within the four-hour window leading up to anticipated sexual activity. During the study, the patients do not use condoms or topical anesthetics.

Patients and their partners are assessed at the end of each week. Efficacy measures include (1) frequency of attempted intercourse, (2) latency to attempted ejaculation (from penetration), (3) frequency of successful attempts at intercourse without premature ejaculation, (4) number of incidences of premature ejaculation, and (5) time to ejaculation as reported by both the patients and their partners based on subjective measurements. In addition, the patients are assessed using the following psychopathological rating instruments: Hamilton Depression Rating Scale (HDRS), Clinical Global Impression (CGI), COVI Anxiety Scale, Atypical Depressive Disorders Scale-Changes (ADDS-C) and an adverse event form.

The response to treatment is scored The mean or median values are analyzed by using parametric tests including Friedman two-way analysis of variance (ANOVA) and the Wilcoxon matched-pairs signed-ranks test to assess differences in measurements within the groups, and the Mann-Whitney test for differences between the groups.

Differences between groups on discrete variables are tested for statistical significance by using Fisher's exact test. A two-tailed p value, 0.05 is considered significant for these analyses.

Each of the formulations prepared and administered for systemic absorption is expected to be effective in treating premature ejaculation. The use of the formulations results in an extension of intravaginal ejaculation latency time in patients with premature ejaculation. The data from patient-rated and partner-rated latency to ejaculation is compared. Both of these parameters show greater improvement with clomipramine-containing formulations as compared to placebo. In addition, those patients who attempted to treat their premature ejaculation with previous modalities report greater satisfaction with as-needed administration of the formulations provided in the examples. Specifically, these patients cited greater flexibility with the timing of the dose, and fewer side effects (in part due to not administering clomipramine on a daily basis).

WE CLAIM:

1. A method for treating premature ejaculation, which comprises administering to a male individual in need of such treatment, on an as-needed basis, a therapeutically effective amount of an antidepressant drug selected from the group consisting of tricyclic antidepressants, tetracyclic antidepressants, monoamine oxidase inhibitors, azaspirone antidepressants, and atypical non-SRI antidepressants.

2. The method of claim 1, wherein the antidepressant drug is contained within a pharmaceutical formulation.

3. The method of claim 2, wherein the pharmaceutical formulation is a unit dosage form.

4 The method of claim 3, wherein the antidepressant drug is administered immediately prior to sexual activity.

5. The method of claim 4, wherein the antidepressant drug is administered about 0.25 to about 3.5 hours prior to sexual activity.

6. The method of claim 5, wherein the active agent is administered about 0.5 to about 3.0 hours prior to sexual activity

7. The method of claim 6, wherein the active agent is administered about 1 to about 2.5 hours prior to sexual activity.

8. The method of any one of claims 4, 5, 6 and 7, wherein the sexual activity is sexual intercourse.

9. The method of claim 2, wherein the formulation is an immediate release dosage form.

10. The method of claim 3, wherein the formulation is an immediate release unit dosage form.

11. The method of claim 1, wherein the active agent is administered orally.

12. The method of claim 11, wherein the pharmaceutical formulation is selected from the group consisting of tablets, capsules, caplets, solutions, suspensions syrups granules, beads, powders and pellets.

13. The method of claim 12, wherein the pharmaceutical formulation comprises a tablet.

14. The method of claim 12, wherein the pharmaceutical formulation comprises a capsule.

15. The method of claim 1, wherein the active agent is administered transmucosally.

16. The method of claim 15, wherein the active agent is administered sublingually.

17. The method of claim 15, wherein the active agent is administered buccally.

18. The method of claim 15, wherein the active agent is administered intranasally.

19. The method of claim 15, wherein the active agent is administered transurethrally.

20. The method of claim 15, wherein the active agent is administered rectally.

21. The method of claim 1, wherein the active agent is administered by inhalation.

22. The method of claim 1, wherein the active agent is administered transdermally.

23. The method of claim 1, wherein the active agent is administered parenterally.

24. The method of claim 1, wherein the antidepressant drug is selected from the group consisting of tricyclic antidepressants, tetracyclic antidepressant drugs, and combinations thereof.

25. The method of claim 24, wherein the antidepressant drug is selected from the group consisting of amitryptiline, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, imipramine, iprindole, lofepramine, maprotiline, melitracen, metapramine, mianserin, mirtazapine, nortryptiline, propizepine, protriptyline, quinupramine, setiptiline, tianeptine, trimipramine, and combinations thereof.

26. The method of claim 25, wherein the antidepressant drug is clomipramine or an acid addition salt thereof.

27. The method of claim 26, wherein the antidepressant drug is clomipramine hydrochloride.

28. The method of claim 1, wherein the antidepressant drug is selected from the group consisting of monoamine oxidase inhibitors.

29. The method of claim 28, wherein the antidepressant drug is selected from the group consisting of amiflamine, brofaromine, clorgyline, α-ethyltryptamine, iproclozide, iproniazid, isocarboxazid, mebanazine, moclobemide, nialamide, pargyline, phenelzine,

pheniprazine, pirlindole, safrazine, selegiline, toloxatone, tranylcypromine, and combinations thereof.

30. The method of claim 1, wherein the antidepressant drug is selected from the group consisting of azaspirone antidepressants.

31. The method of claim 30, wherein the antidepressant drug is selected from the group consisting of buspirone, gepirone, ipsapirone, tandospirone, tiaspirone, and combinations thereof.

32. The method of claim 1, wherein the antidepressant drug is an atypical non-SRI antidepressant selected from the group consisting of amesergide, amineptine, benactyzine, bupropion, fezolamine, levoprotiline, medifoxamine, mianserin, minaprine, oxaflozane, oxitriptan, rolipram, teniloxazine, tofenacin, trazodone, tryptophan, viloxazine, and combinations thereof.

33. The method of claim 1, further comprising administering at least one additional active agent with the antidepressant drug.

34. The method of claim 33, wherein the additional active agent is a vasoactive agent selected from the group consisting of nitroglycerin, isosorbide dinitrate, erythrityl tetranitrate, amyl nitrate, sodium nitroprusside, molsidomine, linsidomine chlorhydrate, S-nitroso-N-acetyl-d,l-penicillamine, S-nitroso-N-cysteine and S-nitroso-N-glutathione, diazenium diolates ("NONOates"), phenoxybenzamine, dibenamine, doxazosin, terazosin, phentolamine, tolazoline, prazosin, trimazosin, alfuzosin, tamsulosin, indoramin, ergotamine, acetergamine, brazergoline, bromerguride, cianergoline, delorgotrile, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotrile, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, proterguride, diazoxide, hydralazine, minoxidil nimodepine, pinacidil, cyclandelate, dipyridamole, isoxsuprine, chlorpromazine, haloperidol, yohimbine, prostaglandin E_0, prostaglandin E_1, prostaglandin A_1, prostaglandin B_1, prostaglandin $F_{1\alpha}$, 19-hydroxy-prostaglandin A_1, 19-hydroxy- prostaglandin B_1, prostaglandin E_2, prostaglandin A_2,

prostaglandin B_2, 19-hydroxy- prostaglandin A_2, 19-hydroxy- prostaglandin B_2, prostaglandin E_3, prostaglandin $F_{3\alpha}$, carboprost tromethamine, dinoprost tromethamine, dinoprostone, lipoprost, gemeprost, metenoprost, sulprostone, tiaprost, vasoactive intestinal peptide, and combinations thereof.

35. The method of claim 33, wherein the additional active agent is a phosphodiesterase inhibitor.

36. The method of claim 35, wherein the phosphodiesterase inhibitor is a Type III, Type IV, Type V, or nonspecific phosphodiesterase inhibitor.

37. The method of claim 33, wherein the additional active agent is selected form the group consisting of cianopramine, citalopram, femoxetine, fluoxetine, fuvoxamine, ifoxetine, milnacipran, nomifensine, oxaprotiline, paroxetine, sertraline, sibutramine, venlafaxine, viqualine, zimeldine, zlovoxamine, etoperidone, methylphenidate, nefazodone, opipramol, 2-methyl serotonin, lysergic acid diethylamide, ergot alkaloids, 8-hydroxy-(2-N,N-dipropylamino)-tetraline, 1-(4-bromo-2,5-dimethoxypheryl)-2-aminopropane, cisapride, sumatriptan, *m*-chlorophenylpiperazine, zacopride, mezacopride, ondansetron, granisetron, metoclopramide, tropisetron, dolasetron, trimethobenzamide, methysergide, risperidone, ketanserin, ritanserin, clozapine, R(+)--(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol, azatadine, cyproheptadine, fenclonine, dexfenfluramine, fenfluramine, chlorpromazine, methoxamine, methpentermine, metaraminol, mitodrine, clonidine, apraclonidine, guanfacine, guanabenz, methyldopa, amphetamine, methamphetamine, epinephrine, norepinephrine, ethylnorepinephrine, phenylephrine, ephedrine, pseudoephedrine, pemoline, naphazoline, tetrahydrozoline, oxymetazoline, xylometazoline, phenylpropanolamine, phenylethylamine, dopamine, dobutamine, colterol, isoproterenol, isotharine, metaproterenol, terbutaline, tyramine, hydroxyamphetamine, ritodrine, prenalterol, albuterol, isoetharine, pirbuterol, bitolterol, fenoterol, formoterol, procaterol, salmeterol, mephenterine, propylhexedrine, phenoxybenzamine, phentolamine, tolazoline, prazosin, terazosin, doxazosin, trimazosin, yohimbine, labetalol, urapidil, alfuzosin, bunazosin, tamsulosin, haloperidol, phenothiazines, butyrophenones, propranolol, nadolol, timolol, pindolol, metoprolol,

atenolol, esmolol, acebutolol, bopindolol, carteolol, oxprenolol, penbutolol, carvedilol, medroxalol, naftopidil, bucindolol, levobunolol, metipranolol, bisoprolol, nebivolol, betaxolol, carteolol, celiprolol, sotalol, propafenone, indoramin, bethanidine, debrisoquine, guabenxan, guanadrel, guanazodine, guanethidine, guanoclor, guanoxan, alprazolam, brotizolam, chlordiazepoxide, clobazepam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazapam, oxazepam, prazepam, quazepam, temazepam, triazolam, pharmacologically acceptable salts thereof, and combinations of any of the foregoing.

38. The method of claim 37, wherein the additional active agent is selected from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazepam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazapam, oxazepam, prazepam, quazepam, temazepam, triazolam, and pharmaceutically acceptable salts thereof.

39. The method of claim 37, wherein the additional active agent is selected from the group consisting of fluoxetine, fluvoxamine, paroxetine, sertraline, and pharmaceutically acceptable salts thereof.

40. A pharmaceutical formulation for treating premature ejaculation, comprising a rapid release formulation of a therapeutically effective amount of an antidepressant drug selected from the group consisting of tricyclic antidepressants, tetracyclic antidepressants, MAO inhibitors, azaspirone antidepressants, and atypical non-SRI antidepressants, and a pharmaceutically acceptable carrier.

41. The formulation of claim 40, wherein the antidepressant drug is selected from the group consisting of tricyclic antidepressants, tetracyclic antidepressant drugs, and combinations thereof.

42. The formulation of claim 41, wherein the antidepressant drug is selected from the group consisting of amitryptiline, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, imipramine,

iprindole, lofepramine, maprotiline, melitracen, metapramine, mianserin, mirtazapine, nortryptiline, propizepine, protriptyline, quinupramine, setiptiline, tianeptine, trimipramine, and combinations thereof.

43. The formulation of claim 42, wherein the antidepressant drug is clomipramine or an acid addition salt thereof.

44. The formulation of claim 43, wherein the antidepressant drug is clomipramine hydrochloride.

45. The formulation of claim 40, wherein the antidepressant drug is selected from the group consisting of monoamine oxidase inhibitors.

46. The formulation of claim 45, wherein the antidepressant drug is selected from the group consisting of amiflamine, brofaromine, clorgyline, α-ethyltryptamine, iproclozide, iproniazid, isocarboxazid, mebanazine, moclobemide, nialamide, pargyline, phenelzine, pheniprazine, pirlindole, safrazine, selegiline, toloxatone, tranylcypromine, and combinations thereof.

47. The formulation of claim 40, wherein the antidepressant drug is selected from the group consisting of azaspirone antidepressants.

48. The formulation of claim 47, wherein the antidepressant drug is selected from the group consisting of buspirone, gepirone, ipsapirone, tandospirone, tiaspirone, and combinations thereof.

49. The formulation of claim 40, wherein the antidepressant drug is an atypical non-SRI antidepressant selected from the group consisting of amesergide, amineptine, benactyzine, bupropion, fezolamine, levoprotiline, medifoxamine, mianserin, minaprine, oxaflozane, oxitriptan, rolipram, teniloxazine, tofenacin, trazodone, tryptophan, viloxazine, and combinations thereof.

50. The formulation of claim 40, in unit dosage form.

51. The formulation of claim 50, wherein the antidepressant drug is present in an amount of about 0.1 mg to about to about 300 mg.

52. The formulation of claim 51, wherein the amount is in the range of about 1 mg to about 100mg.

53. The formulation of claim 52, wherein the amount is in the range of about 1 mg to about 50 mg.

54. The formulation of claim 40, in the form of a rapidly disintegrating tablet.

55. The formulation of claim 40, in the form of an effervescent tablet.

56. The formulation of claim 40, in the form of an open matrix network tablet.

57. A formulation of claim 40, adapted for transmucosal drug administration, wherein the carrier is suitable for transmucosal drug delivery buccally, sublingually, intranasally, rectally, or by inhalation.

58. The formulation of claim 57, comprising a solid dosage form for application to the buccal mucosa, and wherein the carrier is suitable for buccal drug delivery.

59. The formulation of claim 58, wherein the carrier is a hydrolyzable polymer.

60. The formulation of claim 59, wherein the dosage form further comprises an adhesive suitable for affixing the dosage form to the buccal mucosa.

61. The formulation of claim 57, comprising a dosage form for application to the sublingual mucosa, and wherein the carrier is suitable for sublingual drug delivery.

62. The formulation of claim 57, comprising a dosage form for application to the rectal mucosa, and the carrier is suitable for rectal drug delivery.

63. The formulation of claim 62, comprising a rectal suppository.

64. The formulation of claim 57, comprising a dosage form suitable for inhalation.

65. The formulation of claim 64, comprising a liquid.

66. The formulation of claim 64, comprising a dry powder.

67. The formulation of claim 64, comprising an aerosol composition.

68 The pharmaceutical formulation of claim 40, comprising an intranasal solution.

69. The formulation of claim 40, in the form of a gum.

70. The formulation of claim 40, in the form of a transdermal drug delivery device adapted to be affixed to an individual's body surface.

71 A packaged kit for a patient to use in the treatment of premature ejaculation, comprising: a pharmaceutical formulation of an antidepressant drug selected from the group consisting of tricyclic antidepressants, tetracyclic antidepressants, MAO inhibitors, azaspirone antidepressants, and atypical non-SRI anticepressants; a container housing the pharmaceutical formulation during storage and prior to administration; and instructions for carrying out drug administration in a manner effective to treat premature ejaculation.

72. The packaged kit of claim 71, wherein the pharmaceutical formulation is a rapid-release dosage form containing a unit dosage of the antidepressant drug, the unit dosage being a therapeutically effective dosage for treatment of premature ejaculation.

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(54) Title: COMPOSITIONS AND METHODS FOR ENHANCEMENT OF SEXUAL FUNCTION

(57) Abstract: Novel compositions and methods which utilize an erection-enhancing agent and an ejaculation-delaying agent, such that these agents provide an overlapping and/or synergistic effect, are provided. These composition and methods can be beneficially utilized for treating sexual dysfunction and/or for enhancing sexual function.

COMPOSITIONS AND METHODS FOR ENHANCEMENT OF SEXUAL FUNCTION

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to compositions and methods for treating sexual dysfunctions and/or enhancing sexual function.

Sexual dysfunctions may begin early in a person's life, or they may develop after an individual has previously experienced enjoyable and satisfying sex. A problem may develop gradually over time, or may occur suddenly as a total or partial inability to participate in one or more stages of the sexual act.

The causes of sexual dysfunctions can be physical, psychological, or both. Psychological factors include both interpersonal problems and psychological problems within the individual, such as depression.

Physical factors contributing to sexual dysfunctions include drugs (alcohol, nicotine, narcotics, stimulants, antihypertensives, antihistamines, and some psychotherapeutic drugs); injuries to the back; problems with an enlarged prostate gland; problems with blood supply; nerve damage (as in spinal cord injuries); disease (diabetic neuropathy, multiple sclerosis, tumors, and, rarely, tertiary syphilis); failure of various organ systems (such as the heart and lungs); endocrine disorders (thyroid, pituitary, or adrenal gland problems); hormonal deficiencies (low testosterone, estrogen, or androgens); and some birth defects.

Sexual dysfunctions are generally classified into 4 categories: sexual desire disorders, sexual arousal disorders, orgasm disorders, and sexual pain disorders.

Sexual arousal disorders in men include erectile dysfunction, which involves partial or complete failure to attain or maintain an erection adequately for intercourse. Erectile dysfunction is a very common problem, affecting from about 40 % to 60 % of men at some time in their life, and about 52 % of men between 40 to 70 years old [1]. However, only about 10 % of men suffering from erectile dysfunction are willing to seek medical help.

Patients suffering from erectile dysfunction generally respond well to medication of the phosphodiesterase type 5 (PDE5) family. For example, 81 % of subjects studied were found to respond well to oral administration of 20 mg of tadalafil (Cialis™) [2], and between 74 % to 91 % were found to respond well to oral

administration of 20mg of vardenafil (Levitra™) [4] and 82 % were found to respond well to oral administration of 50-100 mg of sildenafil (Viagra™).

In addition to erectile dysfunction patients, it has been found that many consumers of PDE5 are physically healthy men, with no pathological sexual problems, who are aiming to improve the quality of their sexual performance by enhancing extent and duration of erection.

The principal drugs belonging to the PDE5 family are tadalafil (Cialis™), vardenafil (Levitra™) and sildenafil (Viagra™).

It has been shown that about 79 % of patients treated with tadalafil were able to have sexual intercourse with a satisfactory erection [1] within about 2 to 36 hours after administration.

Pharmacokinetic studies have shown that tadalafil (20 mg) is absorbed after oral administration, with a maximum observed plasma concentration (C_{max}) of 378 μg/L and a time to reach maximum plasma concentration (T_{max}) of 2 hours (20 mg dose) [1, 2]. Systemic exposure (AUC) increases proportionately with doses from 2.5 mg to 20 mg. The increase in C_{max} is slightly less than proportional over that dose range. During once-daily 20 mg dosing, steady-state plasma concentrations were attained within approximately 5 days and the degree of drug accumulation was 1.6 fold.

Pharmacokinetic studies have shown that sildenafil (50-100 mg) is absorbed after oral administration, with a maximum observed plasma concentration (C_{max}) of 18 ng/ml and a time to reach maximum plasma concentration (T_{max}) of 60 minutes (50-100 mg dose) [1, 2].

Studies with vardenafil have been shown that about 82 % of subjects studied can have sexual intercourse with a satisfactory erection [3] within 25 minutes to 5 hours after an administrated dose of 20 mg vardenafil. Vardenafil is rapidly absorbed after oral administration, with C_{max} being reached as early as 15 minutes post-administration. After oral dosing of vardenafil, AUC and C_{max} increase in almost direct proportion to the dose over the recommended dose range (5-20 mg). 82 % of subjects studied can have sexual intercourse with a satisfactory erection within 14 minutes to 6 hours after an administered dose of 50-100 mg vardenafil.

Ejaculatory dysfunctions include delayed ejaculation and premature ejaculation. Premature ejaculation is the most common and underestimated male sexual disorder.

Premature ejaculation is a frequent and distinct medical condition, affecting from 20-60 % of men worldwide, which can severely impact quality of life, affecting the physical and emotional well-being of patients and their partners. More common than erectile dysfunction, this condition can affect men at any point in their lives, and one in four men experience poor control over ejaculation on a frequent basis.

Men with poor control over ejaculation tend to be less satisfied with sexual intercourse and their sexual relationship, and may suffer more difficulties with sexual anxiety and arousal compared to non-sufferer. In one study [6], men classified with probable premature ejaculation self-reported poor control over ejaculation, low satisfaction with sexual intercourse, low satisfaction with sexual relationship, low interest in actually having sexual intercourse, difficulty in becoming sexually aroused, and difficulty relaxing during intercourse. These findings highlight the negative impact of premature ejaculation on quality of life, sexual performance and enjoyment of sex.

Based on psychopharmacological studies there is evidence that premature ejaculation is related to a diminished serotonergic neurotransmission, and 5-HT2C or 5-HT1A receptor disturbances. Moreover, animal studies show the presence of a distinct ejaculation-related neural circuit in the central nervous system [7].

Some psychoactive drugs, particularly tricyclic antidepressants, such as clomipramine, and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine and sertraline, can delay ejaculation as a side effect. Almost all members of the SSRI family have been shown to be able to delay ejaculation, though to various extents. Figure 1 presents representative results, described in published studies [15, 16], showing the effect of various antidepressant and placebo on the ejaculatory latency time of men.

Clomipramine is a chlorinated analogue of imipramine [1] with both antidepressant and antiobsessional properties [2, 3], which penetrates the blood-brain barrier readily, reaching concentrations in the brain that are ten times greater than plasma concentrations after a single parenteral dose [4, 7].

Clomipramine inhibits norepinephrine and serotonin uptake into central nerve terminals, possibly by blocking the membrane-pump of neurons, thereby increasing the concentration of transmitter monoamines at receptor sites. Clomipramine also possesses anticholinergic properties, weak antihistamine and antiserotonin properties, potentiates the effect of norepinephrine and other drugs acting on the central nervous system, has a quinidine-like effect on the heart and may impair cardiac conduction.

Clomipramine has been shown to block ejaculation without suppressing orgasm [8, 9]. Clomipramine has an effect on the excretory phase of ejaculation, by inhibiting contraction of the longitudinal fibers of the deferent ducts responsible for the sperm progression, without affecting the contractile activity of their circular fibers which act as a clamp, blocking the passage of the semen [17].

A significant increase in time to ejaculation has been demonstrated in men who took 25 milligrams of clomipramine 12 to 24 hours before anticipated sexual activity. The latency to ejaculation ranged from about 1.5 to 2 minutes up to about 8 minutes, which was considered to be in the range in which sexual satisfaction was reported [10].

Another study reported that 50 mg of clomipramine can extend time to climax in premature ejaculators to more than 8 minutes [11, 12]. The researcher also noted that the advantage of taking only a small dose of clomipramine, only as needed, helps reduce the number of side effects that often occur when people take antidepressants over long periods of time.

Plasma levels of clomipramine usually peak 2-6 hours after dosage but much individual variation occurs. The half-life of clomipramine ranges from 8.6 to 36 hours.

Premature ejaculation is frequently associated with erectile dysfunction. However, clomipramine alone has been shown to be ineffective in men with premature ejaculations who were also impotent [10], while sildenafil and PDE5 alone was ineffective for men with premature ejaculation. The administration of PDE5 may even aggravate premature ejaculation.

Furthermore, healthy subjects frequently seek to improve the quality of their sexual relationships, by both strengthening erection and delaying time to ejaculation, in order to experience a longer and more intense orgasm and provide their partner

with increased sexual pleasure. For such subjects, administration of an erection enhancing agent and an ejaculation-delaying agent would be desirable.

The use of PDE5 drugs allows for lengthier foreplay, which increases female desire but also leads to stronger arousal for the male partner, thus presenting a higher risk of premature ejaculation, or at least ejaculation before the desired time. Therefore, these subjects may benefit from co-administration of an ejaculation-delaying agent.

Men suffering from performance anxiety leading to erectile dysfunction or loss of erection during foreplay or penetration frequently have problems with control of ejaculation, which will often be premature. There is therefore a real need for a solution to the problem of premature ejaculation combined with erectile dysfunction.

Furthermore, women suffering from difficulty in reaching climax or from pain during penetration need a partner who can control his ejaculation without losing his erection in order to enable her to relax, without fearing a too rapid ejaculation. In this case also, there is a need to enable the healthy partner to delay his ejaculation without losing his erection, thus contributing to the treatment and improvement of his partner's sexuality.

The use of the SSRI drug paroxetine together with the phosphodiesterase type 5 inhibitor sildenafil, has been reported for treatment of potent patients with premature ejaculation [13]. In this study, patients received either paroxetine alone, 3-4 hours before sexual intercourse, or a combined therapy of paroxetine, 3-4 hours before sexual intercourse, and sildenafil, 1 hour before sexual intercourse, while evaluating the effect of the addition of sildenafil on premature ejaculation.

In addition, the effect of SSRIs in the treatment of premature ejaculation in patients treated with sildenafil for erectile enhancement has been reported [14]. In this study, the effect of the SSRI sertraline on premature ejaculation in patients having primary premature ejaculation was compared to its effect in patients having sildenafil-corrected erectile dysfunction. All patients received sertraline 4 hours before sex. Sertraline was found effective as ejaculation delaying agent only for patients having primary premature ejaculation.

Prolonged treatment with SSRIs, however, has been shown to adversely affect sexual dysfunction. Between 30 % and 50 % of SSRI-treated patients experience sexual dysfunction. Several studies, aiming at reducing SSRI-induced sexual

dysfunction have been published. Thus, for example, it was reported that administration of ropinrole, an anti-parkinsonian dopamine agonist, was effective in treating sexual dysfunction induced by citalopram, sertraline, paroxetine, fluoxetine and venlafaxine treatment [Ginzberg D. L., *Primary Psychiatry,* 2003:10(2), 22-26]. U.S. Patent Application Publication No. 2003/0055070 teaches the use of PDE5 inhibitors for treating SSRI-induced sexual dysfunction. None of these publications, however, addresses a combined treatment of erectile dysfunction and premature ejaculation.

U.S. Patent Application Publication No. 2005/0009835 teaches a combined therapy that comprises co-administration and/or co-formulation of a PDE5 inhibitor and 1-deprenyl or propargylamine compounds, the latter being monoamine oxidase inhibitors that enhance dopamine activity and increase cGMP generation, and thereby may augment the action of the PDE5 inhibitor in treating sexual dysfunction. This patent application, however, fails to teach a combined therapy that addresses both erectile dysfunction and premature ejaculation.

WO 02/079152 discloses a novel SSRI compound which was found effective in treating, *inter alia*, premature ejaculation. While this patent application teaches the use of this compound, in combination with an erection dysfunction agent such as sildenafil, for treating sexual dysfunction, the effect of such a combined therapy has not been demonstrated.

WO 02/41883 and U.S. Patents Nos. 6,495,154 and 6,946,141 teach a method of treating premature ejaculation, which is effected by administration of a cyclic (e.g., tricyclic, tetracyclic and other) non-SRI antidepressant such as clomipramine, on an "as needed" basis, which allows administration of the active agent shortly (within a time frame of 0.25-3.5 hours) before anticipated sexual activity. According to the teachings of this patent application, an additional active agent such as a PDE5 inhibitor can be co-administered together with the active agent. The teachings of these patents and patent application are based on a rapid-release pharmaceutical formulation. This patent application, however, fails to teach a method that is directed at simultaneously providing an ejaculation delaying effect and an erection enhancing effect.

Thus, while the prior art teaches various methods that involve co-administration of an erection enhancement agent and anti-depressants such as SSRIs

and tricyclic anti-depressants, the prior art does not teach or suggest co-administration of an erection-enhancing agent and an ejaculation-delaying agent for the treatment of patients suffering from erectile dysfunction. The prior art also does not teach or suggest co-administration of the two agents to healthy subjects seeking to enhance erection and delay ejaculation.

Furthermore, the known agents for enhancement of erection and delay of ejaculation involve drugs which reach maximum plasma concentrations at different times, requiring administration of the individual medications at separate times, which is highly inconvenient for the patient. The prior art does not teach or suggest a treatment which provides substantially simultaneous co-administration of an agent for enhancement of erection and an agent for delay of ejaculation. The prior art further does not teach or suggest co-formulation of an agent for enhancement of erection and an agent for delay of ejaculation and particularly fail to teach such a co-formulation which provides an overlapping maximal efficacy of these agents.

There is thus a widely recognized need for and it would be highly advantageous to have, compositions and methods for enhancement of sexual function, devoid of the above limitations.

SUMMARY OF THE INVENTION

The present invention successfully addresses the shortcomings of the presently known methods of enhancing sexual function by providing methods and compositions for co-administration of an erection-enhancing agent and an ejaculation-delaying agent which provide an overlapping and/or synergistic effect of these agents and thus can be efficiently utilized in the treatment of patients suffering from sexual dysfunction, premature ejaculation and/or erectile dysfunction.

Thus, according to one aspect of the present invention there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, the composition being such that an efficacy window of the an erection-enhancing agent and an efficacy window of the ejaculation-delaying agent substantially overlap.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of an

erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, the composition being such that the erection-enhancing agent and the ejaculation-delaying agent act in synergy. The pharmaceutically effective amount of the erection-enhancing agent therefore preferably equals to or is lower than 25 mg per dosage unit, whereby the pharmaceutically effective amount of the ejaculation-delaying agent is preferably lower than 50 mg per dosage unit.

According to still another aspect of the present invention there is provided a pharmaceutical composition comprising clomipramine, as an ejaculation-delaying agent, and a PDE5 inhibitor, as an erection enhancing agent.

According to further features in preferred embodiments of the invention described below, the pharmaceutical compositions described herein are such that a maximal efficacy window of the erection-enhancing agent and a maximal efficacy window of the ejaculation-delaying agent overlap for at least 20 minutes.

According to still further features in the described preferred embodiments the pharmaceutical compositions described herein are designed such that a plasma peak concentration of the ejaculation-delaying agent and a plasma peak concentration of the erection-enhancing agent occur substantially simultaneously.

According to still further features in the described preferred embodiments the at least the erection-enhancing agent is provided in a delayed release form.

According to still further features in the described preferred embodiments the release of the erection-enhancing agent is delayed by from about 2 to about 3 hours relative to release of the ejaculation-delaying agent.

According to still further features in the described preferred embodiments the ejaculation-delaying agent is clomipramine.

According to still further features in the described preferred embodiments the erection-enhancing agent is selected from the group consisting of a phosphodiesterase type 5 inhibitor, arginine and human DNA.

According to still further features in the described preferred embodiments the phosphodiesterase type 5 inhibitor is selected from the group consisting of tadalafil, vardenafil and sildenafil.

According to still further features in the described preferred embodiments the pharmaceutical composition is formulated as a pharmaceutical dosage unit.

According to still further features in the described preferred embodiments an amount of the clomipramine ranges from about 15 mg to about 30 mg per dosage unit.

According to still further features in the described preferred embodiments the erection-enhancing agent comprises tadalafil.

According to still further features in the described preferred embodiments the amount of the tadalafil ranges from about 10 mg to about 20 mg per dosage unit and is preferably about 10 mg.

According to still further features in the described preferred embodiments the erection-enhancing agent comprises vardenafil.

According to still further features in the described preferred embodiments an amount the vardenafil ranges from about 10 mg to about 20 mg per dosage unit and is preferably about 10 mg.

According to still further features in the described preferred embodiments the erection-enhancing agent comprises sildenafil.

According to still further features in the described preferred embodiments an amount of the sildenafil is about 25 mg per dosage unit.

According to still further features in the described preferred embodiments a release of the tadalafil is delayed by about 2 hours relative to a release of the clomipramine.

According to still further features in the described preferred embodiments a release of the vardenafil is delayed by about 3 hours relative to a release of the clomipramine.

According to still further features in the described preferred embodiments the release of the sildenafil is delayed by about 3 hours relative to a release of the clomipramine.

According to still further features in the described preferred embodiments the pharmaceutical compositions described herein are provided in a delivery form suitable for oral administration.

According to still further features in the described preferred embodiments the pharmaceutical compositions described herein further comprise a pharmaceutically acceptable carrier.

According to an additional aspect of the present invention there is provided a method of enhancing sexual satisfaction, the method comprising co-administering a

pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, such that an efficacy window of the erection-enhancing agent and an efficacy window of the ejaculation-delaying agent substantially overlap, thereby enhancing sexual dysfunction.

According to still an additional aspect of the present invention there is provided a method of enhancing sexual satisfaction, the method comprising co-administering a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, the erection-enhancing agent and the ejaculation-delaying agent acting in synergy, thereby enhancing sexual dysfunction.

According to yet an additional aspect of the present invention there is provided a use of an erection-enhancing agent and an ejaculation-delaying agent, wherein an efficacy window of the erection-enhancing agent and an efficacy window of the ejaculation-delaying agent substantially overlap, for the preparation of a medicament for enhancing sexual satisfaction.

According to a further aspect of the present invention there is provided a use of an erection-enhancing agent and an ejaculation-delaying agent, wherein the erection-enhancing agent and the ejaculation-delaying acting in synergy, for the preparation of a medicament for enhancing sexual satisfaction.

According to still a further aspect of the present invention there is provided a method of treating erectile dysfunction, the method comprising co-administering to a subject in need thereof a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, such that an efficacy window of the an erection-enhancing agent and an efficacy window of the ejaculation-delaying agent substantially overlap, thereby treating erectile dysfunction.

According to yet a further aspect of the present invention there is provided a method of treating erectile dysfunction, the method comprising co-administering to a subject in need thereof a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, the erection-enhancing agent and the ejaculation-delaying agent acting in synergy, thereby treating erectile dysfunction.

According to another aspect of the present invention there is provided a method of treating erectile dysfunction, the method comprising co-administering to a subject in need thereof a pharmaceutically effective amount of a phosphodiesterase type 5 inhibitor, as an erection-enhancing agent and a pharmaceutically effective amount of clomipramine, as an ejaculation-delaying agent, thereby treating erectile dysfunction.

According to still another aspect of the present invention there is provided a use of an erection-enhancing agent and an ejaculation-delaying agent, wherein an efficacy window of the erection-enhancing agent and an efficacy window of the ejaculation-delaying agent substantially overlap, for the preparation of a medicament for treating erectile dysfunction

According to yet another aspect of the present invention there is provided a use of an erection-enhancing agent and an ejaculation-delaying agent, wherein the erection-enhancing agent and the ejaculation-delaying agent act in synergy, for the preparation of a medicament for treating erectile dysfunction.

According to still another aspect of the present invention there is provided a use of a phosphodiesterase type 5 inhibitor as an erection-enhancing agent and clomipramine as an ejaculation-delaying agent, for the preparation of a medicament for treating erectile dysfunction.

According to an additional aspect of the present invention there is provided a method of treating sexual dysfunction, the method comprising substantially simultaneously co-administering to a subject in need thereof a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, such that an efficacy window of the an erection-enhancing agent and an efficacy window of the ejaculation-delaying agent substantially overlap.

According to still an additional aspect of the present invention there is provided a method of treating sexual dysfunction, the method comprising substantially simultaneously co-administering to a subject in need thereof a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, the an erection-enhancing agent and the ejaculation-delaying agent acting in synergy, thereby treating sexual dysfunction.

According to yet an additional aspect of the present invention there is provided a method of treating sexual dysfunction, the method comprising co-administering to a subject in need thereof a pharmaceutically effective amount of a phosphodiesterase type 5 inhibitor as an erection-enhancing agent and a pharmaceutically effective amount of clomipramine as an ejaculation-delaying agent.

Preferably, the co-administering is performed substantially simultaneously.

According to a further aspect of the present invention there is provided a use of an erection-enhancing agent and an ejaculation-delaying agent, wherein an efficacy window of the erection-enhancing agent and an efficacy window of the ejaculation-delaying agent substantially overlap, for the preparation of a medicament for treating sexual dysfunction.

According to still a further aspect of the present invention there is provided a use of an erection-enhancing agent and an ejaculation-delaying agent, wherein the erection-enhancing agent and the ejaculation-delaying agent acting in synergy, for the preparation of a medicament for treating sexual dysfunction.

According to yet a further aspect of the present invention there is provided a use of a phosphodiesterase type 5 inhibitor as an erection-enhancing agent and clomipramine as an ejaculation-delaying agent, for the preparation of a medicament for treating sexual dysfunction.

According to an additional aspect of the present invention there is provided a method of treating ejaculatory dysfunction caused by treatment with an agent for the treatment of erectile dysfunction, the method comprising substantially simultaneously co-administering to a subject in need thereof a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, such that an efficacy window of the an erection-enhancing agent and an efficacy window of the ejaculation-delaying agent substantially overlap.

According to still an additional aspect of the present invention there is provided a use of an erection-enhancing agent and an ejaculation-delaying agent, wherein an efficacy window of the erection-enhancing agent and an efficacy window of the ejaculation-delaying agent substantially overlap, for the preparation of a medicament for treating ejaculatory dysfunction caused by treatment with an agent for the treatment of erectile dysfunction.

According to further features in preferred embodiments of the invention described below, the erectile dysfunction is caused by treatment with an ejaculation-delaying agent.

According to still further features in the described preferred embodiments the pharmaceutically effective amount of the erection-enhancing agent equals to or is lower than 20 mg per dosage unit.

According to still further features in the described preferred embodiments the pharmaceutically effective amount of the ejaculation-delaying agent is lower than 50 mg per dosage unit.

According to still further features in the described preferred embodiments at least the erection-enhancing agent is provided in a delayed release form.

According to still further features in the described preferred embodiments a release of the erection-enhancing agent is delayed by from about 2 to about 3 hours relative to a release of the erection-delaying agent.

According to still further features in the described preferred embodiments the ejaculation-delaying agent is clomipramine.

According to still further features in the described preferred embodiments the erection-enhancing agent is a phosphodiesterase type 5 inhibitor.

According to still further features in the described preferred embodiments the phosphodiesterase type 5 inhibitor is selected from the group consisting of tadalafil, vardenafil and sildenafil.

According to still further features in the described preferred embodiments the ejaculation-delaying agent is clomipramine.

According to still further features in the described preferred embodiments the clomipramine and the erection-enhancing agent are each provided as a pharmaceutical dosage unit.

According to still further features in the described preferred embodiments an amount of the clomipramine ranges from about 15 mg to about 30 mg per dosage unit.

According to still further features in the described preferred embodiments the erection-enhancing agent comprises tadalafil.

According to still further features in the described preferred embodiments an amount of the tadalafil ranges from about 10 mg to about 20 mg per dosage unit.

According to still further features in the described preferred embodiments an amount of the tadalafil ranges is about 10 mg per dosage unit.

According to still further features in the described preferred embodiments the erection-enhancing agent comprises vardenafil.

According to still further features in the described preferred embodiments an amount of the vardenafil ranges from about 10 mg to about 20 mg per dosage unit.

According to still further features in the described preferred embodiments an amount of the vardenafil ranges is about 10 mg per dosage unit.

According to still further features in the described preferred embodiments the erection-enhancing agent comprises sildenafil.

According to still further features in the described preferred embodiments an amount of the sildenafil is about 25 mg per dosage unit.

According to still further features in the described preferred embodiments a release of the tadalafil is delayed by about 2 hours relative to a release of the clomipramine.

According to still further features in the described preferred embodiments a release of the vardenafil is delayed by about 3 hours relative to a release of the clomipramine.

According to still further features in the described preferred embodiments a release of the sildenafil is delayed by about 3 hours relative to a release of the clomipramine.

According to still further features in the described preferred embodiments the administering is effected orally.

According to still further features in the described preferred embodiments the dysfunction is due to drug use.

According to still further features in the described preferred embodiments the drug is selected from the group consisting of alcohol, nicotine, a narcotic, a stimulant, an antihypertensive, an antihistamine, and a psychotherapeutic agent.

According to still further features in the described preferred embodiments the dysfunction is due to a medical condition.

According to still further features in the described preferred embodiments the medical condition is selected from the group consisting of a back injury, an enlarged prostate gland, a circulatory problem, nerve damage, diabetic neuropathy, multiple

sclerosis, a tumor, heart failure, lung failure, an endocrine disorder, a hormone deficiency and a birth defect.

According to still further features in the described preferred embodiments a maximal efficacy window of the erection-enhancing agent and a maximal efficacy window of the ejaculation-delaying agent overlap for at least 20 minutes.

According to still further features in the described preferred embodiments a plasma peak concentration of the erection-enhancing agent and a plasma peak concentration of the ejaculation-delaying agent occur substantially simultaneously.

According to still further features in the described preferred embodiments the erection-enhancing agent and the ejaculation-delaying agent are provided as a single dosage unit.

According to still further features in the described preferred embodiments the erection-enhancing agent and the ejaculation-delaying agent are provided as separate dosage units.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

As used herein, the term "comprising" means that other steps and ingredients that do not affect the final result can be added. This term encompasses the terms "consisting of" and "consisting essentially of".

The phrase "consisting essentially of" means that the composition or method may include additional ingredients and/or steps, but only if the additional ingredients and/or steps do not materially alter the basic and novel characteristics of the claimed composition or method.

As used herein, the singular form "a," "an," and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

As used herein the term "about" refers to ± 10 %.

Throughout this disclosure, various aspects of this invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

The phrase "therapeutically effective amount", also referred to herein interchangeably as "pharmaceutically effective amount" refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the condition being treated.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIG. 1 presents background art results showing the intravaginal latency times in patients treated with placebo or various antidepressants administered before sexual activity (upper part) and upon daily dosing (lower part) [15, 16]. Each point represents the intravaginal latency time for drug or placebo in a single arm of a randomized trial.

FIGs. 2a-b are bar graphs presenting the effect of a combined therapy of clomipramine and a PDE5 inhibitor, according to preferred embodiments of the present invention, on premature ejaculation (Figure 2a) and on erection dysfunction (Figure 2b).

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of novel compositions and methods which utilize an erection-enhancing agent and an ejaculation-delaying agent, such that the efficacy windows of these agents substantially overlap and/or which act in synergy, and hence can be beneficially used for treating sexual dysfunction and/or for enhancing sexual function.

The principles and operation of the compositions and methods according to the present invention may be better understood with reference to the accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Although the prior art teaches agents for enhancement of erection and agents for delaying ejaculation, it does not teach or suggest a pharmaceutical composition comprising an erection-enhancing agent and an ejaculation-delaying agent or co-administration of an erection-enhancing agent and an ejaculation-delaying agent, in order to increase sexual satisfaction or treat erectile dysfunction. More specifically, the prior art fails to teach or suggest co-formulation and/or co-administration of an erection-enhancing agent and an ejaculation-delaying agent that would act so as to

simultaneously exert an erection-enhancing affect and an ejaculation-delaying effect during a sexual intercourse.

Known methods of co-administration require administration of the individual medications at separate times, which is highly inconvenient for the patient, thereby reducing patient compliance. The prior art does not teach or suggest a method of substantially simultaneous co-administration of such agents. The prior art further fails to teach or suggest a combined therapy of an erection-enhancing agent and an ejaculation-delaying agent which act in synergy, particularly with regard to erection enhancement.

The present invention overcomes the deficiencies of the prior art by providing novel formulations which enable co-administration of an erection-enhancing agent and an ejaculation-delaying agent such that an erection-enhancement effect and an ejaculation-delay effect are exhibited simultaneously and/or synergistically.

Such formulations may comprise either a unitary dosage form, comprising an erection-enhancing agent and an ejaculation-delaying agent, or at least two individual dosage forms, each comprising one of an erection-enhancing agent and an ejaculation-delaying agent.

As is demonstrated in the Examples section that follows, it has been found that a combined therapy of clomipramine as an exemplary ejaculation-delaying agent and a phosphodiesterase type 5 inhibitor as an exemplary erection-enhancing agent may be utilized for simultaneously treating erectile dysfunction and premature ejaculation, whereby such a combined therapy further provides for a synergistic effect of these two agents, particularly with regard to erection enhancement.

Thus, according to one aspect of the present invention, there are provided novel pharmaceutical compositions, each comprising an erection-enhancing agent and an ejaculation-delaying agent.

The pharmaceutical compositions disclosed herein are particularly beneficial for enhancing sexual function and/or treating sexual dysfunction, as is detailed herein.

As used herein, the phrase "sexual function" refers to any one or combination of features involved in various stages of the sexual act and encompasses, for example, sexual desire, erection, ejaculation, ejaculatory latency time, and/or orgasm.

As used herein the term "sexual dysfunction" refers to difficulty during any stage of the sexual act that prevents an individual from enjoying sexual activity.

"Sexual dysfunction" encompasses decreased sexual desire, the inability to have or sustain a penile erection (erectile dysfunction), the inability to ejaculate, ejaculatory latency time (premature ejaculation) and/or the inability to experience orgasm.

As used herein, an "erectile dysfunction" refers to the inability of a male mammal to achieve and maintain penile erection for satisfactory sexual intercourse.

The phrase "premature ejaculation" as used herein intends a sexual dysfunction wherein a male experiences persistent or recurrent ejaculation with minimal sexual stimulation before, upon, or shortly after penetration.

The pharmaceutical composition includes a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent (also referred to herein collectively as "active ingredients" or "active agents").

As used herein the phrase "erection-enhancing agent" refers to an agent which potentiates and/or prolongs genital blood flow, as is further detailed hereinbelow.

As used herein, the phrase "ejaculation-delaying agent" refers to an agent which extends the latency period between induction of erection and occurrence of ejaculation.

As used herein, the phrase "pharmaceutical composition" refers to either a single packaged pharmaceutical dose unit (further referred to herein as a "unitary dosage form") that includes both active ingredients or two separate units (e.g. two dosage forms) each including a single active ingredient and both preferably further packaged into a single delivery device (e.g. capsule).

In one embodiment, the pharmaceutical composition described herein are designed such that the efficacy window of the erection-enhancing agent and the efficacy window of the ejaculation-delaying agent substantially overlap.

As used herein, the phrase "efficacy window" describes a time frame during which an active agent exhibits a desired pharmacological effect, herein an erection-enhancing effect or an ejaculation-delaying effect, upon administration. In other words, this phrase describes that time period at which the plasma concentration of an active agent is equal to or higher than a minimal pharmacologically effective concentration thereof.

As is well known in the art, an efficacy window of an agent depends on various factors such as systemic absorbance rate, the time required to reach a plasma peak concentration and/or clearance rate.

As described hereinabove, commonly used erection-enhancing agents and ejaculation-delaying agents display different efficacy windows. As is further discussed hereinabove, it is often desirable to treat subjects suffering from sexual dysfunction with both an erection-enhancing agent and an ejaculation-delaying agent. It is further often desirable to treat subject suffering from erectile dysfunction with both an erection-enhancing agent and an ejaculation-delaying agent. It is further often desirable to treat subject suffering from premature ejaculation with both an erection-enhancing agent and an ejaculation-delaying agent.

Such a combined treatment is desirable since it enables a men subject to experience both satisfactory penile erection and satisfactory intravaginal latency period prior to ejaculation, within the same sexual event. However, this desired outcome can only be achieved if both agents exhibit their effect within the same time frame.

Thus, the pharmaceutical compositions presented herein are designed such that a window efficacy of the erection-enhancing agent and a window efficacy of the ejaculation-delaying agent substantially overlap.

As used in the context of this and other aspects of the present invention, the phrase "substantially overlap" with respect to the efficacy windows of the active agents means that during a certain time period upon administration of the composition described herein, both the erection-enhancing agent and the ejaculation-delaying agent exhibit a desired pharmacological effect to some extent, namely, a plasma concentration of each agent is equal to or is higher than a minimum pharmacologically effective concentration of the agent. The efficacy windows of the active agents can overlap for, for example, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 1 hour, 2 hours, 3 hours and even for longer time periods. The efficacy windows of the active agents can overlap such that during the overlapping period, both agents exhibit a maximal efficacy, such that one agent exhibits a maximal efficacy while the other agent exhibits a partial efficacy or such that both agents exhibit a partial efficacy.

Preferably, the efficacy windows of the active agents overlap for at least 20 minutes, so as to allow a subject to experience the overlapping pharmacological effects of both active agents during the sexual event.

Further preferably, the composition describes herein is designed such that it provides at least 20 minutes of overlapping maximal efficacy of the two active ingredients. Thus, preferably, the composition described herein is such that a maximal efficacy window of the erection-enhancing agent and the maximal efficacy window of the ejaculation-delaying agent overlap for at least 20 minutes.

As used herein, the phrase "maximal efficacy window" describes that time frame upon administration of the active agent during which the agent exhibits a maximal efficacy.

A maximal efficacy is typically related to the plasma peak concentration of an active agent.

Thus, further preferably, the composition of the present invention is designed such that a plasma peak concentration of each of the active ingredients occurs substantially simultaneously, namely, within the same time period upon administration.

One approach for achieving the above is to attenuate the release of erection-enhancing agent with respect to the release of the ejaculation-delaying agent. In order to achieve such staggered release, both the erection-enhancing agent and the ejaculation-delaying agent may be in a delayed release form of varying release profile, or the ejaculation-delaying agent may be in immediate release form and only the erection-enhancing agent in a delayed release form. In any case, release of the erection-enhancing agent is preferably delayed by from about 2 to about 3 hours relative to release of the ejaculation-delaying agent. Preferably, each of the erection-enhancing agent and the ejaculation-delaying agent are delivered as individual pulses, at spaced-apart time intervals. Hence, for example, release of the ejaculation-delaying agent may be substantially immediate, i.e. occurring within 1-2 hours of ingestion. This initial release may be followed by a time interval of between 2 and 3 hours during which substantially no drug is released from the dosage form, after which the erection-enhancing agent is then released.

The composition of the present invention may be administered according to any suitable dosage regime. For example, the composition may be administered on a daily basis, or only as required, on an "as needed" basis.

The composition of the present invention may be provided in any form known to the art.

Thus, the composition can be formulated as a unitary dose, i.e., a single packaged dose which includes both active ingredients, or it can be formulated as two separate dose units each separately packaged, although preferably such formulation is further packaged into a single delivery device (e.g. capsule), since one object of the present invention is to facilitate simultaneous co-administration of the two active ingredients.

The latter formulation is exemplified by capsules housing tablets or drug-containing beads or particles, a first portion of which comprise the erection-enhancing agent as active ingredient, and a second portion of which comprise the ejaculation-delaying agent as active ingredient, wherein each portion provides a different drug release profile. The capsule material may be either hard or soft, and as will be appreciated by those skilled in the art of pharmaceutical science, typically comprises a tasteless, easily administered and water soluble compound such as gelatin, starch or cellulose. A preferred capsule material is gelatin. The capsules are preferably sealed, such as with gelatin bands or the like.

A unitary dosage form may comprise a single tablet with the first and second dosage units each representing an integral and discrete layer thereof. For example, drug-containing particles or drug-containing beads can be compressed together into a single tablet using conventional tabletting means.

Delayed release, whether with regard to a composition comprising a unitary dosage form, or to methods involving administration of individual dosage forms, may be achieved by any method known in the art. As will be appreciated by those skilled in the art, a number of methods are available for preparing drug-containing tablets or other dosage units which provide a variety of drug release profiles. Such methods include coating a drug or drug-containing composition, increasing the drug's particle size, placing the drug within a matrix, and forming complexes of the drug with a suitable complexing agent. Delayed release may be provided, for example, by coating

a drug or a drug-containing composition with a selected membrane coating material, typically although not necessarily a polymeric material.

To bring about the desired pulsatile release profile for a dosage form comprised of encapsulated portions of tablets, beads, or particles, the portions comprising the ejaculation-delaying agent are provided with little or no coating material, and those comprising the erection-enhancing agent are provided with some degree of coating material. Thus, for example, a first tablet, which releases drug substantially immediately, may have a total coating weight of less than about 10 %, and the second tablet may have a total coating weight in the range of approximately 10 % to 30 %. The preferred coating weights for particular coating materials may be readily determined by those skilled in the art by evaluating individual release profiles for dosage units prepared with different quantities of various coating materials.

When a coating is used to provide delayed release dosage units, particularly preferred coating materials comprise bioerodible, gradually hydrolyzable and/or gradually water-soluble polymers. The "coating weight," or relative amount of coating material per dosage unit, generally dictates the time interval between ingestion and drug release. Suitable membrane coating materials for effecting delayed release include, but are not limited to: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethyl cellulose phthalate, cellulose ester-ether phthalate, hydroxypropylcellulose phthalate, alkali salts of cellulose acetate phthalate, alkaline earth salts of cellulose acetate phthalate, hydroxypropylmethyl cellulose hexahydrophthalate, cellulose acetate hexahydrophthalate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, vinyl polymers and copolymers such as polyvinyl pyrrolidone, polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate.

Conventional coating procedures and equipment may be used to coat the dosage units, i.e., the drug-containing tablets, beads or particles. For example, a delayed release coating composition may be applied using a coating pan, an airless spray technique, fluidized bed coating equipment, or the like.

Alternatively, the delayed release dosage units, e.g, tablets or particles, may be formulated by dispersing the drug within a matrix of a suitable material such as an insoluble plastic, a hydrophilic polymer, or a fatty compound. The insoluble plastic matrices may be comprised of, for example, polyvinyl chloride or polyethylene. Hydrophilic polymers useful for providing a matrix for a delayed release dosage unit include, but are not limited to, those described above as suitable coating materials. Fatty compounds for use as a matrix material include, but are not limited to, waxes generally (e.g., carnauba wax) and glyceryl tristearate. Once the active ingredient is mixed with the matrix material, the mixture can be compressed into tablets or processed into individual drug-containing particles.

Further examples of compositions in which the erection-enhancing agent is delayed with respect to the ejaculation-delaying agent include a formulation in which the ejaculation-delaying agent is provided in an outer, immediate release layer, which is released as a first pulse, while the erection-enhancing agent is contained within a core which is separated from the outer layer by a film layer of an enteric coating. The enteric coating slowly dissolves after the delivery of the first pulse of drug allowing the release of the second pulse.

Pharmaceutical compositions suitable for use in context of the present invention include compositions wherein the active ingredients are contained in an amount effective to achieve the intended purpose. More specifically, a therapeutically effective amount or a pharmaceutically effective amount means an amount of an agent effective to prevent, alleviate or ameliorate symptoms of a condition.

Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any agent used in the various aspects of the present invention, the therapeutically effective amount or dose can be estimated initially from activity assays in animals (e.g., humans). For example, a dose can be formulated to achieve a circulating concentration range that includes the IC_{50} as determined by activity assays

(e.g., the concentration of the agent, which achieves a half-maximal erection enhancement efficacy or ejaculation delaying efficacy). Such information can be used to more accurately determine useful doses and regiments.

Toxicity and therapeutic efficacy of the active agents described herein can be determined by standard pharmaceutical procedures in experimental subjects

The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

Dosage amount and interval may be adjusted individually to provide plasma levels of the active agents which are sufficient to maintain the desired effects, termed the minimal effective concentration (MEC). Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using the MEC value. Preparations should be administered using a regimen, which maintains plasma levels above the MEC for 10-90 % of the time, preferable between 30-90 % and most preferably 50-90 %.

The amount of a composition to be administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

In another embodiment of the present invention, the pharmaceutical compositions described herein are such that the erection-enhancing agent and the ejaculation-delaying agent act in synergy.

As is demonstrated in the Examples section that follows, it was surprisingly found that a combined therapy that utilizes an erection-enhancing agent and an ejaculation-delaying agent results in a synergistic effect, which allows to use relatively low doses of these agents, while achieving a treatment success rate higher than that obtained when each of these agents is utilized alone.

The synergistic activity of these agents has been particularly demonstrated with regard to erection enhancement. Thus, while utilizing relatively low doses of an erection-enhancing agent, in combination with an ejaculation-delaying agent, a significant improvement in erection of patients suffering from erectile dysfunction

was observed. The synergistic effect of the combined treatment taught herein is particularly demonstrated when comparing the success rate of this combined treatment with the success rate of an erection-enhancing agent when utilized alone. Thus, as is detailed in the Examples section that follows, the success rate reported upon treatment with a relatively low-dose dosage regime of an exemplary erection-enhancing agent in patients having mild, moderate or severe erectile dysfunction was significantly improved when patients similarly diagnosed by mild, moderate or severe erectile dysfunction received similar treatment regime of an erection-enhancing agent, in combination with an ejaculation-delaying agent.

As used herein, the phrase "mild erectile dysfunction" describes a subjectively rated erection that ranges from about 60 % to about 90 % of the subject's normal (100 %) erection.

As used herein, the phrase "moderate erectile dysfunction" describes a subjectively rated erection that ranges from about 30 % to about 60 % of the subject's normal (100 %) erection.

As used herein, the phrase "severe erectile dysfunction" describes a subjectively rated erection that ranges from about 0 % to about 30 % of the subject's normal (100 %) erection.

Hence, according to preferred embodiments of the present invention, a pharmaceutically effective amount of an erection-enhancing agent equals to or is lower than 25 mg per unit dosage. A pharmaceutically effective amount of an ejaculation-delaying agent is preferably lower than 50 mg per unit dosage.

Ejaculation-delaying agents suitable for use in the context of the present invention are preferably psychoactive drugs, more preferably antidepressants. Non-limiting examples of suitable antidepressants include a selective serotonin reuptake inhibitor (such as citalopram, escitalopram oxalate, fluoxetine, fluvoxamine, paroxetine, and sertraline); a tricyclic antidepressant (such as amitryptiline, amoxapin, carbamezipin, clomipramine, desipramine, doxepin, imipramine, nortryptiline, protryptiline, mirtazepine and trimipramine); a monoamine oxidase inhibitor (such as deprenyl, isocarboxazid, moclobemide, phenelzine and tranylcypromine); and a serotonin and noradrenaline uptake inhibitor (such as duloxetine, milnacipran and venlafaxine), or a combination thereof. Preferably, the ejaculation-delaying agent is a tricyclic antidepressant.

According to the presently most preferred embodiments of the present invention, the ejaculation-delaying agent is clomipramine.

Further according to preferred embodiments of the present invention, the erection-enhancing agent is a phosphodiesterase type 5 inhibitor, more preferably at least one of tadalafil, vardenafil and sildenafil.

Thus, preferred pharmaceutical compositions according to the present embodiments comprise clomipramine and at least one of tadalafil, vardenafil and sildenafil.

Alternatively, the erection-enhancing agent may be a natural product, such as arginine or human DNA.

Each of the active agents described herein can be utilized either as is or as a pharmaceutically acceptable salt, a solvate, or a hydrate thereof.

The phrase "pharmaceutically acceptable salt" refers to a charged species of the parent compound and its counter ion, which is typically used to modify the solubility characteristics of the parent compound and/or to reduce any significant irritation to an organism by the parent compound, while not abrogating the pharmacological activity and properties of the administered compound.

The term "solvate" refers to a complex of variable stoichiometry (e.g., di-, tri-, tetra-, penta-, hexa-, and so on), which is formed by a solute (the hybrid compound) and a solvent, whereby the solvent does not interfere with the biological activity of the solute. Suitable solvents include, for example, ethanol, acetic acid and the like.

The term "hydrate" refers to a solvate, as defined hereinabove, where the solvent is water.

The present invention further encompasses various crystalline forms (polymorphs) of the active agents described herein.

In cases where the active agent comprises one or more asymmetric centers, it can be utilized either as a purified stereoisomer or as a racemic mixture.

Derivatives and analogs of the active agents described herein are also encompassed by the present invention.

The term "derivative" describes a compound which has been subjected to a chemical modification while maintaining its main structural features. Such chemical modifications can include, for example, replacement of one or more substituents and/or one or more functional moieties, oxidation, reduction, and the like.

The term "analog" describes a compound that has structural features that are similar to that of the active agent and hence exhibits the same pharmacological activity.

Further preferably, each of the active agents described herein is provided as a pharmaceutical dosage unit, either a single unit or two units, as detailed herein.

Thus, preferably, the pharmaceutical composition comprises a pharmaceutical dosage unit of clomipramine. Preferably, the amount of the clomipramine ranges from about 15 mg to about 50 mg per dosage unit, most preferably from about 15 mg to about 30 mg per dosage unit.

Further preferably, the pharmaceutical composition comprises a pharmaceutical dosage unit of a PDE5 inhibitor as described herein. Preferably, the amount of tadalafil and vardenafil ranges from about 10 mg to about 20 mg per dosage unit and more preferably is about 10 mg; and the amount of sildenafil is about 25 mg per dosage unit.

The time required for clomipramine to reach peak plasma concentration is known to be about 2 hours longer than that required by tadalafil, and 3 hours longer than that required by either vardenafil or sildenafil. Therefore, in order to achieve overlapping efficacy windows of clomipramine and tadalafil, either as a unitary dosage form, or in separate dosage forms, release of tadalafil is preferably delayed by about 2 hours relative to release of clomipramine. In order to achieve overlapping efficacy windows of clomipramine and vardenafil or sildenafil, either as a unitary dosage form, or in separate dosage forms, and release of vardenafil or sildenafil is preferably delayed by about 3 hours relative to release of clomipramine.

The pharmaceutical composition preferably comprises, in addition to the erection-enhancing agent and the ejaculation-delaying agent, a pharmaceutically acceptable carrier, and may optionally further comprise one or more components selected from binding agents, stabilizers, diluents, excipients, surfactants, flavors, and odorants.

Herein, the phrase "pharmaceutically acceptable carrier" refers to a carrier or a diluent that does not cause significant irritation to a subject and does not abrogate the pharmacological activity and properties of the administered compounds.

Herein the term "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound.

Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

Suitable routes of administration may, for example, include oral, rectal, transmucosal, transdermal, intestinal or parenteral delivery, including intramuscular, subcutaneous and intramedullary injections as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. Preferably, the compositions are formulated for oral administration.

Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For oral administration, the active ingredients can be formulated readily by combining the active ingredients with pharmaceutically acceptable carriers well known in the art. Such carriers enable the active ingredients of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain tablets or dragee cores.

Suitable excipients include, without limitation, fillers or diluents, disintegrating agents, lubricants, surfactants, and preservatives.

Non-limiting examples of fillers or diluents include dicalcium phosphate dihydrate; calcium sulfate; kaolin; silicon dioxide, titanium oxide; alumina; talc; sugars, including lactose, lactose monohydrate, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, microcrystalline cellulose, sodium carbomethylcellulose; and/or

physiologically acceptable polymers such as polyvinylpyrrolidone (PVP) or croscarmellose sodium.

Suitable disintegrating agents include, without limitation, cross-linked polyvinyl pyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate, or sodium starch glycolate

.Non-limiting examples of lubricants include magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, polyethylene glycol, and mixtures thereof;

Examples of surfactants include, but are not limited to, long alkyl chain sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylhexyl)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate.

Suitable preservatives include but are not limited to C12 to C15 alkyl benzoates, alkyl p-hydroxybenzoates, aloe vera extract, ascorbic acid, benzalkonium chloride, benzoic acid, benzoic acid esters of C9 to C15 alcohols, butylated hydroxytoluene, castor oil, cetyl alcohols, chlorocresol, citric acid, cocoa butter, coconut oil, diazolidinyl urea, diisopropyl adipate, dimethyl polysiloxane, DMDM hydantoin, ethanol, fatty acids, fatty alcohols, hexadecyl alcohol, hydroxybenzoate esters, iodopropynyl butylcarbamate, isononyl iso-nonanoate, jojoba oil, lanolin oil, methylparaben, propylparaben, mineral oil, oleic acid, olive oil, polyethers, polyoxypropylene butyl ether, polyoxypropylene cetyl ether, potassium sorbate, silicone oils, sodium propionate, sodium benzoate, sodium bisulfite, sorbic acid, stearic fatty acid, vitamin E, vitamin E acetate and derivatives, esters, salts and mixtures thereof.

The pharmaceutical composition may optionally be provided in any form suitable for oral administration, including, for example, a tablet, a pill, a dragee, a capsule, a liquid, a paste, a pellet, a syrup, a slurry, or a suspension. Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

For example, tablets may be formed by direct compression of a powdered, crystalline or granular drug-containing composition, alone or in combination with diluents, binders, lubricants, disintegrants, colorants or the like. As an alternative to direct compression, compressed tablets can be prepared using wet-granulation or dry-

granulation processes. Tablets may also be molded rather than compressed, starting with a moist material containing a suitable water-soluble lubricant. Drug-containing particles or beads are also prepared using conventional means, typically from a fluid dispersion. Further techniques for composition and administration of active ingredients may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition, which is incorporated herein by reference as if fully set forth herein.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active ingredient doses.

Compositions of the present invention may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising the erection-enhancing agent and the ejaculation-delaying agent of the present invention, formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition, as is detailed herein.

As is mentioned hereinabove, the above described pharmaceutical compositions can be utilized in methods of enhancing sexual satisfaction or treating sexual dysfunction.

Such methods can be used to enhance sexual function of a healthy subject by enhancing erection or delaying the latency time to ejaculation or to treat a subject

suffering from a sexual dysfunction, such as erectile dysfunction or premature ejaculation, or a combination thereof.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

The sexual dysfunction, erectile dysfunction or ejaculatory dysfunction may be due to use of a drug, such as, for example, alcohol, nicotine, a narcotic, a stimulant, an antihypertensive, an antihistamine, and a psychotherapeutic agent. Alternatively, the dysfunction may be due to a medical condition, such as, for example, a back injury, an enlarged prostate gland, a circulatory problem, nerve damage, diabetic neuropathy, multiple sclerosis, a tumor, heart failure, lung failure, an endocrine disorder (such as a thyroid disorder, a pituitary disorder and an adrenal gland disorder), a hormone deficiency (such as low testosterone, low estrogen and low androgen), and a birth defect.

As discussed hereinabove, an association is frequently found between erectile dysfunction and premature ejaculation. For example, the psychological stress of maintaining an erection in a subject suffering from erectile dysfunction may lead to problems with control of ejaculation. Similarly, the stress of controlling ejaculation in a subject suffering from premature ejaculation may lead to inability to achieve erection. Furthermore, an increased incidence of erectile dysfunction has been reported in subjects receiving ejaculation-delaying agents for treatment of premature ejaculation.

The compositions described herein may further be beneficial in the treatment of erectile dysfunction caused by treatment with an ejaculation-delaying agent, and treatment of premature ejaculation caused by treatment with an erection-enhancing agent.

The present invention is therefore further of use of an erection-enhancing agent and an ejaculation-delaying agent, as described herein, for the preparation of medicaments for treating the conditions described herein.

The present invention is therefore further of methods which are effected by co-administration of an erection-enhancing agent and an ejaculation-delaying agent together as a multi-dosage form composition or as part of the same, unitary dosage

form. "Co-administration" also includes administering a delayed release erection-enhancing agent and an ejaculation-delaying agent separately but as part of the same therapeutic treatment program or regimen. The components need not necessarily be administered at essentially the same time, although they can if so desired. Thus "co-administration" includes, for example, administering an erection-enhancing agent and an ejaculation-delaying agent as separate dosages or dosage forms, but at the same time.

Thus, according to further aspects of the present invention there are provided a method of enhancing sexual satisfaction, and a method of treating erectile dysfunction, each being effected by co-administering to a subject a pharmaceutically effective amount of an erection-enhancing agent, as described herein, and a pharmaceutically effective amount of an ejaculation-delaying agent, as described herein.

The methods and uses described herein are effected such that an efficacy window of the erection-enhancing agent and an efficacy window of an ejaculation-delaying agent substantially overlap, as described hereinabove.

Alternatively, or in addition, the methods and uses described herein are effected such that the erection-enhancing agent and the ejaculation-delaying agent act in synergy, as detailed herein.

Hence, the present invention further provides a method of treatment of sexual dysfunction, which is effected by co-administering to a subject a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent. Co-administering these agents is preferably effected substantially simultaneously.

The present invention further provides a method of treating ejaculatory dysfunction caused by treatment with an agent for the treatment of erectile dysfunction, comprising substantially simultaneously co-administering a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent.

As discussed hereinabove, agents for the enhancement of erection and for the delay of ejaculation are known in the art. Such agents may be used for the treatment of erectile dysfunction and for the treatment of premature ejaculation, respectively.

However, since the known agents for enhancement of erection and delay or ejaculation involve drugs which reach maximum plasma concentrations at different times, known methods of co-administration require administration of the individual medications at separate times, which is highly inconvenient for the patient, thereby reducing patient compliance. The prior art does not teach or suggest a method of substantially simultaneous co-administration of such agents.

The methods of the present invention overcome the disadvantages of the prior art by utilizing an erection-enhancing agent and an ejaculation-delaying agent, such that the efficacy windows of these agents substantially overlap. This can be achieved, for example, by using formulations in which the release of the erection-enhancing agent is delayed relative to the release of the ejaculation-delaying agent, such that both agents reach a plasma peak concentration substantially simultaneously, providing at least 20 minutes of overlapping maximal efficacy.

The method of the present invention are further advantageously superior to the presently known methods, by utilizing lower unit dosages of the active agents, based on the synergistic effect exhibited by these agents.

Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions, illustrate the invention in a non limiting fashion.

EXAMPLE 1

The purpose of the study was to investigate the effects of co-administration of Clomipramine and various PDE5 inhibitors on patients suffering from both premature ejaculation and erectile disfunction.

Patients suffering from ejaculation time equal to or lower than 2 minutes and/or unsatisfactory erectile dysfunction, subjectively rated on a scale of 100%, were selected for retrospective analysis.

Patients were diagnosed during a meeting and received a combination therapy of a commercial PDE5 inhibitor and clomipramine, taken on an "as need" basis. After 8 weeks, the patients' performance was rated.

Patients suffering from both erectile dysfunction and premature ejaculation were treated either with low-dose commercially available dosage units of clomipramine (25 mg per dosage unit) or with unique low doses of clomipramine (15 and 30 mg per dosage) and with low-dose commercially available dosage units of a commercial PDE5 inhibitor (10 mg of tadalafil or vardenafil; 25 mg of sildenafil).

The results are presented in Table 1 below and in Figures 2a and 2b and clearly show the potent effect of a combination therapy of clomipramine and a PDE5 inhibitor in simultaneously treating both premature ejaculation and erectile dysfunction.

In addition, the obtained results clearly indicate that although relatively low doses of both clomipramine and the PDE5 inhibitor were prescribed and used in most of the patients, a significant erection enhancement (e.g., from less than 50 % to 100 %) was recorded in more than 90 % of the participants.

Thus, for example, 100% of patients suffering from mild erectile dysfunction (e.g., 60 % to 90 % subjectively rated erection and treated with 10 mg of tadalafil or vardenafil in combination with clomipramine reported 100 % erection at the end of the study (after 8 weeks). Over 83% of patients suffering from moderate erectile dysfunction (e.g., 30 % to 60 % subjectively rated erection) and treated with 10 mg of tadalafil or vardenafil in combination with clomipramine reported 100 % erection at the end of the study (after 8 weeks). Over 88% of patients suffering from severe erectile dysfunction (e.g., 0 % to 30 % subjectively rated erection) and treated with 10 mg of tadalafil or vardenafil in combination with clomipramine reported 100 % erection at the end of the study (after 8 weeks).

Such a high rate of success in erectile dysfunction therapy has never been observed hitherto with such low doses of commercially available PDE5 inhibitors, when used alone. Thus, for example, the highest success rate reported for erectile dysfunction monotherapy with a 10 mg dosage unit of tadalafil, measured as percents

of subjects attaining normal erectile function at study end point, is 51.8 % for mild ED, 41 % for moderate ED and 25 % for severe ED (see, [18-21]).

The obtained results therefore demonstrate a synergistic effect of the combined therapy utilized herein on erectile dysfunction. Such a synergistic effect allows a treatment regimen that utilizes significantly lower doses of at least the PDE5 inhibitor and optionally of both clomipramine and the PDE5 inhibitor, while achieving a high rate of treatment success. Evidently, such a treatment regime is highly advantageous as it reduces the risk of adverse side effects associated with clomipramine and/or PDE5 inhibitors treatment. In Table 1 below, "NC" denotes no complain; PE denotes premature ejaculation; ED denotes erectile dysfunction; x denotes positive diagnosis; and 0 denotes negative diagnosis.

The statistical analysis of the results presented in Figures 1a and 1b is presented in Tables 2 and 3 below, respectively.

Table 2

Column1 *Ejaculation time before treatment*		*Column2* *Ejaculation time after treatment*	
Mean	1.031034483	Mean	9.698275862
Standard Error	0.102412133	Standard Error	0.776813458
Standard Deviation	0.779947568	Standard Deviation	5.916035045
Count	58	Count	58
Confidence Level (95.0%)	0.205076757	Confidence Level (95.0%)	1.555542107

Table 3

Column1 *Erection satisfaction before treatment*		*Column2* *Erection satisfaction after treatment*	
Mean	38.87931034	Mean	96.03448276
Standard Error	4.599907781	Standard Error	1.43290463
Standard Deviation	35.03185397	Standard Deviation	10.91267655
Count	58	Count	58
Confidence Level (95.0%)	9.211156377	Confidence Level (95.0%)	2.869342006

Table 1

Patient ID	Ejaculation Time (minutes)		Erection (% satisfaction)		Treatment				Diagnosis		AGE (years)
	before treatment	after treatment	before (%)	after (%)	Viagra® (mg)	Levitra® (mg)	Cialis® (mg)	Clomipramine (mg)	PE	ED	
5	2	10	NC	NC		0	0	30	x	0	35
8	1	20	NC	NC		0	0	15	x	0	29
11	0.5	15	NC	NC		0	0	25	x	0	29
15	0.5	10	NC	NC		0	0	30	x	0	31
38	2	10	NC	NC		0	0	30	x	0	36
40	0.5	5	60	100		0	10	30	x	0	43
65	3	15	NC	NC		0	0	30	x	0	41
80	0	8	NC	NC		0	0	30	x	0	25
94	0.15	10	90	100		0	0	10	x	0	44
114	0.5	10	100	100		0	0	15	x	0	53
143	0	7	NC	NC		0	0	25	x	0	24
166	0.1	4		NC		0	0	30	x	0	62

	before treatment	after treatment	before (%)	after (%)	Viagra® (mg)	Levitra® (mg)	Cialis® (mg)	Clomipramine (mg)	PE	ED	
186	2	5	NC	NC		0	0	30	x	0	28
199	4	20	NC	NC		0	0	25	x	0	25
226	0.5	20	NC	NC		0	0	30	x	0	39
272	0.5	15	NC	NC		0	0	30	x	0	31
316	0	0.25				0	0	30	x	0	32
431	0.5	3				0	0	30	x	0	27
459	0.15	4				0	0	30	x	0	29
462	0.5	20				0	0	25	x	0	20
24	2	10	20	100		10	0	30	x	x	29
26	0.15	6	0	80		10	0	30	x	x	63
35	0.1	8	0	50		0	10	30	x	x	65
41	0.5	3	20	80		0	20	30	x	x	43
53	2	10	50	100		0	10	30	x	x	36
54	0.05	10	50	100		0	10	30	x	x	29

	before treatment	after treatment	before (%)	after (%)	Viagra® (mg)	Levitra® (mg)	Cialis® (mg)	Clomipramine (mg)	PE	ED	
55	0	10	50	100		0	10	30	x	x	30
63	0.15	8	0	100		0	20	30	x	x	59
72	1	4	0	100		10	0	30	x	x	49
77	2	10	70	100		0	20	30	x	x	65
89	0.5	4	80	100		0	20	30	x	x	57
90	0	4	0	60		20	0	30	x	x	50
95	0.1	20	0	100		0	20	30	x	x	48
97	0.15	5	50	100		0	20	30	x	x	38
99	0.3	15	0	100		0	10(5)	30	x	x	20
108	1	4	100	100		0	0	15	x	x	58
109	2	7	0	100		0	20	15	x	x	37
111	3	7	70	100		0	10	30	x	x	50
124	0.25	8	75	100		0	10	30	x	x	38
169	2	7	90	100		0	0	25	x	x	65

	before treatment	after treatment	before (%)	after (%)	Viagra® (mg)	Levitra® (mg)	Cialis® (mg)	Clomipramine (mg)	PE	ED	
178	0.5	4	80	100		0	10	30	x	x	55
184	1	8	80	100		0	10	25	x	x	21
187	0.05	3	50	80		0	10	30	x	x	53
228	2	7	80	100		0	10	30	x	x	32
263	2	2	0	60		0	20	25	x	x	67
270	2	15	70	100		0	10	30	x	x	24
286	0.5	10	0	100		0	10	30	x	x	34
292	1	20	80	100		0	10	30	x	x	30
295	2	15	0	100		0	10	15	x	x	54
309	1	8	0	100		0	10	30	x	x	29
313	2	10	50	100		0	10	30	x	x	40
315	2	12	0	100		0	10	30	x	x	29
320	1	6	0	100		0	10	25	x	x	31
327	0.5	3	0	100		0	10	25	x	x	34
	before	after	before	after	Viagra®	Levitra®	Cialis®	Clomipramine	PE	ED	

	treatment	treatment	(%)	(%)	(mg)	(mg)	(mg)	(mg)			
337	1	10	80	100		0	10	30	x	x	47
340	2	30	90	100		0	10	30	x	x	40
344	0.2	20	0	100		0	10	25	x	x	32
417	0.15	7	80	100		0	10	30	x	x	43
438	0.5	4	50	100		0	10	25	x	x	52
452	0	6	40	80		0	10	25	x	x	58
455	1	10	60	100		0	10	30	x	x	37
460	1	2.5	0	100		0	10	30	x	x	42
466	0.5	15	0	100		10	0	30	x	x	29
472	1	10	0	100		0	10	30	x	x	38
476	2	5	0	100		0	10	30	x	x	28
480	1	20	0	100		0	10	30	x	x	43
503	1	15	80	100		0	10	30	x	x	35
510	1	5	50	80		0	20	30	x	x	61
	before treatment	after treatment	before (%)	after (%)	Viagra® (mg)	Levitra® (mg)	Cialis® (mg)	Clomipramine (mg)	PE	ED	

513	2	20	60	100		0	10	30	x	x	60
527	1	5	80	100		10	0	30	x	x	41
538	0.5	5	0	100		0	10	30	x	x	30
539	0.15	20	50	100		0	10	15	x	x	50
540	2	5	50	100	25	0	0	12.5	x	x	26
548	1	10	60	100		0	10	25	x	x	44

EXAMPLE 2

A dosage form for administration of an erection-enhancing agent and an ejaculation-delaying agent

The active ingredients are co-formulating into a single tablet or capsule, upon mixing and/or milling with suitable excipients.

Thus, the components of a tablet for oral administration are clomipramine (15 mg or 30 mg), vardenafil (10 mg), and gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch and titanium dioxide as inactive ingredients.

EXAMPLE 3

A pulsatile release dosage form for administration of an erection-enhancing agent and an ejaculation-delaying agent

The dosage form is prepared by formulation of two individual compressed tablets, each having a different release profile, followed by encapsulating the two tablets into a gelatin capsule and then closing and sealing the capsule. The components of the two tablets are as follows.

Tablet 1: Immediate release formulation comprising clomipramine (30 mg) as active ingredient; gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch and titanium dioxide as inactive ingredients.

Tablet 2: Delayed release formulation comprising tadalafil (10 mg) as active ingredient; lactose monohydrate, croscarmellose sodium, hydroxypropylcellulose, microcrystalline cellulose, sodium lauryl sulfate and magnesium stearate as inactive ingredients.

Tablet 1 is uncoated. Tablet 2 is coated with methacrylic acid copolymer (delayed release coating material), triethyl citrate and talc.

EXAMPLES 4-25

Dosage forms for administration of an erection-enhancing agent and an ejaculation-delaying agent

Additional dosage forms are prepared by co-formulation of the active ingredients into a single dosage form, as described in Example 2 above or by formulation of two individual compressed tablets, each having a different release profile, followed by encapsulating the two tablets into a gelatin capsule and then closing and sealing the capsule, as described in Example 3 hereinabove. The inactive ingredients in each of the two tablets are as described in Examples 2 and 3 hereinabove. The active ingredients in each tablet are presented in Table 4 below.

Table 4

Example	Tablet 1: Ejaculation-delaying agent	Tablet 2: Erection-enhancing agent
4	30 mg clomipramine	20 mg tadalafil
5	15 mg clomipramine	10 mg tadalafil
6	15 mg clomipramine	20 mg tadalafil
7	30 mg clomipramine	10 mg vardenafil
8	30 mg clomipramine	20 mg vardenafil
9	15 mg clomipramine	10 mg vardenafil
10	15 mg clomipramine	20 mg vardenafil
11	30 mg clomipramine	25 mg sildenafil
12	30 mg clomipramine	50 mg sildenafil
13	15 mg clomipramine	25 mg sildenafil
14	15 mg clomipramine	50 mg sildenafil
15	20 mg paroxetine	10 mg tadalafil
16	20 mg paroxetine	10 mg tadalafil
17	10 mg paroxetine	20 mg tadalafil
18	10 mg paroxetine	20 mg tadalafil
19	20 mg paroxetine	10 mg vardenafil
20	20 mg paroxetine	20 mg vardenafil
21	10 mg paroxetine	10 mg vardenafil

22	10 mg paroxetine	20 mg vardenafil
23	20 mg paroxetine	25 mg sildenafil
24	20 mg paroxetine	50 mg sildenafil
25	10 mg paroxetine	25 mg sildenafil
26	10 mg paroxetine	50 mg sildenafil

Table 4 (Cont.)

EXAMPLE 26

The formulation and method described in Examples 2 and 3 hereinabove is repeated, except that drug-containing beads are used in place of tablets. For a pulsatile release formulation a first fraction of beads is prepared by coating an inert support material such as lactose with the erection-enhancing agent which provides the first (immediate release) pulse. A second fraction of beads is prepared by coating immediate release beads with an amount of delayed release coating material sufficient to provide a drug release-free period of 2-3 hours. The two groups of beads may be encapsulated as in Example 2, or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application

shall not be construed as an admission that such reference is available as prior art to the present invention.

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, the composition being such that an efficacy window of said an erection-enhancing agent and an efficacy window of said ejaculation-delaying agent substantially overlap.

2. A pharmaceutical composition comprising a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, the composition being such that said erection-enhancing agent and said ejaculation-delaying agent act in synergy.

3. The pharmaceutical composition of claim 2, wherein said pharmaceutically effective amount of said erection-enhancing agent equals to or is lower than 25 mg per dosage unit.

4. The pharmaceutical composition of claim 3, wherein said pharmaceutically effective amount of said ejaculation-delaying agent is lower than 50 mg per dosage unit.

5. A pharmaceutical composition comprising clomipramine, as an ejaculation-delaying agent, and a PDE5 inhibitor, as an erection enhancing agent.

6. The pharmaceutical composition of any of claims 1-5, being such that a maximal efficacy window of said erection-enhancing agent and a maximal efficacy window of said ejaculation-delaying agent overlap for at least 20 minutes.

7. The pharmaceutical composition of any of claims 1-5, being designed such that a plasma peak concentration of said ejaculation-delaying agent and a plasma peak concentration of said erection-enhancing agent occur substantially simultaneously.

8. The pharmaceutical composition of any of claims 1-5, wherein at least said erection-enhancing agent is provided in a delayed release form.

9. The pharmaceutical composition of any of claims 1 to 4 and 6 to 8, wherein said ejaculation-delaying agent is clomipramine.

10. The pharmaceutical composition of any of claims 1 to 4 and 6 to 9, wherein said erection-enhancing agent is selected from the group consisting of a phosphodiesterase type 5 inhibitor, arginine and human DNA.

11. The pharmaceutical composition of any of claims 5 and 9, wherein said erection-enhancing agent is a phosphodiesterase type 5 inhibitor selected from the group consisting of tadalafil, vardenafil and sildenafil.

12. The pharmaceutical composition of claim 11, being formulated as a pharmaceutical dosage unit.

13. The pharmaceutical composition of claim 12, wherein an amount of said clomipramine ranges from about 15 mg to about 30 mg per dosage unit.

14. The pharmaceutical composition of claim 12, wherein said erection-enhancing agent comprises tadalafil or vardenafil.

15. The pharmaceutical composition of claim 14, wherein an amount of said erection-enhancing agent ranges from about 10 mg to about 20 mg per dosage unit.

16. The pharmaceutical composition of claim 14, wherein an amount of said erection-enhancing agent is about 10 mg.

17. The pharmaceutical composition of claim 12, wherein said erection-enhancing agent comprises sildenafil.

18. The pharmaceutical composition of claim 17, wherein an amount of said sildenafil is about 25 mg per dosage unit.

19. The pharmaceutical composition of any of claims 1-18, being provided in a delivery form suitable for oral administration.

20. A method of enhancing sexual satisfaction, the method comprising co-administering a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, such that an efficacy window of said erection-enhancing agent and an efficacy window of said ejaculation-delaying agent substantially overlap, thereby enhancing sexual dysfunction.

21. A method of enhancing sexual satisfaction, the method comprising co-administering a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, said erection-enhancing agent and said ejaculation-delaying agent acting in synergy, thereby enhancing sexual dysfunction.

22. Use of an erection-enhancing agent and an ejaculation-delaying agent, wherein an efficacy window of said erection-enhancing agent and an efficacy window of said ejaculation-delaying agent substantially overlap, for the preparation of a medicament for enhancing sexual satisfaction.

23. Use of an erection-enhancing agent and an ejaculation-delaying agent, wherein said erection-enhancing agent and said ejaculation-delaying acting in synergy, for the preparation of a medicament for enhancing sexual satisfaction.

24. A method of treating erectile dysfunction, the method comprising co-administering to a subject in need thereof a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, such that an efficacy window of said an erection-enhancing agent and

an efficacy window of said ejaculation-delaying agent substantially overlap, thereby treating erectile dysfunction.

25. A method of treating erectile dysfunction, the method comprising co-administering to a subject in need thereof a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, said erection-enhancing agent and said ejaculation-delaying agent acting in synergy, thereby treating erectile dysfunction.

26. A method of treating erectile dysfunction, the method comprising co-administering to a subject in need thereof a pharmaceutically effective amount of a phosphodiesterase type 5 inhibitor, as an erection-enhancing agent and a pharmaceutically effective amount of clomipramine, as an ejaculation-delaying agent, thereby treating erectile dysfunction.

27. Use of an erection-enhancing agent and an ejaculation-delaying agent, wherein an efficacy window of said erection-enhancing agent and an efficacy window of said ejaculation-delaying agent substantially overlap, for the preparation of a medicament for treating erectile dysfunction.

28. Use of an erection-enhancing agent and an ejaculation-delaying agent, wherein said erection-enhancing agent and said ejaculation-delaying agent act in synergy, for the preparation of a medicament for treating erectile dysfunction.

29. Use of a phosphodiesterase type 5 inhibitor as an erection-enhancing agent and clomipramine as an ejaculation-delaying agent, for the preparation of a medicament for treating erectile dysfunction.

30. A method of treating sexual dysfunction, the method comprising substantially simultaneously co-administering to a subject in need thereof a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, such that an

efficacy window of said an erection-enhancing agent and an efficacy window of said ejaculation-delaying agent substantially overlap.

31. A method of treating sexual dysfunction, the method comprising substantially simultaneously co-administering to a subject in need thereof a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, said an erection-enhancing agent and said ejaculation-delaying agent acting in synergy, thereby treating sexual dysfunction.

32. A method of treating sexual dysfunction, the method comprising co-administering to a subject in need thereof a pharmaceutically effective amount of a phosphodiesterase type 5 inhibitor as an erection-enhancing agent and a pharmaceutically effective amount of clomipramine as an ejaculation-delaying agent.

33. The method of claim 32, wherein said co-administering is performed substantially simultaneously.

34. Use of an erection-enhancing agent and an ejaculation-delaying agent, wherein an efficacy window of said erection-enhancing agent and an efficacy window of said ejaculation-delaying agent substantially overlap, for the preparation of a medicament for treating sexual dysfunction.

35. Use of an erection-enhancing agent and an ejaculation-delaying agent, wherein said erection-enhancing agent and said ejaculation-delaying agent acting in synergy, for the preparation of a medicament for treating sexual dysfunction.

36. Use of a phosphodiesterase type 5 inhibitor as an erection-enhancing agent and clomipramine as an ejaculation-delaying agent, for the preparation of a medicament for treating sexual dysfunction.

37. A method of treating ejaculatory dysfunction caused by treatment with an agent for the treatment of erectile dysfunction, the method comprising substantially

simultaneously co-administering to a subject in need thereof a pharmaceutically effective amount of an erection-enhancing agent and a pharmaceutically effective amount of an ejaculation-delaying agent, such that an efficacy window of said an erection-enhancing agent and an efficacy window of said ejaculation-delaying agent substantially overlap.

38. Use of an erection-enhancing agent and an ejaculation-delaying agent, wherein an efficacy window of said erection-enhancing agent and an efficacy window of said ejaculation-delaying agent substantially overlap, for the preparation of a medicament for treating ejaculatory dysfunction caused by treatment with an agent for the treatment of erectile dysfunction.

39. The method or use of any of claims 24 to 28, wherein said erectile dysfunction is caused by treatment with an ejaculation-delaying agent.

40. The method or use of any of claims 21, 23, 25, 26, 28, 29, 31 and 32, wherein said pharmaceutically effective amount of said erection-enhancing agent equals to or is lower than 20 mg per dosage unit.

41. The method or use of claim 40, wherein said pharmaceutically effective amount of said ejaculation-delaying agent is lower than 50 mg per dosage unit.

42. The method or use of any of claims 20 to 38, wherein said ejaculation-delaying agent is clomipramine.

43. The method or use of any of claims 20 to 38, wherein said erection-enhancing agent is a phosphodiesterase type 5 inhibitor.

44. The method or use of claim 43, wherein said phosphodiesterase type 5 inhibitor is selected from the group consisting of tadalafil, vardenafil and sildenafil.

45. The method of claim 44, wherein said ejaculation-delaying agent is clomipramine.

46. The method of any of claims 20, 24, 30 and 37, wherein said administering is effected orally.

47. The method or use of any of claims 20 to 38, wherein said erection-enhancing agent and said ejaculation-delaying agent are provided as a single dosage unit.

48. The method or use of any of claims 20 to 38, wherein said erection-enhancing agent and said ejaculation-delaying agent are provided as separate dosage units.

Figure 1

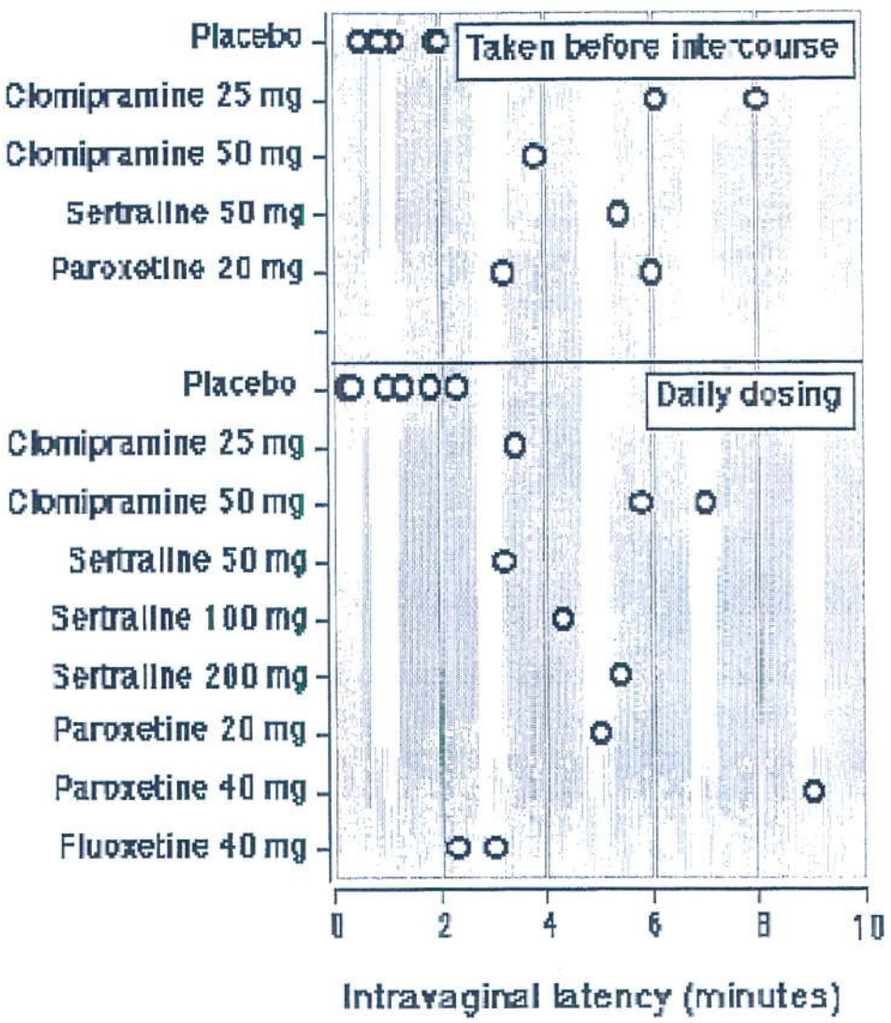

Placebo
Clomipramine 25 mg
Clomipramine 50 mg
Sertraline 50 mg
Paroxetine 20 mg
Taken before intercourse
Placebo
Clomipramine 25 mg
Clomipramine 50 mg
Sertraline 50 mg
Sertraline 100 mg
Sertraline 200 mg
Paroxetine 20 mg
Paroxetine 40 mg
Fluoxetine 40 mg
Daily dosing
0
2
4
6
8
10
Intravaginal latency (minutes)

Figure 2a

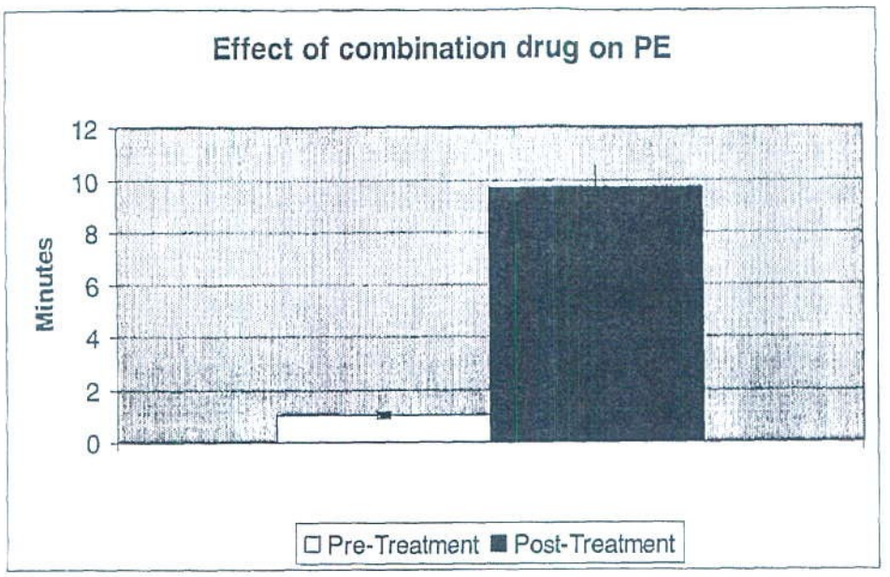
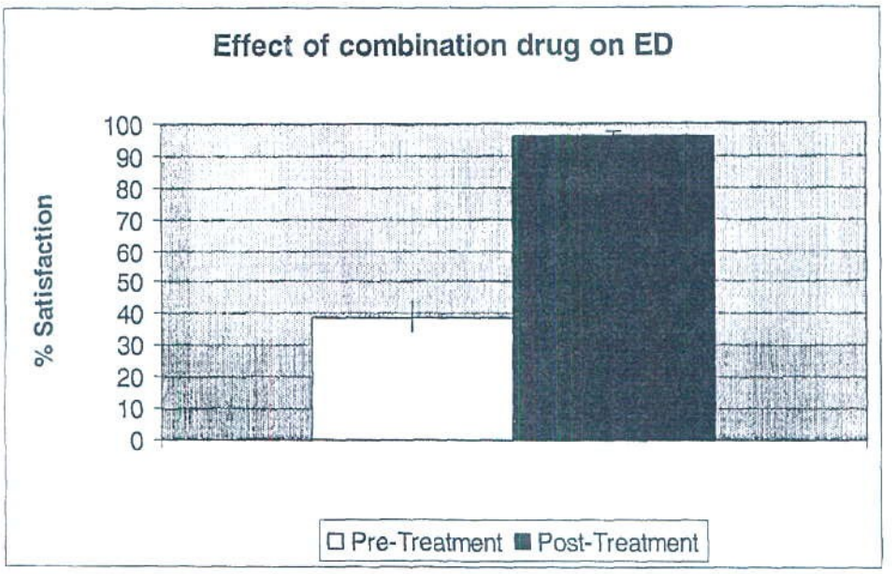


Figure 2b



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(54) **Title:** COMPOSITIONS FOR THE TREATMENT OF SEXUAL DYSFUNCTION

(57) **Abstract:** A method for treating sexual dysfunction, especially premature ejaculation, by administering to a patient an effective amount of a tricyclic antidepressant (*eg* clomipramine) and a cholinergic/muscarinic agent (*eg* pilocarpine) to a mucus membrane, such as the nasal mucosa.

TITLE: COMPOSITIONS FOR THE TREATMENT OF SEXUAL DYSFUNCTION

Field of the Invention

The invention relates to methods and compositions for the treatment of sexual dysfunction, and particularly to the treatment of premature ejaculation.

The invention has been developed primarily for use as a pharmaceutical composition for the treatment of premature ejaculation comprising the administration of a therapeutically effective amount of a tricyclic antidepressant with anticholinergic side effects and a cholinergic (muscarinic) agent and will be described hereinafter with reference to this application. However, it will be appreciated that the invention is not limited to this particular field of use.

Background Art

Antidepressants have been administered orally, in tablet form, to treat premature ejaculation, although there are significant side effects with this approach. In particular, antidepressants can lead to nausea, vomiting, dizziness, dry mouth and blurred vision. Furthermore, their effects are very sensitive to the amount and timing of food and alcohol ingested, as well as the amount of fat on the patient, so their effects can be unpredictable. However the major disadvantage with oral administration of antidepressants in tablet form for treating sexual dysfunction is the substantial delay in the onset of a therapeutic effect, which may be hours or more.

Premature ejaculation has been treated in the past by the topical application of compositions containing local anaesthetics, such as lidocaine, to the skin of the penis to reduce sensitivity.

One limitation of such a method of treatment is that the composition must be substantially removed from the skin prior to intercourse to avoid transferring the anaesthetic to a female partner, thereby reducing reduced vaginal sensitivity.

Overapplication of the topical anaesthetic composition is also possible, leading to substantially diminished enjoyment of intercourse by the male.

The current inventor's previous patent application PCT/AU2004/000931, published as WO2005/004855 discloses the use of antidepressants, preferably administered intra-nasally, to treat sexual dysfunction.

Clomipramine has been found by the present inventor to be a very satisfactory in treating sexual dysfunction. However, when used for extended periods of time, or in large doses, side effects have been observed. These include drying of the mucosa, particularly the nasal mucosa, especially when delivered directly to the mucus membranes.

Thus, there remains a need for a treatment of sexual dysfunction which is convenient and simple to use and does not require a constant dosage regimen or even multiple doses to achieve desired results (i.e., would be available on demand), is non-invasive, allows a rapid and predictable capacity to improve the quality of the sexual response, and which is largely free from unwanted side effects.

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

Definitions

Before describing the present invention in detail, it is to be understood that this invention is not limited to the exemplified active agents, dosage forms, dosing regimens,

or the like. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The terms also encompass pharmaceutically acceptable, pharmacologically active derivatives of those active agents specifically mentioned herein, including, but not limited to, salts, esters, amides, prodrugs, active metabolites, conjugates, analogs, and the like When the terms "clomipramine", "cholinergic agent", "muscarinic agent", "tricyclic antidepressants" and "pilocarpine" are used, then it is to be understood that applicants intend to include the active agent per se as well as pharmaceutically acceptable, pharmacologically active salts, esters, amides, prodrugs, metabolites, conjugates, analogs, etc. The terms "cholinergic agent" and "muscarinic agent" are used interchangeable herein.

By "pharmaceutically acceptable", such as in the recitation of a "pharmaceutically acceptable carrier" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained.

"Carriers" or "vehicles" as used herein refer to conventional pharmaceutically acceptable carrier materials suitable for drug administration, and include any such materials known in the art that are nontoxic and do not interact with other components of a pharmaceutical composition or drug delivery system in a deleterious manner.

The terms "treating" and "treatment" as used herein refer to the ability to effect the time to ejaculation relative to that individual's response in the absence of therapy as

provided herein. Preferably, upon treatment according to the present invention, an individual's time to ejaculation is increased by at least a factor of two, more preferably a factor of four and most preferably a factor of at least ten.

By an "effective" amount or a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect, i.e., delayed ejaculation as explained above. The amount that is "effective", however, will vary from subject to subject, depending on the age and general condition of the individual, the particular active agent or agents, and the like. Thus, it is not always possible to specify an exact "effective amount". However, an appropriate "effective" amount in any individual case may be determined by the administering clinician.

The invention is specifically directed to "as-needed" dosing, also referred to as "pro re nata" dosing, "prn" dosing, and "on-demand" dosing or administration, is meant the administration of an active agent at a time just prior to the time at which drug efficacy is wanted, e.g., just prior to anticipated sexual activity, and within a time interval sufficient to provide for the desired effect. "As-needed" administration herein does not involve priming doses or administration at regular time intervals on an ongoing basis.

"Mucosal" drug delivery is meant administration of a drug to the mucosal surface of an individual so that the drug passes through the mucosal tissue and into the individual's blood stream. Mucosal (or transmucosal) drug delivery may be intra-nasally delivery as preferred here but may also be "buccal" or "transbuccal", referring to delivery of a drug by passage through an individual's buccal mucosa and into the bloodstream. Another form of transmucosal drug delivery herein is "sublingual" drug delivery, which refers to delivery of a drug by passage of a drug through an individual's

sublingual mucosa and into the bloodstream. The delivery may also be by inhalation where respiratory mucosa is involved in absorbing the active agent(s). An additional form of transmucosal drug delivery herein is "rectal" or "transrectal" drug delivery, referring to delivery of a drug by passage of a drug through an individual's rectal mucosa and into the bloodstream.

Summary of the Invention

According to a first aspect the invention provides a method for treating sexual dysfunction to a subject in need thereof comprising administering to the subject an effective amount of a tricyclic antidepressant and a cholinergic/muscarinic agent to a mucus membrane.

The tricyclic antidepressant may have anticholinergic side effects and may be chosen from the group consisting of nortriptyline, clomipramine, dothiepin, imipramine, amitriptyline and doxepin. However, a preferred tricyclic antidepressant is clomipramine.

Preferably the sexual dysfunction is male sexual dysfunction, and most preferably premature ejaculation.

The cholinergic/muscarinic agent may be chosen from the group consisting of pilocarpine, methacholine, carbachol, bethanechol. However, the cholinergic/muscarinic agent is preferably pilocarpine.

Preferably the clomipramine and cholinergic agent are administered prior to sexual activity.

In one embodiment, the clomipramine and the cholinergic agent are administered separately, however, it is more preferred if the clomipramine and the cholinergic agent are administered concurrently.

The clomipramine and the cholinergic agent are preferably administered to the mucosa, and most preferably the clomipramine and the cholinergic agent are administered to the nasal mucosa. In alternative embodiments the clomipramine and the cholinergic agent are administered to the pulmonary mucosa (inhalation) or the buccal mucosa (troche).

Preferably the clomipramine is administered in an amount of between 0.1 and 1000 mg per dose, more preferably in an amount of between 1 and 100 mg per dose and even more preferably in an amount of between 5 and 25 mg per dose.

Preferably the cholinergic agent is administered in an amount of between 0.01 and 1000 mg per dose, more preferably in an amount of between 0.01 and 10 mg per dose and even more preferably in an amount of between 0.01 and 5.0 mg per dose.

It will be appreciated that in preferred embodiments the cholinergic/muscarinic agent and the tricyclic antidepressant are each titrated to suit the individual patients requirements.

Preferably, the clomipramine and cholinergic agent are taken together intra-nasally within 30 minutes prior to intercourse. Most preferably the clomipramine and cholinergic agent are administered intra-nasally by means of one or two metered doses shortly before intercourse.

According to a second aspect the invention provides a method for prolonging sexual intercourse involving a male, the method including the step of administering to the mucus membrane of the male prior to intercourse an amount of a tricyclic antidepressant effective to delay ejaculation and a cholinergic/muscarinic agent.

According to a third aspect, the invention provides a method for prolonging sexual intercourse involving a male over a prolonged number of episodes, the method including the step of administering to the mucus membrane of the male prior to intercourse an

amount of a tricyclic antidepressant effective to delay ejaculation and a cholinergic/muscarinic agent.

According to a fourth aspect the invention provides a composition for the treatment of premature ejaculation, said composition comprising a tricyclic antidepressant and a cholinergic/muscarinic agent. The antidepressant is preferably clomipramine which is preferably formulated as the hydrochloride salt.

As indicated, the cholinergic/muscarinic agent is preferably pilocarpine.

The composition preferably includes a carrier to facilitate the administration of the antidepressant.

The composition is preferably formulated for mucosal administration, and can be a troche for buccal administration, a suppository for rectal administration, or, most preferably, formulated for intra-nasal administration.

Preferably, the intra-nasal spray is in the form of an aqueous or non-aqueous gel, suspension, liposomal dispersion, emulsion or microemulsion or in powdered, microsphere, coated microsphere or liposomal form.

The composition may also be formulated for administration to the lungs *via* inhalation and in the form of a dry powder (preferably with a particle size of the dry powder less than 10 microns), a micronized drug suspended in a liquefied propellant (e.g. an aerosol with chlorofluorocarbon or hydrofluoroalkane propellant), or a drug dissolved, either alone or by way of a cosolvent, in a liquefied propellant.

Preferably surfactants may be included in the formulations of the present invention. Preferred surfactants include oleic acid, sorbitan trioleate, lecithin and their mixtures thereof.

According to a fifth aspect the invention provides the use of a tricyclic antidepressant and a cholinergic/muscarinic agent in the manufacture of a medicament for administration to the mucus membrane for the treatment of premature ejaculation.

As above, the cholinergic/muscarinic agent is preferably pilocarpine. The medicament is preferably formulated for intra-nasal administration.

Unless the context clearly requires otherwise, throughout the description and the claims, the words 'comprise', 'comprising', and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein are to be understood as modified in all instances by the term "about".

Detailed Description

Without wishing to be bound by theory, it is believed the mucosal, and particularly the intra-nasal mucosal route of the present invention allows the drugs to bypass the first metabolism of the liver, and cross the blood/brain barrier to act straight away on the brain. This mode of action may serve to explain the small doses used to achieve success, the rapid onset of action and the consistency in dose/response patterns.

As mentioned, the inventor has found that the antidepressant agent, clomipramine, typically used for the treatment of clinical depression, in combination with a cholinergic/muscarinic agent such as pilocarpine, is capable of delaying ejaculation when administered by intra-nasally (or to the lung or buccal mucosa) while minimising side effects typical of such antidepressants such as vomiting, nausea and dizziness, and further with minimization or alleviation of nasal dryness. Preferably the antidepressant

and the cholinergic/muscarinic agent are delivered to the same site concurrently or sequentially.

Clomipramine can be administered intra-nasally at a fraction of the dose usually used to treat depression, with rapid onset of action and with a high degree of predictability. For example, when clomipramine is delivered directly to the mucus membrane a therapeutic effect will result in about 10 to 15 minutes (compared to oral administration in tablet form which will provide a therapeutic effect in hours or more). However, clomipramine alone can cause the nasal mucosa to dry up. As the nasal mucosa dries up, dryness and cracking of the nasal surfaces can result. This can lead to feelings of discomfort, and can also allow for the onset of bacterial infection. Further, the drying of the mucosa means that the absorption of clomipramine is reduced, and consequently a larger dose is required to achieve the primary effect. The only option is to discontinue medication and allow the patients nasal mucosa to recover. However, that can take time and during that period, sexual dysfunction (premature ejaculation) is likely to recur.

The addition of a cholinergic/muscarinic agent has been found to surprisingly counteract the drying of the mucosa without counteracting the desired effects of clomipramine in countering sexual dysfunction when delivered directly to the mucus membrane. Other antidepressants may be used in combination with the cholinergic/muscarinic agent, and they may be used alone or with one or more carriers for facilitating the application of the antidepressant agent to the skin or to the mucosa. Clomipramine is usually provided as clomipramine hydrochloride, but any pharmaceutically acceptable form is acceptable.

Preferably, the clomipramine is administered in an amount effective to delay premature ejaculation, of between 0.1 and 1000mg per dose, depending upon the

severity of the patients problems, as well as other factors such as patient size. More preferably, the dosage will be between 1 and 100mg antidepressant, even more preferably between 5 and 25 mg antidepressant. Again, the exact dosage will be readily determined by a trained clinician.

Preferably, the cholinergic/muscarinic agent is administered in an amount effective to delay premature ejaculation, of between 0.01 and 1000mg per dose, depending upon the nature of active ingredient used and the severity of the patients problems, as well as other factors such as patient size. More preferably, if the active agent is pilocarpine, the dosage will be between 0.01 and 10mg, even more preferably between 0.01 and 5 mg. The exact dosage will be readily determined by a trained clinician.

Compositions for mucosal administration may be in many forms. Most typically, the invention is formulated as a spray for intra-nasal administration, although it may be formulated for buccal administration in the form of a troche or in the form of a suppository for rectal administration. Those skilled in the art will appreciate that the important consideration is to select the dosages of clomipramine and cholinergic agent in combination to provide a sufficient therapeutic effect to prevent premature ejaculation whilst preventing nasal dryness.

Nasal formulations include gels, suspensions, liposomal dispersions, emulsions or microemulsions and may be any combination of aqueous and non-aqueous components. Alternatively, the nasal formulations may be in powdered form, such as microspheres, liposomes, coated microspheres (for example, such as those with a cellulose or polysaccharide coating).

The nasal formulations of the present invention may include conventional additives and excipients, such as buffers, thickening agents, soothing agents, sweeteners and membrane conditioners or transport agents, antioxidants, preservatives, penetrating

agents and other carriers which will be known by those skilled in the art. It is preferably dispensed *via* a metered spray vessel. Administering the dose in a metered fashion enables a use of a defined quantity of the active ingredient involved.

Nasal formulations may typically include water, polyethylene glycols (various pharmaceutically acceptable PEG's,) glycerine, DMSO, ascorbic acid or ascorbate salts or bisulfites.

Preferably, the dosage is taken intra-nasally just prior to intercourse, between 10 and 30 minutes prior to intercourse, most preferably around 20 minutes prior to intercourse.

The nasal composition may be administered by means of one or two metered doses shortly before intercourse.

The volume of one actuation of a metered dose is generally 20 to 500 microlitres. by way of a troche or suppository which are administered slightly further ahead of time.

A typical intra-nasal spray of the present invention contains clomipramine such that a single dose typically delivers from 2 to 50 mg clomipramine. The amount of pilocarpine is typically such that the single dose delivered is 0.1 mg.

Since the present invention relates to treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate unit dosage forms are combined: for example, a clomipramine pharmaceutical composition and a pilocarpine pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. Thus, a kit may comprise, in separate containers in a single package, pharmaceutical compositions for use in combination to treat sexual dysfunction which comprises in one container a therapeutically effective amount of clomipramine or

a pharmaceutically acceptable salt, solvate, hydrate or crystalline polymorph form thereof in a pharmaceutically acceptable carrier and in a second container a therapeutically effective amount of pilocarpine or a pharmaceutically acceptable salt, solvate or hydrate thereof in a pharmaceutically acceptable carrier.

The formulations can be prepared using conventional pharmaceutical excipients and additives using conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like. Other ingredients for desired formulation and preparation of dosage forms is described in standard texts and manuals, for example *Pharmaceutics – The Science of Dosage Form Design*, Ed. Michael E. Aulton, Churchill Livingstone Press (1998); *The Pharmaceutical Code*, Edition 12, Ed. W. Lund, The Pharmaceutical Press (1994).

The present invention will now be described with reference to the following examples which should be considered in all respects as illustrative and non-restrictive.

Examples

EXAMPLE 1 - FORMULATION

Clomipramine		100mg
Pilocarpine		0.2%
Antioxidant		1%
Preservative		0.5%
Dimethyl sulfoxide		0.02%
Purified Water	to	100.

EXAMPLE 2- TREATMENT

A subject had been treated successfully for premature ejaculation by administering clomipramine intra-nasally. However, after some time the subject developed a dry nose, which became uncomfortable, and appeared to be exhibiting a reduced response to clomipramine. After a rest period, with no medication, the patients nasal mucosa recovered but premature ejaculation re-emerged as a problem. A formulation in accordance with example 1 was administered to a subject who again exhibited successful treatment of premature ejaculation without the detrimental side effects of nasal dryness. No other side effects were detected as a result of the combination therapy of the present invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method for treating sexual dysfunction to a subject in need thereof comprising administering to the subject an effective amount of a tricyclic antidepressant and a cholinergic/muscarinic agent to a mucus membrane.

2. A method according to claim 1 wherein the sexual dysfunction is premature ejaculation.

3. A method according to claim 1 or 2 wherein the tricyclic antidepressant is chosen from the group consisting of nortriptyline, clomipramine, dothiepin, imipramine, amitriptyline and doxepin.

4. A method according to claim 3 wherein the tricyclic antidepressant is clomipramine.

5. A method according to any one of the preceding claims wherein the cholinergic/muscarinic agent is chosen from the group consisting of pilocarpine, methacholine, carbachol, bethanechol.

6. A method according to claim 5 wherein the cholinergic/muscarinic agent is pilocarpine.

7. A method according to any one of the preceding claims wherein the tricyclic antidepressant and the cholinergic/muscarinic agent are administered together to the nasal mucosa.

8. A method according to any one of the preceding claims wherein the tricyclic antidepressant is administered prior to sexual activity

9. A method according to any one of the preceding claims wherein the tricyclic antidepressant is administered in an amount of between about 0.1 and 1000 mg per dose, and the cholinergic/muscarinic agent is administered in an amount of between 0.01 and 1000 mg per dose.

10. A method for prolonging sexual intercourse involving a male, the method including the step of administering to the mucus membrane of the male prior to intercourse an amount of a tricyclic antidepressant effective to delay ejaculation and a cholinergic/muscarinic agent.

11. A method for prolonging sexual intercourse involving a male over a prolonged number of episodes, the method including the step of administering to the mucus membrane of the male prior to intercourse an amount of a tricyclic antidepressant effective to delay ejaculation and a cholinergic/muscarinic agent.

12. A composition for the treatment of premature ejaculation, said composition comprising a tricyclic antidepressant and a cholinergic/muscarinic agent.

13. A composition according to claim 12 wherein the cholinergic/muscarinic agent is pilocarpine and the tricyclic antidepressant is clomipramine.

14. A composition according to claim 12 or claim 13 formulated for mucosal administration.

15. The use of a tricyclic antidepressant and a cholinergic/muscarinic agent in the manufacture of a medicament for administration to the mucus membrane for the treatment of premature ejaculation.

16. The use according to claim 15 wherein the cholinergic agent is pilocarpine and the tricyclic antidepressant is clomipramine.

17. The use according to claim 15 or claim 16 formulated for mucosal administration.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000310

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61K 31/135 (2006.01) *A61K 31/335* (2006.01) *A61K 31/55* (2006.01)
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A61K 31/27 (2006.01) *A61K 31/4178* (2006.01) *A61P 15/12* (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)
DWPI, MEDLINE, CA keywords:Tricyclic antidepressant, TCA, nortryptyline, Chlomipramine, dothiepin, imipramine, amitryptyline, doxepin, Muscarinic, cholinergic, pilocarpine, methacholine, carbachol and bethanechol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2006/125042 A1(BOEHRINGER INGELHEIM PHARMA GMBH & Co. KG) 23 November 2006 Pages 2, 8, 10, 16-18 and 21	1-4, 7-12, 14, 15, 17 12, 14
X Y	WO 2005/115471 A2 (NEUROCURE LTD) 8 December 2005 Pages 4, 5, 11, 13, 14, 15, 18, 19 and 21 and claims 25-32	12, 14 12, 14

[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

"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
02 April 2008	10 APRIL 2008
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer **Grant McNeice** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : (02) 6283 2617

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International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Glenert, U., "Effects of chronic anethole trithione and amitryptyline treatment on rat parotid gland signalling", Eur. J. Pharmacology- Molecular Pharmacology Section, 1992, vol. 226, 43-52 Abstract, pages 45 (para 1), 48 (Table 2), 49 (Table 4, col. 1, last 2 lines, col 2, 1st line), 50 (col. 2, last paragraph)	12, 14,
Y	Dringenberg H.C. et al. "Effect of tacrine on EEG slowing in the rat: enhancement by concurrent monoamine therapy": Neurobiology of Aging. 2000 Jan-Feb; 21(1), 135-43 Abstract, page 137 (last 3 lines).	12, 14
X Y	WO 2002/053104 A2 (Epstein, M.H. et al.) 11 July 2002 Pages 2, 3 and 7 and claim 12	12, 14 12, 14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2008/000310

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2006125042	CA	2608363	EP	1888071	US	2006264511
WO	2005115471	US	2005277626				
WO	02053104	US	2002161002				

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

END OF ANNEX

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

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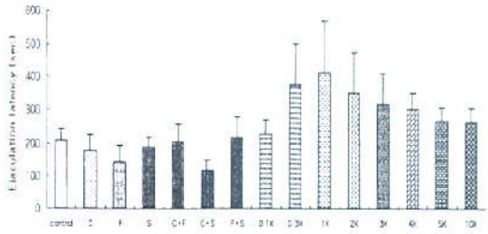
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Published:
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(54) Title: PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF PREMATURE EJACULATION

FIG. 1



(57) Abstract: The present invention provides an oral pharmaceutical composition for the treatment of premature ejaculation, and the composition provides the effective and excellent treatment of premature ejaculation as well as reduced side effects like nausea, vomiting, drowsiness, sedation effect, awakening effect, and weight-loss etc.

WO 2009/142428 A2

PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF PREMATURE EJACULATION

Field of the Invention

The present invention relates to a pharmaceutical composition for the treatment of premature ejaculation, comprising clomipramine or pharmaceutically acceptable salts, sertraline or pharmaceutically acceptable salts and fluoxetine or pharmaceutically acceptable salts as active ingredients.

Background of the Invention

Premature ejaculation (PE), also known as rapid ejaculation, is defined as occurring if the man persistently or recurrently ejaculates in response to minimal stimulation before, during, or shortly after penetration and before the patient (or partner) wishes it. Premature ejaculation is mainly caused by psychological factors. It has hereditary characteristics and abnormality in the neuron or other networks can also contribute to premature ejaculation. Premature ejaculation is one of quite common sexual dysfunctions and 1/3 of men suffer from premature ejaculation.

According to WHO, premature ejaculation is quantitatively defined as the intravaginal ejaculation latency time (IELT) is 60 seconds or less. It is known that ejaculation delay is related to the activation of 5HT2c, while rapid ejaculation is associated with 5HT1a. It is assumed that the low level of 5HT (serotonin) neurotransmission, the hypofunction of 5HT2c receptor, or the hyperfunction of 5HT1a leads to premature ejaculation. It can also be related to other factors including hypersensitivity of nervous system, penis sensitivity, somatic cell-vulnerability, deterrent effect of the serotonin operating system, etc. (US Publication No. 2007-0043030; *Trends in Neuroscience*, 2007, (30):79-84).

Premature ejaculation is the most common symptom of the male sexual dysfunction, but there has not been conducted insufficient research thereon. A

research by Masters and Johnson in 1970 announcing that premature ejaculation could be easily fixed by behavior therapy was the established theory, and the cause of the premature ejaculation was considered as similar to that of impotence or libido degradation. However, it has been found that behavior therapy has the limits and the medical treatment of premature ejaculation came to attention in 1990s.

In the early stage of medical treatment of premature ejaculation, clomipramine (Anafranil®) which is a representative tricyclic antidepressant (TCAs) was used. There is reported the ejaculation latency effect by medicating clomipramine with the oral dose of 25mg or 50mg per day (*J Clin Psychiatry*. 1995, (56):402-407). Further, it is reported that when 50mg of clomipramine was administered to premature ejaculation patients with an average age of 44, some side effects including constipation, dry-mouth, nausea, drowsiness, headache and dizziness, etc. were shown up, although ejaculation was delayed (*The Journal of Urology*, 1998, (159):425-427). Such side effects occur since clomipramine affect not only serotonin but also other neurotransmitters.

For the above problems, researchers have begun to focus on a Selective Serotonin Reuptake Inhibitor (SSRI) for the treatment of premature ejaculation. Sertraline (Zoloft®), one of representative SSRIs, was used for the treatment of premature ejaculation. It is reported that when 50mg to 200mg per day of sertraline was administered to premature ejaculation patients, while the ejaculation was delayed, side effects including nausea, vomiting, etc. also occurred and such side effects lead to lowering the medication effect (*The Journal of Urology*, 1998, (159):1935-1938; US Pat. No. 4940731).

Among other SSRIs, fluoxetine (Prozac®), known as an antidepressant, was administered for the treatment of premature ejaculation. US Pat. No. 5151448 describes that fluoxetine was administered to the patients with premature ejaculation. Also, as reported in *The Journal of Urology*, 1998, (159): 425-427, 40mg of fluoxetine was administered to premature ejaculation patients, but the ejaculation delay effect was weak. Besides, the side effects including drowsiness, dry-mouth, nausea, vomiting, etc. were reported. When fluoxetine

was administered to premature ejaculation patients as shown in *The Journal of Urology*, 2003, (170):164-165, the side effects such as nausea, headache, and insomnia occurred. Therefore, fluoxetine cannot be successfully used for the treatment of premature ejaculation.

US Pat. No. 6495154 describes a rapid-release pharmaceutical formulation containing clomipramine which can be conveniently administered on demand, but did not suggest concrete solutions to the side effects mentioned above. US Publication No. 2007-0043030 also describes a composition for pulmonary inhalation comprising clomipramine in order to accomplish rapid treatment effect and to reduce side effects. However, there was no concrete results showing the treatment effect of medicine and diminishing the side effects. Furthermore, there is not suggested any combinational compositions of various antidepressants or other therapeutic agents.

Therefore, new therapeutic agents for the treatment of premature ejaculation, which has effective and excellent treatment effects and reduce side effects like nausea, vomiting, drowsiness, sedation effect, awakening effect, and weight-loss, etc. has been required in the relevant industry.

Summary of the Invention

Accordingly, it is an object of the present invention to provide a pharmaceutical composition for the treatment of premature ejaculation.

It is another object of the present invention to provide a method for treating premature ejaculation.

In accordance with one aspect of the present invention, there is provided a pharmaceutical composition for the treatment of premature ejaculation, comprising clomipramine or a pharmaceutically acceptable salt thereof, sertraline or a pharmaceutically acceptable salt thereof and fluoxetine or a pharmaceutically acceptable salt thereof as active ingredients.

In accordance with another aspect of the present invention, there is provided a method for the treatment of premature ejaculation, comprising

administering a composition which comprises clomipramine or a pharmaceutically acceptable salt thereof, sertraline or a pharmaceutically acceptable salt thereof and fluoxetine or a pharmaceutically acceptable salt thereof as active ingredients, to a subject in need of treatment of premature ejaculation.

Brief Description of Drawings

The above and other objects and features of the present invention will become apparent from the following description of the invention, when taken in conjunction with the accompanying drawings, which respectively show:

Fig. 1: Change of ejaculation latency time according to Example 2; and

Fig. 2: Change of body weights according to Example 3.

Detailed Description of the Invention

A pharmaceutical composition according to the present invention will now be described more fully with respect to exemplary embodiment of the invention.

The present inventors have endeavored to develop a pharmaceutical composition for the treatment of premature ejaculation, and found that the oral administration of a mixture of clomipramine, sertraline and fluoxetine treats premature ejaculation and reduces side effects significantly.

More particularly, the present inventors have found that when administered in a mixture of clomipramine, sertraline and fluoxetine, drug adsorption increases through the drug interactions.

The terms "clomipramine," "sertraline" and "fluoxetine," as used herein, mean each free base form thereof. "A pharmaceutically acceptable salt" of clomipramine, sertraline or fluoxetine refers to nontoxic salts in a dose, and includes conventional salts such as inorganic acids, organic acids or nontoxic salts.

Examples of such inorganic acids include, but are not limited to, hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid,

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hydriodic acid, nitrous acid, and phosphorous acid. Examples of said organic acids include acetic acid, lactic acid, citric acid, malic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, benzoic acid, phthalic acid, gluconic acid, saccharinic acid, methane sulfonic acid, ethane disulfonic acid, aliphatic mono and dicarboxylate, phenyl-substituted alkanoate, hydroxyl alkanoate and alkanedicate, aromatic acid, and aliphatic and aromatic sulfonic acid. Preferred organic acid is hydrochloric acid (hydrochloride).

Said nontoxic salts include, but are not limited to, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogen phosphate, dihydrogen phosphate, metaphosphate, pyrophosphate chloride, bromide, iodide, fluoride, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butene-1,4-dioate, hexane-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitro benzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, benzenesulfonate, toluenesulfonate, chlorobenzenesulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, beta-hydroxybutyrate, glycolate, malate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, and mandelate.

The present invention provides a pharmaceutical composition for the treatment of premature ejaculation, comprising clomipramine or a pharmaceutically acceptable salt thereof, sertraline or a pharmaceutically acceptable salt thereof and fluoxetine or a pharmaceutically acceptable salt thereof as active ingredients.

In the pharmaceutical composition, clomipramine or a pharmaceutically acceptable salt thereof, sertraline or a pharmaceutically acceptable salt thereof and fluoxetine or a pharmaceutically acceptable salt thereof are preferably contained in the weight ratio of about 1 : 1~2 : 0.5~1.

According to an aspect of the present invention, a pharmaceutical composition for the treatment of premature ejaculation comprising 0.7~75.0 mg

of clomipramine, 1.1~113.0 mg of sertraline and 0.5~59.0 mg of fluoxetine as an effective daily dose for a human is provided. Preferably, a pharmaceutical composition for the treatment of premature ejaculation comprising 0.7~22.5 mg of clomipramine, 1.1~33.9 mg of sertraline and 0.5~17.7 mg of fluoxetine as an effective daily dose for a human is provided. More preferably, a pharmaceutical composition for the treatment of premature ejaculation comprising 2.2~22.5 mg of clomipramine, 3.3~33.9 mg of sertraline and 1.7~17.7 mg of fluoxetine as an effective daily dose for a human is provided. Most preferably, a pharmaceutical composition for the treatment of premature ejaculation comprising 7.5 mg of clomipramine, 11.3 mg of sertraline and 5.9 mg of fluoxetine as an effective daily dose for a human is provided.

The inventive treatment drug for premature ejaculation shows less side effects and significant treatment effects through the combination of clomipramine, sertraline and fluoxetine, and in particular shows maximized treatment effects and minimized side effects in said dose range.

The amounts of clomipramine, sertraline and fluoxetine herein represent the calculated values based on the free base forms of each active ingredient.

The pharmaceutical composition of the present invention may be administered orally, e.g., in a tablet, capsule, suspension, granule, gel, pill, tincture, decoction, infusion, spirit, fluid extract, elixir, extract, syrup, powder, aromatic water, lemonade and the like.

In the pharmaceutical composition of the present invention, tablets may be, for example, in the form of sugar-coated tablets, film-coated tablets, enteric-coated tablets, peroral tablets, sublingual tablets, buccal tablets, chewable tablets, dispensing tablets, multilayered tablets, press-coated tablets, effervescent tablets, solution tablets, hypodermic tablets and the like. It should be understood that various modifications and changes may be made for said tables by those skilled in the art

The pharmaceutical composition of the present invention may also be prepared in the form of sustained-release formulations, controlled-release

formulations, repeat-action formulations, immediate-release formulations, fast-disintegrated formulations and like.

According to another aspect of the present invention, the pharmaceutical composition of the present invention may comprise 0.7~75.0 mg of clomipramine, 1.1~113.0 mg of sertraline and 0.5~59.0 mg of fluoxetine as active ingredients in a unit dosage form, in combination with a pharmaceutically acceptable carrier. Preferably, the composition may comprise 0.7~22.5 mg of clomipramine, 1.1~33.9 mg of sertraline and 0.5~17.7 mg of fluoxetine as active ingredients in a unit dosage form, in combination with a pharmaceutically acceptable carrier. More preferably, the composition may comprise 2.2~22.5 mg of clomipramine, 3.3~33.9 mg of sertraline and 1.7~17.7 mg of fluoxetine as active ingredients in a unit dosage form, in combination with a pharmaceutically acceptable carrier. Most preferably, the composition may comprise 7.5 mg of clomipramine, 11.3 mg of sertraline and 5.9 mg of fluoxetine as active ingredients in a unit dosage form, in combination with a pharmaceutically acceptable carrier.

The pharmaceutical composition for the treatment of premature ejaculation may comprise clomipramine or a pharmaceutically acceptable salt thereof, sertraline or a pharmaceutically acceptable salt thereof and fluoxetine or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

The pharmaceutically acceptable carriers may include additives such as e.g., excipients, disintegrants, binders, lubricants, emulsifiers, suspending agents, stabilizers and the like. If desired, sweetening and/or flavoring agents may be added as well. The pharmaceutical composition of the present invention may be administered orally in various formulations, such as a tablet, capsule, aqueous liquid or suspension and the like. For tablets, carriers such as lactose and corn starch, etc. and lubricants such as magnesium stearate, etc. may be conventionally added. For capsules, lactose and/or dried corn starch may be used as diluents. For aqueous liquids, the active ingredients may be formulated in combination with emulsifiers and/or suspending agents. If desired, a specific sweetening and/or flavoring agents may be added.

The pharmaceutical composition of the present invention may be in the form of pharmaceutical formulations, e.g., in the form of solid, semi-solid or liquid forms. The formulations may contain a mixture of organic or inorganic carriers or excipients suitable for external, internal or parenteral use.

The pharmaceutical composition of the present invention may contain one or more pharmaceutically acceptable carriers in the form of a tablet, pellet, capsule, liquid, emulsifier, suspending agent, troche and other suitable forms, binders (e.g., microcrystalline cellulose, gum tragacanth or gelatin), excipients (e.g., starch or lactose), disintegrants (e.g., alginic acid, primogel or corn starch), lubricants (e.g., magnesium stearate or sterotex), glidants (e.g., colloid silicon dioxide), sweeteners (e.g., sucrose or saccharin), or flavoring agents (e.g., peppermint, methyl salicylate or orange flavor) may be added. Capsules in a unit dosage form may contain liquid carriers (e.g., polyethylene glycol or fatty acid oil) in addition to said additives. Other various substances, such as coatings, may be used to convert physical forms of a dosage unit. For example, a tablet or pill may be coated with sugars, shellacs or other coating agents. Syrup may contain sucrose as a sweetening agent, specific preservatives, dyes, coloring and/or flavoring agents. The additives used in preparing such various preparations should be pharmaceutically pure and nontoxic.

The inventive composition also may be in the form of solution or suspension, and may contain one or more adjuvants selected from the group consisting of sterilized diluents (e.g., water for injection), saline solutions (e.g., sodium chloride or mannitol), fixed oils, polyethylene glycol, glycerin, propylene glycol or other synthetic solvents, antibacterial agents (e.g., benzyl alcohol or methylparaben), antioxidants (e.g., ascorbic acid or sodium bisulfide), chelating agents (e.g., EDTA or ethylene diaminetetraacetic acid) and buffers (e.g., acetic acid salt, citric acid salt or phosphoric acid salt). Parenteral formulations may be packaged into amples, disposable syringes, or multiple dose vials made of glass or plastic.

The pharmaceutical composition of the present invention for the treatment

of premature ejaculation can further contain, in addition to clomipramine, sertraline and fluoxetine, other drugs, e.g., one or more selected from the group consisting of serotonin agonists, serotonin antagonists, adrenergic agonists, adrenergic antagonists, adrenergic neuron blockers, impotence treatment drugs, phosphodiesterase 5 inhibitors, erection inducers and a combination thereof. In particular, phosphodiesterase 5 inhibitors include, but are not limited to, silenafil, tadalafil, vardenafil, udenafil and the like, and erection inducers include, but are not limited to, phentolamine, papaverine, alprostadil, etc. It should be understood that, if desired, those skilled in the art can select suitable drugs among said drugs, and can use another additional drugs together with said drugs.

The pharmaceutical composition of the present invention may be administered to a patient prior to engaging in sexual activity, preferably 30 min to 3 hours prior to engaging in sexual activity. The administration method may be changed depending on the characteristics of a patient.

As mentioned above, the pharmaceutical composition of the present invention, comprising clomipramine, sertraline and fluoxetine as active ingredients, provides the effective and excellent treatment of premature ejaculation as well as reduced side effects like nausea, vomiting, drowsiness, sedation effect, awakening effect, and weight-loss, etc.

Furthermore, the composition is efficacious in enhancing dosage effects and patients' compliances, by minimizing side effects resulted from each drug.

Whereas, the present invention also provides a method for the treatment of premature ejaculation comprising administering a composition which comprises clomipramine or pharmaceutically acceptable salts thereof, sertraline or pharmaceutically acceptable salts thereof and fluoxetine or pharmaceutically acceptable salts thereof as active ingredients, to a subject in need of treatment of premature ejaculation. The subject is preferably a mammal, more preferably a human.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Further, percentages given below for solid in solid mixture, liquid in liquid, and solid in liquid are on a wt/wt, vol/vol and wt/vol basis, respectively, and all the reactions were carried out at room temperature, unless specifically indicated otherwise.

Example 1: Pharmacokinetics Study

<1-1> Materials and Methods

7-week-old male Crl:CD (SD) rats weighing around 200g were fasted for 16 hours, and then cannulated with polyethylene tubing (PE-50) in the carotid artery and divided into 4 groups of 10 rats. The rats of Group 1 were orally administered with a single dose of clomipramine 2.70 mg/kg; Group 2, with sertraline 6.02 mg/kg; Group 3, with fluoxetine 2.41 mg/kg; and Group 4, with a triple-drug combination (a dose of clomipramine 2.70 mg/kg, sertraline 6.02 mg/kg and fluoxetine 2.41 mg/kg). Blood samples (about 200 μl) were collected by polyethylene tubing at 0.5, 1, 2, 3, 4, 5, 7, 9, 11 and 24 hours after the drug administration. Rats were supplemented with about 200 μl of heparinized saline (20 IU/ml) at each sampling times. The collected blood samples were centrifuged (MicroMax, International Equipment Company, USA) at 10,000 rpm for 1 min to obtain plasma samples, and then the amounts of clomipramine, sertraline and fluoxetine in the plasma samples were determined by using simultaneous LC/MS/MS method.

<1-2> Evaluation Methods

The maximum plasma concentration (Cmax) and the time to reach Cmax (Tmax) were obtained from the plasma concentration-time curve. The area under the plasma concentration-time curve (AUC) was calculated by using the trapezoidal rule.

<1-3> Results

The administration of triple-drug combination of the present invention led to the increases in Cmax and AUC of fluoxetine (known as a substrate of CYP2C9, 2C19 and 2D6 (a major enzyme)) in all animals, owing to the inhibition of CYP2D6 and CYP2C9 by clomipramine and sertraline. In case of clomipramine, the increases of Cmax and AUC were detected due to the inhibition of CYP2D6 by fluoxetine and sertraline. In case of sertraline (known as a substrate metabolized by various enzymes such as CYP2C9, 2C19, 2D6 and 3A4), Cmax and AUC were higher than those from the single drug administration data, but only AUC increased significantly.

According to the present invention, single-oral administration of the triple-drug combination resulted in escalated systemic exposure of clomipramine, fluoxetine and sertraline in the body than single drug administration, and drug-drug interaction was clearly shown in order of fluoxetine > clomipramine > sertraline.

Results of the determination of AUC and C_{max} with triple-drug combination and single drugs are shown in Table 1.

Table 1

Compound	Dose (mg/kg)	PK parameter	Single drug	Triple-drug combination	Increasing rate (%)
Clomipramine	2.70	AUC (ng·h/ml)	12.7	36.3	185.8
		C_{max} (ng/ml)	6.7	13.8	106.0
Sertraline	6.02	AUC (ng·h/ml)	476.2	803.6	68.8
		C_{max} (ng/ml)	81.1	95.8	18.1
Fluoxetine	2.41	AUC (ng·h/ml)	55.5	289.3	421.3
		C_{max} (ng/ml)	23.3	62.1	166.5

As shown in Table 1, the triple-drug combination (clomipramine 2.70 mg/kg, sertraline 6.02 mg/kg and fluoxetine 2.41 mg/kg) led to the increases in AUC and C_{max} when compared with those of the single drug administration. These results demonstrate that AUC and C_{max} were escalated by drug-drug interaction of the triple-drug combination. As a result, the effective ejaculation delay can be expected even with low dose.

Example 2: Pharmacological effect evaluation (rats)

<2-1> Materials and Methods

According to the method of *Brain Res Brain Res Protoc*, 1997, (1):203-9, this experiment was executed by employing male and female Crl:CD (SD) rats above 20 weeks old as test animals.

(1) Ovariectomy and induction of estrus

The female rats were anesthetized by the intraperitoneal injection of combination of ketamine 75 mg/kg and xylazine 25 mg/kg. After performing laparotomy, the ovaries were removed and peritoneal wall was closed with sutures. 2 ml of 10% ampicillin was injected intraperitoneally and the female rats had recovery period of 7 days. Ovariectomied females were brought into artificial estrus by subcutaneous injection of 20 μg/rat of estradiol benzoate, dissolved in 0.2 ml of sesame oil, about 52 hours before the administration of a test compound, followed by s.c injection of 1 mg/rat of progestrerone, dissolved in 0.2 ml of sesame oil, about 4 hours before the administration of a test compound.

(2) Screening test and copulatory experience

Screening test was performed in an observation cage (60x40x30 cm) with plexiglass front. Before screening test, the male rats were allowed to adapt to the observation cage for 10 minutes and then the female rats with artificial estrus were brought into the cage. If male rats had ejaculated within 30 minutes, they were regarded as sexually active ones. Selected male rats went through copulatory experience for 5 times at 3 days intervals.

(3) Administration and evaluation

The experienced males were divided into 15 groups of about 10 animals so that the mean ejaculation latency time (ELT) of groups are similar. Test compound was single orally administered.

Group 1 as a negative control was administered with 0.5% methylcellulose 1500 (Sigma Co., hereinafter as "MC 1500"). Groups 2 ~ 4 as single drug-administered groups were administered with clomipramine, sertraline and fluoxetine, respectively. Groups 5 ~ 7 were administered with double-drug combinations. Groups 8 ~ 15 were administered with triple-drug combinations having various doses. Detailed doses are represented in Table 2 below.

After 2 hours and 50 minutes from the administration of test compounds, the male rats were allowed to adapt to the observation cage for 10 minutes. Then copulatory behavior test was initiated with the introduction of female rats with artificial estrus into the observation cage. The ejaculation latency time (ELT) as the time from the first intromission until the ejaculation was evaluated.

<2-2> Results

Results of ELT on rats from the experiments described above are represented as the mean±S.E.M and are shown in Table 2 and Figure 1.

Table 2

Group		Test comp. & dose (mg/kg)	Ejaculation latency time, mean±S.E.M. (sec)	Increasing rate (%)
1	Negative control	0.5% MC 1500	206.8 ± 37.4	
2	Single drug	C: 2.70	177.2 ± 47.5	-14.3
3	Single drug	S: 6.02	185.8 ± 31.7	-10.2
4	Single drug	F: 2.41	141.3 ± 51.2	-31.7
5	Double-drug combination	C: 2.70 + F: 2.41	201.3 ± 54.8	-2.7
6	Double-drug combination	C: 2.70 + S: 6.02	116.1 ± 32.5	-43.9
7	Double-drug combination	F: 2.41 + S: 6.02	219.4 ± 59.2	6.1
8	Triple-drug combination (0.1X)	C:0.09 + S:0.14 + F:0.07	227.0 ± 40.1	9.8
9	Triple-drug combination (0.3X)	C:0.27 + S 0.41 + F:0.21	375.5 ± 122.4	81.6

10	Triple-drug combination (1X)	C:0.90 + S:1.36 + F:0.71	409.1 ± 158.2	97.8
11	Triple-drug combination (2X)	C:1.80 + S:2.72 + F:1.42	350.1 ± 120.3	69.3
12	Triple-drug combination (3X)	C:2.70 + S:4.08 + F:2.13	314.3 ± 92.1	52.0
13	Triple-drug combination (4X)	C:3.60 + S:5.44 + F:2.84	300.1 ± 50.3	45.1
14	Triple-drug combination (5X)	C:4.50 + S:6.80 + F:3.55	263.7 ± 42.2	27.5
15	Triple-drug combination (10X)	C:9.00 + S:13.60 + F:7.10	260.8 ± 43.8	26.1

(C : clomipramine, S : sertraline, F : fluoxetine)

The ELT of Group 1 (negative control group) was 206.8±37.4 sec. In case of Groups 2 ~ 4 (single-drug groups), the ELT was not longer than that of the negative control group. Also, there was no increase of the ELT in Groups 5 and 6 (double-drug combination groups) compared with negative control group.

However, the ELTs of triple-drug combinations (clomipramine + sertraline + fluoxetine) of Group 8 to Group 15 were 227.0±40.1 sec, 375.5±122.4 sec, 409.1±158.2 sec, 350.1±120.3 sec, 314.3±92.1 sec, 300.1±50.3 sec, 263.7±42.2 sec and 260.8±43.8 sec, respectively. The increasing rate (%) of their ELTs compared with the negative control group were 9.8%, 81.6%, 97.8%, 69.3%, 52.0%, 45.1%, 27.5% and 26.1%, respectively.

Considering all the results of the above, all of the triple-drug combinations of Group 8 to Group 15 increased the ELT compared with the negative control group in the dosage of 0.1X ~ 10X. Especially, Group 10 (the triple-drug combination of 1X dose) showed outstanding increasing rate (about 98%) of ELT compared with the negative control group. Also, all the groups of triple-drug combinations were found having excellent effects on delay of ejaculation, compared with the single drugs and the double-drug combinations.

In conclusion, triple-drug combinations (clomipramine, sertraline and fluoxetine) have excellent effects for treating premature ejaculation compared with the single drugs and double-drug combinations.

Example 3: Side effect evaluation (rats)

<3-1> Materials and Methods

7-week-old male Crl:CD (SD) rats were divided into five groups of 10 rats. A negative control group was administered with 0.5% MC 1500, and triple-drug combination (clomipramine + fluoxetine + sertraline) group, with 4 doses (indicated with 3X, 5X, 7X and 10X) of the triple-drug combination once a day for 7 days. Detailed doses are represented in Table 3 below. Then animals were observed twice a day for clinical signs, and their body weights were measured before the initiation of the experiment and on the 1st, 3rd, 5th and 7th day from the initiation.

<3-2> Evaluation Methods

Toxic effects of triple-drug combination were evaluated by comparing the treated groups with the negative control group. Especially when the gain or loss of body weights during the experiment period is statistically significant, it is considered as toxic effects.

Statistical analyses for body weight were performed for comparisons between the treated groups and the negative control group. Differences were considered significant for findings of $p<0.05$, $p<0.01$ and $p<0.001$. First, a given parameter was examined by Levene's test for evaluation of homogeneity of variance. If the variance was homogeneous, Dunnett's t-test was used to compare each dose group with the negative control group. If the variance of Levene's test was not homogeneous, the rank-transform test was used to compare each dose group with the negative control group. The transformed data were reexamined by Levene's test for evaluation of homogeneity of variance. If the

variance was homogeneous, Dunnett's t-test was used to compare each dose group with the negative control group.

<3-3> Results

Body weight changes of rats from the experiments described above are represented as the mean±S.D. and are shown in Table 3 and Figure 2.

Table 3

Dosage (mg/kg/day)	Day					Body weight change (g)
	0	1	3	5	7	
Negative control (0.5% MC 1500)	258.89 ±6.87	270.38 ±7.71	289.61 ±9.40	303.33 ±10.05	316.82 ±9.74	57.9
3X (C:2.70 + S:4.08 + F:2.13)	258.43 ±7.36	268.25 ±9.08	286.01 ±10.05	300.43 ±11.48	313.94 ±13.52	55.5
5X (C:4.50 + S:6.80 + F:3.55)	256.90 ±7.26	262.93 ±7.80	277.82 ±8.41	291.85* ±9.04	303.88* ±8.82	47.0
7X (C:6.30 + S:9.52 + F:4.97)	258.11 ±6.94	253.57*** ±9.82	268.08*** ±15.58	286.89*** ±7.38	296.27*** ±10.15	38.2
10X (C:9.00 + S:13.60 + F:7.10)	257.57 ±7.29	256.10** ±8.33	272.16** ±8.33	283.92*** ±10.88	296.42*** ±12.36	38.9

(C : clomipramine, S : sertraline, F : fluoxetine)

Each values of the experiment were represented as the mean (weight, (g)) ± S.D.

*, **, *** : Significantly different from the negative control at $p<0.05$, $p<0.01$ and $p<0.001$, respectively.

Body weight change compared with a negative control group has been used as a representative factor to evaluate the toxicological sign of a drug. When the triple-drug combination was administered for 7 days, the body weight

decreased about 4% on days 5 and 7 in the 5X Group compared with the negative control group. Further, body weights significantly decreased about 6~8% on days 1 to 7 in the 7X and 10X Group compared with the negative control group. When the body weight change for 7 days of each treatment groups was compared with the negative control group, the body weight gain significantly decreased by -19%, -34% and -33% for 5X, 7X, and 10X groups, respectively. The maximum tolerated dose (MTD) is generally chosen based on decrease of less than 10% in body weight gain compared with a negative control in the toxicity study. According to the above results, the MTD of triple-drug combinations in the present invention was determined as below 5X dose.

Example 4: Pharmacological effect evaluation - clinical study

<4-1> Calculation of human dose

Based on the rat dose of Example 2, the human dose can be calculated. More specifically, based on US FDA's guide, "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers", the human equivalent dose (HED) can be calculated by using the calculating formula below. The calculation is based on the assumption that a rat is 150g, and a person is 60kg.

$$HED = \text{animal dose(mg/kg)} \times (\text{animal weight(kg)/human weight(kg)})^{0.33}$$

As to the triple-drug combination of the present invention, if 1X dose of a rat is converted into the human body dose, it is calculated as clomipramine 7.4mg, sertraline 11.2mg, and fluoxetine 6.0mg. Based on Example 2, the rat doses of Groups 8 ~ 15 are converted into the human body doses as to the triple-drug combination. Detailed human body doses are represented in Table 4 below.

Table 4

Group	Test comp. & dose (mg)		
	Clomipramine	Sertraline	Fluoxetine

0.1X	0.7	1.1	0.5
0.3X	2.2	3.3	1.7
1X	7.5	11.3	5.9
2X	15.0	22.6	11.8
3X	22.5	33.9	17.7
4X	30.0	45.2	23.6
5X	37.5	56.5	29.5
7X	52.5	79.1	41.3
10X	75.0	113.0	59.0

<4-2> Experimental method

Patients with premature ejaculation of 60 seconds or less were divided into 4 groups of twenty people. The patient group 1 was administered as a daily dose with clomipramine 22.4mg; the patient group 2, with sertraline 50.0mg; the patient group 3, with fluoxetine 20.0mg; and the patient group 4, with the triple-drug combination of the present invention including clomipramine 7.5mg, sertraline 11.3mg, and fluoxetine 5.9mg. A dose was taken 3 hours before the sexual intercourse begins, and the administration period was for 3 weeks. The effect of the administration of the drugs to the patients examined through interviews with the patients. A drug was determined as effective when the patient's ejaculation latency time had been 10 minutes or more.

<4-3> Results

Results of the human treatment effect from the experiments described above are shown in Table 5.

Table 5

Patient group and dose	No. of Patients	Patient no. with ELT of 10min or over	Treatment effect (%)
Clomipramine (22.4mg)	20	15	75
Sertraline (50.0mg)	20	8	40
Fluoxetine (20.0mg)	20	0	-
Inventive triple-drug	20	19	95

combination (C:7.5mg + S:11.3mg + F:5.9mg)		

(C : clomipramine, S : sertraline, F : fluoxetine)

As shown in Table 5, curative effects of the drugs were exhibited in 75% of the patients administered with clomipramine 22.4mg and about 40% of patients administered with sertraline 50.0mg. However, the curative effect did not show up in the patients administered with fluoxetine 20.0mg. In stark contrast, in the case of patients administered with the triple-drug combination, curative effect appeared in surprising 95% of them, despite of the significantly reduced doses of each drugs.

Example 5: Side effect evaluation - clinical study (nausea)

A side effect incidence rate of nausea was investigated among patients who took each drug in Example 4. As shown in Table 6, the nausea occurred in 90% of the patients who took sertraline 50.0mg, while only 5% of the patients who took the triple-drug combination experienced the nausea. This result demonstrates the notable nausea diminishing effect of the triple-drug combination.

Results of the side effect (nausea) from the experiments described above are shown in Table 6.

Table 6

Patient group and dose	No. of Patients	No. of nausea	Incidence rate (%)
Sertraline (50.0mg)	20	18	90
Inventive triple-drug combination (C:7.5mg + S:11.3mg + F:5.9mg)	20	1	5

(C : clomipramine, S : sertraline, F : fluoxetine)

Example 6: Side effect evaluation - clinical study (sedation)

A side effect incidence rate of sedation was investigated among patients who took each drug in Example 4. As shown in Table 7, the sedation occurred in 70% of the patients who took clomipramine 22.4mg, while about 5% of the patients who took the triple-drug combination experienced the sedation. This

result demonstrates the notable sedation diminishing effect of the triple-drug combination.

Results of the side effect from the experiments described above are shown in Table 7.

Table 7

Patient group and dose	No. of Patients	No. of sedation	Incidence rate (%)
Clomipramine (22.4mg)	20	14	70
Inventive triple-drug combination (C:7.5mg + S:11.3mg + F:5.9mg)	20	1	5

(C : clomipramine, S : sertraline, F : fluoxetine)

Formulation Example 1: Preparation of Tablet

All ingredients of the tablet core shown in Table 8, including clomipramine hydrochloride, sertraline hydrochloride and fluoxetine hydrochloride as active ingredients, were mixed thoroughly and then compressed using a single tablet press to obtain tablets. The tablets were coated with Opadry® (the Opadry white 85F 18422, the Colorcon Corp) to obtain film-coated tablets.

Table 8

	Component	mg/tablet
Tablet core	Clomipramine hydrochloride (Clomipramine free base)	8.4 (7.5)
	Sertraline hydrochloride (Sertraline free base)	12.6 (11.3)
	Fluoxetine hydrochloride (Fluoxetine free base)	6.6 (5.9)
	Microcrystalline cellulose	116.4
	D-mannitol	40.0
	Hydroxypropyl cellulose	6.0
	Croscarmellose sodium	6.0
	Sodium lauryl sulfate	2.0
	Magnesium stearate	2.0
Coating layer	Opadry®	6.0
Total weight		206.0

Formulation Example 2: Preparation of Tablet

All ingredients of the granule inside shown in Table 9, including clomipramine hydrochloride, sertraline hydrochloride and fluoxetine hydrochloride as active ingredients, were mixed. A binder solution prepared by dissolving hydroxypropyl cellulose and polysorbate 80 in water was added thereto to obtain granules. Magnesium stearate was added to the granules and the mixture was compressed to obtain tablets. The tablets were coated with Opadry® to obtain film-coated tablets.

Table 9

		Component	mg/tablet
Tablet core	Granule Inside	Clomipramine hydrochloride (Clomipramine free base)	8.4 (7.5)
		Sertraline hydrochloride (Sertraline free base)	12.6 (11.3)
		Fluoxetine hydrochloride (Fluoxetine free base)	6.6 (5.9)
		Microcrystalline cellulose	112.8
		Sodium starch glycolate	8.0
	Binder solution	Hydroxypropyl cellulose	6.0
		Polysorbate 80	4.0
	Granule outside	Magnesium stearate	1.6
Coating layer		Opadry®	5.0
Total weight			165.0

Formulation Example 3: Preparation of Capsule

All ingredients shown in Table 10, including clomipramine hydrochloride, sertraline hydrochloride and fluoxetine hydrochloride as active ingredients were mixed thoroughly. The resulting mixture was filled in hard (gelatin) to give capsules.

Table 10

Component	mg/capsule
Clomipramine hydrochloride	8.4

(Clomipramine free base)	(7.5)
Sertraline hydrochloride (Sertraline free base)	12.6 (11.3)
Fluoxetine hydrochloride (Fluoxetine free base)	6.6 (5.9)
Microcrystalline cellulose	113.4
Corn starch	50.0
Sodium starch glycolate	5.0
Sodium lauryl sulfate	2.0
Magnesium stearate	2.0
Total weight	200.0

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

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What is claimed is:

1. A pharmaceutical composition for the treatment of premature ejaculation, comprising clomipramine or a pharmaceutically acceptable salt thereof, sertraline or a pharmaceutically acceptable salt thereof and fluoxetine or a pharmaceutically acceptable salt thereof as active ingredients.

2. The composition of claim 1, wherein clomipramine or a pharmaceutically acceptable salt thereof, sertraline or a pharmaceutically acceptable salt thereof and fluoxetine or a pharmaceutically acceptable salt thereof are contained in the weight ratio of 1 : 1~2 : 0.5~1.

3. The composition of claim 1, wherein the pharmaceutically acceptable salt is a hydrochloride.

4. The composition of claim 1, which further comprises a pharmaceutically acceptable carrier.

5. The composition of claim 4, wherein the pharmaceutically acceptable carrier is selected from the group consisting of excipients, disintegrants, binders, lubricants, emulsifiers, suspending agents, stabilizers, sweeteners, flavoring agents and a combination thereof.

6. The composition of claim 1, which further comprises a drug selected from the group consisting of serotonin agonists, serotonin antagonists, adrenergic agonists, adrenergic antagonists, adrenergic neuron blockers, impotence treatment drugs, phosphodiesterase 5 inhibitors, erection inducers and a combination thereof.

7. An oral unit dosage form for the treatment of premature ejaculation, comprising the composition of claim 1 and a pharmaceutically acceptable carrier.

8. The oral unit dosage form of claim 7, which is selected from the group consisting of tablet, capsule, suspension, granule, gel, pill, tincture, decoction, infusion, spirit, fluid extract, elixir, extract, syrup, powder, aromatic water and

lemonade.

9. The oral unit dosage form of claim 7, which comprises 0.7~75.0 mg of clomipramine, 1.1~113.0 mg of sertraline and 0.5~59.0 mg of fluoxetine.

10. The oral unit dosage form of claim 7, which comprises 0.7~22.5 mg of clomipramine, 1.1~33.9 mg of sertraline and 0.5~17.7 mg of fluoxetine.

11. The oral unit dosage form of claim 7, which comprises 2.2~22.5 mg of clomipramine, 3.3~33.9 mg of sertraline and 1.7~17.7 mg of fluoxetine.

12. The oral unit dosage form of claim 7, wherein the pharmaceutically acceptable carrier is selected from the group consisting of excipients, disintegrants, binders, lubricants, emulsifiers, suspending agents, stabilizers, sweeteners, flavoring agents and a combination thereof.

13. The oral unit dosage form of claim 7, which further comprises a drug selected from the group consisting of serotonin agonists, serotonin antagonists, adrenergic agonists, adrenergic antagonists, adrenergic neuron blockers, impotence treatment drugs, phosphodiesterase 5 inhibitors, erection inducers and a combination thereof.

FIG. 1

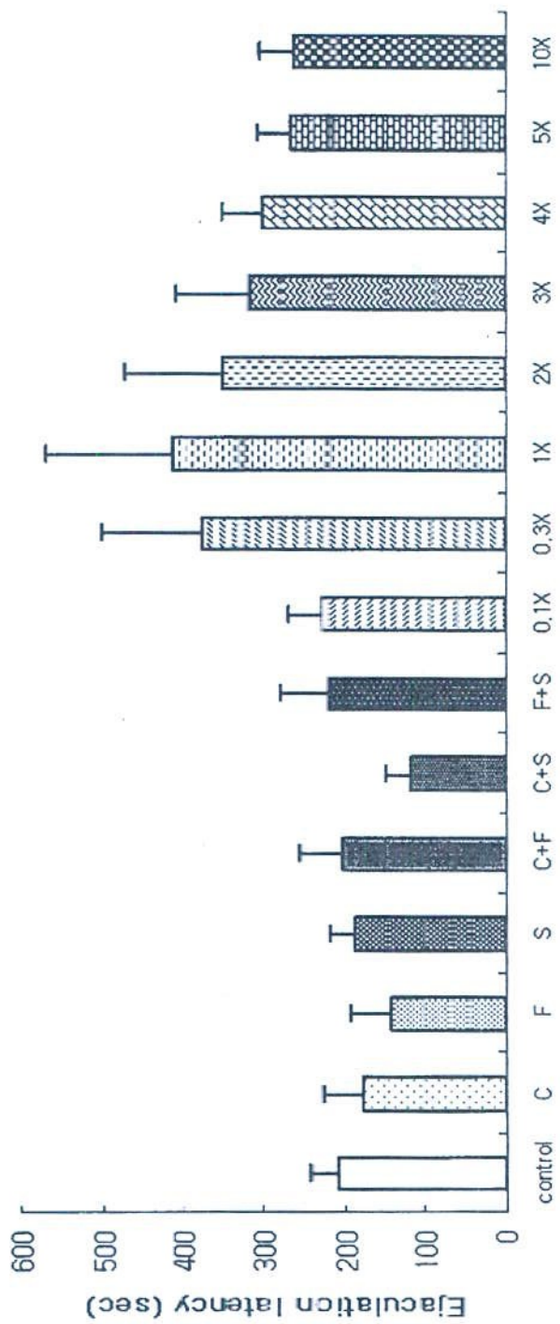
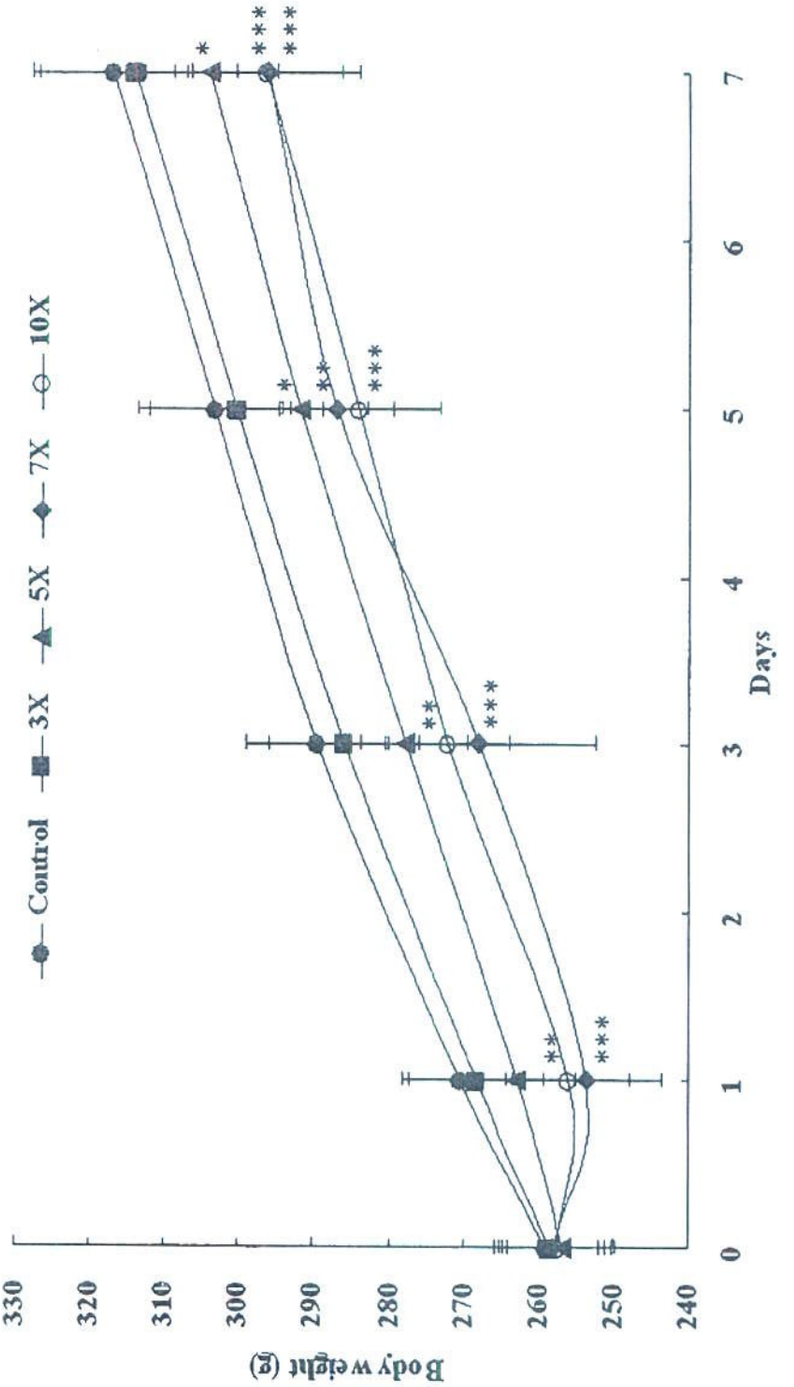

Ejaculation latency (sec)
600
500
400
300
200
100
0
control
C
F
S
C+F
C+S
F+S
0.1X
0.3X
1X
2X
3X
4X
5X
10X

FIG. 2


Control
3X
5X
7X
10X
Body weight (g)
Days
330
320
310
300
290
280
270
260
250
240
0
1
2
3
4
5
6
7
*
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(54) Title: THE USE OF ALFUZOSIN OR TERAZOSIN IN THE TREATMENT OF PREMATURE EJACULATION

(57) Abstract

The use of the a1-blockers drugs, alfuzosin and terazosin in the treatment of premature ejaculation is disclosed.

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THE USE OF ALFUZOSIN IN THE TREATMENT OF PREMATURE EJACULATION

The present invention relates to the use of α1 blockers in the treatment of premature ejaculation.

Primitive psychogenic premature ejaculation is regarded as the most common sexual disorder of the male.

At present, the treatment of choice is psychotherapy, either as a behavioural dual team sex therapy according to Master & Johnson protocol, or individual psychotherapy (Rifelli and Moro. Sessuologia Clinica. Bologna, 1989). The first proved to be active in about 80% of the cases, and it needs an active couple with a strong background of conjugal life free from conflictualities, while the second proved to be active in 40%-60% of the cases (1). This means that a large amount of males do not benefit from the psychotherapy and still suffer from premature ejaculation.

Ejaculation is a centrally integrated peripheral evoked reflex, which occurs thanks to an α1 adrenergic receptor activation.

Effective pharmacological drugs for the treatment of premature ejaculation exist, but they suffer from severe side effects, for example clomipramine and phenoxybenzamine. Other treatments have a limited effectiveness (metoclopramide and the like).

Now it has been found that two specific α1 blockers, alfuzosine and terazosine, are effective in the treatment of psychogenic premature ejaculation

Particularly, said drugs turned out to be effective in patients who proved to have no benefit from psychological therapy.

Therefore, it is an object of the present invention the use of alfuzosine and terazosine and the pharmaceutically acceptable salts thereof for the preparation of a medicament useful for the treatment of psychogenic premature ejaculation.

Alfuzosine and terazosine are α1 blockers used in the treatment of hypertension or in the symptomatic treatment of benign prostatic hyperplasia. Up to now no paper can be found in literature about any possible use thereof in the treatment of psychogenic premature ejaculation, particularly in patients resistant to psychotherapy.

In the following, the clinical evaluation of alfuzosine and terazosine is illustrated.

107 Patients complaining psychogenic premature ejaculation were tested during 2 years. Age range was 21-63 years, mean age 34.3 years: all of them were put into a blind cross-over prospective controlled trial.

Alfuzosine, terazosine and placebo (vitamin C) were used.

Criteria for the participation in the study were absence of: uncontrolled hypertension, orthostatic hypotension, thyroid diseases, uncontrolled diabetes, recent miocardial infarction, use of alfuzosine or of terazosine in the previous 4 months, sexual life characterised by occasional intercourses.

The patients were randomized in three groups: two of 36 and one of 35 patients. Each group used

alfuzosine, terazosine or placebo in a different order. The first group used the drugs as follows: alfuzosine, terazosine, placebo; the second group used first terazosine, followed by placebo and alfuzosine; the third group used first placebo, then alfuzosine and finally terazosine. Each drug was used during two months. Alfuzosine dosage was 2x3 mg/day, terazosine 5 mg/day once a day (the dosage was gradually reached starting from 1 mg/day) and vitamin C 500x2 mg/day.

Six patients dropped out from the study for unknown causes, and 4 patients had to be discharged from the study due to the side effects of the drugs.

At the end of each two-month period of treatment, the patients and their partners were separately asked wether or not they were satisfacted by the activity of the drugs: i.e. wether or not time required to reach ejaculation had been prolonged enough to be satisfactory for both. In 6 cases a disagreement about the times of orgasmic latency was evidenced between patients and their partners and therefore these were discharged from the study.

At the end of the study, 91 cases were evaluated, which were subdivided into a first group of 30 patients, a second of 30 and a third of 31. Results were categorized as follows: positive (satisfactory for both partners) or negative (unsatisfactory for both partners). Data were analyzed with the chi square test.

The results are listed in the following tables.

Table 1 shows the activity of the drugs: alfuzosine proved to be active in 42 patients (46.2%), terazosine in 48 (53,7%) and placebo in 22 (24,2%).

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Table 1

Effect of α1-blockers in the treatment of premature ejaculation psychogenic

I group	alfuzosine	terazosine	placebo
positive results	14 (46.7%)	16 (53.3%)	8 (26.7%)
negative results	16 (53.3%)	14 (46.7%)	22 (73.3%)
TOTAL	30	30	30
II group	terazosine	placebo	alfuzosine
positive results	15 (50.0%)	10 (33.3%)	13 (43.3%)
negative results	15 (50.0%)	20 (66.7%)	17 (56.7%)
TOTAL	30	30	30
III group	placebo	alfuzosine	terazosine
positive results	4 (12.9%)	16 (51.6%)	17 (54.8%)
negative results	27 (87.1%)	15 (48.4%)	14 (45.2%)
TOTAL	31	31	31

The results prove that alfuzosine and terazosine are significantly more active than placebo (chi square 8.70, $p<0.05$ and 14.50, $p<0.01$ respectively) whereas non significant differences were evidenced between alfuzosine and terazosine (chi square 0.55, p not significant). When placebo was used as first (III group), this turned out to be active for 12.9% of cases,; on the other hand, when used after the α-blocker, it proved effective in about 30% of cases, a trend which, even though suggestive, is not significant (chi square 2.55).

Table 2 shows side-effects. The 4 patients who had been discharged from the clinical evaluation were also considered.

Table 2

Side effects induced by the treatment with alfuzosine, terazosine and placebo.

	Appearance of side effects	No side effects
Alfuzosine	5^ (5.2%)	90 (94.8%)
Terazosine	3* (3.2%)	90 (96.7%)
Placebo	1+ (1.1%)	90 (98.9%)

^ 3 patients reported hypotension (2 patients of group 1 interrupted the treatment and received no terazosine), 1 hypotension and epigastralgia, 1 epigastralgia.

* 2 patients of group 2 reported hypotension, interrupted the treatment and received no placebo, 1 reported headache.

\+ 1 patient reported slight epigastralgia.

The results of clinical evaluation prove that α1-blockers alfuzosine and terazosine are effective in the treatment of psychogenic premature ejaculation, particularly in patients resistant to psychotherapy. The use of said drugs proved to be safe from the side effects point of view.

The dosage will be determined by the physician depending on the severity of the pathology and the general conditions of the patient.

Generally, dosages from 1 to 8 mg/day for alfuzosine and from 3 to 15 mg/day for terazosine can be envisaged, possibly subdivided into more daily doses.

According to another object of the invention, alfuzosine and terazosine can also be used in combination in the same medicament, or in combination with one or more compounds effective in the treatment

of premature ejaculation, such as antiandrogens, metoclopramide, clomipramine, phenoxybenzamine, prazosine and lorazepam.

The preferred administration route is the oral one, but other administration routes can also be envisaged.

According to the invention, the drugs herein described will be administered in form of pharmaceutical compositions which can be prepared according to conventional procedures, for example as described in Remington's Pharmaceutical Sciences Handbook, XVII ed. Mack, Pub., USA.

Examples of pharmaceutical compositions are tablets, capsules sugar-coated pills, syrups, chewable formulations; suppositories and injectable formulations (intravenous, subcutaneous, intramuscular).

CLAIMS

1. The use of alfuzosine and the pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment of psychogenic premature ejaculation.

2. The use of terazosine and the pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment of psychogenic premature ejaculation.

3. The use of alfuzosine and the pharmaceutically acceptable salts thereof in combination with one or more compounds selected from antiandrogens, metoclopramide, clomipramine, phenoxybenzamine, prazosine and lorazepam for the preparation of a medicament for the treatment of psychogenic premature ejaculation.

4. The use of terazosine and the pharmaceutically acceptable salts thereof in combination with one or more compounds selected from antiandrogens, metoclopramide, clomipramine, phenoxybenzamine, prazosine and lorazepam for the preparation of a medicament for the treatment of psychogenic premature ejaculation.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/03661

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/505

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)
IPC 6 A61K

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Inter nal Application No
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REFORMAS

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VIGENCIA: INDEFINIDA

CERTIFICA

OBJETO SOCIAL. LA SOCIEDAD EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ REALIZAR, ENTRE OTROS, LAS SIGUIENTES ACTIVIDADES COMERCIALES Y EMPRESARIALES: 2.1) FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISICLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS. COLORANTES, DE PERFUMERÍA, DISPOSITIVOS MÉDICOS Y AFINES. 2.2) LA REPRESENTACIÓN DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. 2.3) FABRICACIÓN, IMPORTACIÓN, DISTRIBUCIÓN Y VENTA DE CUALESQUIERA TIPO DE PRODUCTOS VETERINARIOS. 2.4) LA REALIZACIÓN DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. 2.5) IMPORTAR CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS. REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES, DE PERFUMERÍA, DISPOSITIVOS MÉDICOS Y

AFINES Y/O PRODUCTOS INTERMEDIOS O A GRANEL. PARÁGRAFO UNO: EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAÍCES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAÍCES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR EN MUTUO DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN O NO LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS, O CUALESQUIERA OTRAS EMPRESAS DE OTROS OBJETOS SOCIALES. PARÁGRAFO DOS: ADEMÁS DE LAS ACTIVIDADES REFERIDAS EN ESTE ARTICULO, Y LAS ENUNCIADAS EN EL PARÁGRAFO UNO, COMO SOCIEDAD POR ACCIONES SIMPLIFICADA, PODRÁ REALIZAR CUALQUIER ACTIVIDAD LICITA DE COMERCIO EN EL PAÍS O EN EL EXTERIOR, POR EJEMPLO, Y DE MANERA ILUSTRATIVA MÁS NO LIMITATIVA, GESTIÓN DE LICENCIAS, REGISTROS DE EXPORTACIÓN O IMPORTACIÓN, CONVENIOS RELATIVOS A ESAS ACTIVIDADES Y LOS ACTOS RELACIONADOS CON EL MISMO. PARÁGRAFO TRES: POR RAZÓN DE SU OBJETO SOCIAL, LA SOCIEDAD NO PODRÁ CONSTITUIRSE GARANTE NI FIADORA DE OBLIGACIONES DISTINTAS DE LAS PROPIAS NI GARANTIZAR CON SUS BIENES OBLIGACIONES DE TERCEROS, A MENOS QUE LO AUTORICE EN CADA CASO LA ASAMBLEA GENERAL DE ACCIONISTAS CON EL VOTO DE LA TOTALIDAD DE LOS MIEMBROS PRESENTES EN LA REUNIÓN CORRESPONDIENTE.

CERTIFICA

DIRECCIÓN Y ADMINISTRACIÓN. LA DIRECCIÓN Y ADMINISTRACIÓN DE LA SOCIEDAD ESTARÁ A CARGO DE: A) LA ASAMBLEA GENERAL DE ACCIONISTAS; Y B) LOS REPRESENTANTES LEGALES COMO SE DESCRIBEN EN SUS CARGOS Y FUNCIONES EN LOS PRESENTES ESTATUTOS.

REPRESENTACIÓN LEGAL. ADMINISTRACIÓN. LA ADMINISTRACIÓN DE LA SOCIEDAD CORRESPONDE AL REPRESENTANTE LEGAL, QUE SE DENOMINARÁ GERENTE, QUIEN TENDRÁ HASTA CINCO SUPLENTES. EL GERENTE Y SUS SUPLENTES SERÁN LOS REPRESENTANTES LEGALES QUIENES SERÁN DESIGNADOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS POR UN TÉRMINO INDEFINIDO Y SE MANTENDRÁN VIGENTES HASTA TANTO ESTOS NO SEAN REMOVIDOS DE SUS CARGOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS. LOS SUPLENTES REEMPLAZARÁN AL GERENTE, DURANTE SUS AUSENCIAS TEMPORALES, ABSOLUTAS O ACCIDENTALES.

FUNCIONES DEL REPRESENTANTE LEGAL.: SON FUNCIONES DEL GERENTE: (A) REPRESENTAR A LA SOCIEDAD ANTE LOS ACCIONISTAS, ANTE TERCEROS Y ANTE AUTORIDADES DE LOS ÓRDENES ADMINISTRATIVO O JURISDICCIONAL, CON FACULTADES PARA TRANSIGIR, COMPROMETER Y DESISTIR Y PARA COMPARECER EN JUICIO; (B) SUPERVISAR EL COMPORTAMIENTO DE LOS EMPLEADOS DE LA SOCIEDAD PARA ASEGURAR EL CUMPLIMIENTO DE SUS OBLIGACIONES. (C) CUMPLIR Y HACER CUMPLIR LAS DETERMINACIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. (D) PRESENTAR, EN LAS REUNIONES ORDINARIAS DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL BALANCE GENERAL DE LOS NEGOCIOS DEL RESPECTIVO EJERCICIO, JUNTO CON EL ESTADO DE RESULTADOS, UN PROYECTO SOBRE DISTRIBUCIÓN DE UTILIDADES O SOBRE CANCELACIÓN DE PÉRDIDAS, JUNTO CON UN INFORME SOBRE EL ESTADO DE LOS NEGOCIOS DE LA SOCIEDAD. (E) SUMINISTRAR A LA ASAMBLEA GENERAL DE ACCIONISTAS LOS INFORMES QUE ÉSTAS LE SOLICITEN. (F) OTORGAR LOS PODERES QUE SEAN NECESARIOS PARA LA DEFENSA O REPRESENTACIÓN DE LA SOCIEDAD. (G) SOMETER LAS DIFERENCIAS QUE PUEDAN SURGIR ENTRE LA SOCIEDAD Y TERCEROS A LA DECISIÓN DE ÁRBITROS Y CONCURRIR A LA DESIGNACIÓN DE DICHOS ÁRBITROS Y DEL APODERADO QUE HAYA DE REPRESENTARLA ANTE EL RESPECTIVO TRIBUNAL. (H) EJERCER LIBREMENTE TODOS LOS ACTOS Y ACUERDOS APROPIADOS Y NECESARIOS PARA EL CUMPLIMIENTO DEL OBJETO SOCIAL, Y (I) EJERCER LAS DEMÁS ATRIBUCIONES QUE LE CONFIEREN LAS LEYES Y LOS ESTATUTOS SOCIALES Y LAS DEMÁS QUE LE CORRESPONDAN EN RAZÓN DE LA NATURALEZA DE SU CARGO.

EL GERENTE REQUIERE AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA LLEVAR A CABO LOS SIGUIENTES ACTOS:

1. CELEBRAR TODA CLASE DE CONTRATOS CUYO OBJETO SEA LA APERTURA DE SUCURSALES, AGENCIAS O DEPENDENCIAS, O LA EMISIÓN DE BONOS DE LA SOCIEDAD.

2. APROBAR, CUALQUIERA SEA SU NATURALEZA, TODOS LOS ACTOS QUE IMPLIQUEN RENUNCIA A DERECHOS DE LA SOCIEDAD, TALES COMO TRANSACCIONES, DESISTIMIENTOS, CONCILIACIONES O ACTOS DE SIMILAR NATURALEZA, CUYA CUANTÍA ABSOLUTA SEA SUPERIOR AL EQUIVALENTE EN MONEDA LEGAL COLOMBIANA A LA SUMA DE QUINIENTOS MIL DÓLARES DE LOS ESTADOS UNIDOS DE AMÉRICA (USD $500.000.00). EN LOS ASUNTOS DE NATURALEZA LABORAL ESTE REQUISITO SE EXIGIRÁ CUANDO LA REMUNERACIÓN ANUAL DEL RESPECTIVO TRABAJADOR SEA SUPERIOR A SEISCIENTOS CINCUENTA SALARIOS MÍNIMOS LEGALES MENSUALES VIGENTES (650 SMLMV) DE LA REPÚBLICA DE COLOMBIA.

3. INICIAR CUALQUIER ACCIÓN JUDICIAL O ADMINISTRATIVA CUYA CUANTÍA ABSOLUTA SEA SUPERIOR AL EQUIVALENTE EN MONEDA LEGAL COLOMBIANA A LA SUMA DE QUINIENTOS MIL DÓLARES DE LOS ESTADOS UNIDOS DE AMÉRICA (USD $500.000.00).

4. SUSCRIBIR O REALIZAR CUALQUIER CONTRATO, ACUERDO, ACTO U OPERACIÓN PARA LA ADQUISICIÓN, VENTA, CESIÓN, TRASPASO O DISPOSICIÓN DE ACTIVOS FIJOS DE LA SOCIEDAD CUYO VALOR EN PESOS COLOMBIANOS, O EN CUALQUIER OTRA MONEDA EXCEDA DE UN MILLÓN DE DÓLARES DE LOS ESTADOS UNIDOS DE AMÉRICA (USD $1.000.000).

5. GRAVAR O ASUMIR CUALQUIER GRAVAMEN SOBRE LOS ACTIVOS FIJOS DE LA SOCIEDAD, CUALQUIERA QUE SEA SU VALOR.

6. OTORGAR GARANTÍAS POR PARTE DE LA SOCIEDAD PARA GARANTIZAR OBLIGACIONES DE TERCEROS, SALVO POR/AS OBLIGACIONES DE COMPAÑÍAS FINALES DE LA SOCIEDAD.

7. LAS OPERACIONES FINANCIERAS Y BANCARIAS DEBEN REALIZARSE DE ACUERDO CON LAS POLÍTICAS ESTABLECIDAS POR LA ASAMBLEA GENERAL DE ACCIONISTAS, QUIEN CONFORMARÁ UN COMITÉ DE FINANZAS, PARA ESTE FIN.

PARA CALCULAR EL EQUIVALENTE DE LOS MONTOS ANTERIORES EN PESOS COLOMBIANOS, SERÁ USADA LA TASA REPRESENTATIVA DEL MERCADO (TRM) CERTIFICADA POR LA SUPERINTENDENCIA FINANCIERA O LA ENTIDAD COMPETENTE PARA EL DÍA EN QUE SE SUSCRIBA O REALICE LA TRANSACCIÓN.

CERTIFICA

DOCUMENTO: ACTA No. 134 DEL 26 DE SEPTIEMBRE DE 2014
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE OCTUBRE DE 2014 No. 13926 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

GERENTE
MANUEL CAMILO CAMACHO PEREZ
C.C.80504680

PRIMER SUPLENTE DEL GERENTE
MARIO FRANCISCO PEREZ ANZOLA
C.C.79656956

SEGUNDO SUPLENTE DEL GERENTE
MARIA ISABEL RIVAS PARRA
C.C.52251884

Cámara de Comercio de Cali

CODIGO DE VERIFICACION: 08159ZS8JS
NUMERO DE RADICACION: 20150846719-INT
FECHA DE IMPRESION: VIERNES 27 NOVIEMBRE 2015 08:46:43
PAGINAS: 5 - 9

CERTIFICA

DOCUMENTO: ACTA No. 135 DEL 02 DE OCTUBRE DE 2014
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE OCTUBRE DE 2014 No. 13929 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

TERCER SUPLENTE DEL GERENTE
FRANCISCO JAVIER PICART LAURENZ
C.E.399661

CUARTO SUPLENTE DEL GERENTE
TITO NOE PARRA MURILLO
C.C.79579680

CERTIFICA

DOCUMENTO: ACTA No. 130 DEL 15 DE MAYO DE 2013
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 28 DE MAYO DE 2013 No. 6165 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL FIRMA
BDO AUDIT S.A.
NIT.860600063-9

CERTIFICA

DOCUMENTO: DOCUMENTO PRIVADO DEL 26 DE MAYO DE 2014
ORIGEN: BDO AUDIT S.A.
INSCRIPCION: 27 DE MAYO DE 2014 No. 7276 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL
JESUS DAVID CASTELLANOS ORDOÑEZ
C.C.91486018

CERTIFICA

DOCUMENTO: DOCUMENTO PRIVADO DEL 04 DE JUNIO DE 2014
ORIGEN: BDO AUDIT S.A.
INSCRIPCION: 09 DE JUNIO DE 2014 No. 7877 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL SUPLENTE
CARLOS ANDRES BUENO PORTILLA
C.C.16506322

CERTIFICA

CAPITAL AUTORIZADO: $40,000,000,224
NUMERO DE ACCIONES: 3,333,333,352
VALOR NOMINAL: $12
CAPITAL SUSCRITO: $24,140,480,940
NUMERO DE ACCIONES: 2,011,706,745
VALOR NOMINAL: $12
CAPITAL PAGADO: $24,140,480,940
NUMERO DE ACCIONES: 2,011,706,745
VALOR NOMINAL: $12

CERTIFICA

CERTIFICA ESPECIAL POR VOLUNTAD DEL USUARIO:

DOCUMENTO: DOCUMENTO PRIVADO DEL 22 ENERO DEL 2015
INSCRIPCIÓN: 11 DE FEBRERO DE 2015 NRO. 1943 DEL LIBRO IX

CONSTA EL GRUPO EMPRESARIAL :

MATRIZ: ABBOTT INVESTMENTS LUXEMBOURG S.A.R.L.
DOMICILIO: LUXEMBURGO
NACIONALIDAD: LUXEMBURGUESA
ACTIVIDAD: PARTICIPAR DE CUALQUIER FORMA EN CUALQUIER ACTIVIDAD DE TIPO COMERCIAL, INDUSTRIAL, FINANCIERA U OTRA, EN LUXEMBURGO O EN CUALQUIER COMPAÑÍA O EMPRESA EXTRANJERA.

SUBORDINADA: ABBOTT LABORATORIES DE COLOMBIA S.A
NIT: 860002134-8
DOMICILIO: BOGOTA D.C.
NACIONALIDAD: COLOMBIANA.
ACTIVIDAD: IMPORTACION, EXPORTACION, DISTRIBUICION, COMPRA Y VENTA DE TODA CLASE DE MEDICAMENTOS Y PRODUCTOS QUIMICOS Y FARMACÉUTICOS Y ESPECIALIDADES MEDICINALES PARA USO HUMANO Y VETERINARIO.

SUBORDINADA: LABORATORIOS SYNTHESIS S.A.S
NIT; 860000760-1
DOMICILIO: BOGOTA D.C
NACIONALIDAD: COLOMBIANA.
ACTIVIDAD: IMPORTACION, EXPORTACION, FABRICACIÓN, COMERCIALIZACION, DISTRIBUCION Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIENICOS, VETERINARIOS E IMPLEMENTOS MEDICOS.

SUBORDINADA: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.
NIT.890301463-8

DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: LA FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO, DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO

SUBORDINADA: AMERICAN GENERICS S A S
NIT. 800223214-9
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TITULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS, ETC.

SUBORDINADA: LABORATORIOS NATURMEDIK S.A.S.
NIT. 800226363-1
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TITULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS, ETC.

SUBORDINADA: LABORATORIOS PAULY PHARMACEUTICAL S.A.S.
NIT: 800.097.402-6
DOMICILIO: CALI, VALLE
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TÍTULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS ETC.

SUBORDINADA: DISTRIBUCIONES UQUIFA S.A.S.
NIT: 800182021-7
DOMICILIO: CALI, VALLE
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TÍTULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS ETC.

SUBORDINADA: FOCUS PHARMACEUTICAL S.A.S
NIT: 900.104.555-8
DOMICILIO: CALI, VALLE
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TÍTULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS ETC.

SUBORDINADA: LAFRANCOL PERU S.R.L.
DOMICILIO:LIMA
NACIONALIDAD: PERUANA
ACTIVIDAD: DISTRIBUCION Y COMERCIALIZACION DE PRODUCTOS FARMACEUTICOS DE USO HUMANO.

SUBORDINADA: LAFRANCOL DOMINICANA S.A.S.
DOMICILIO: SANTO DOMINGO
NACIONALIDAD: REPUBLICA DOMINICANA
ACTIVIDAD: FABRICACION DE PRODUCTOS FARMACEUTICOS.

SUBORBINADA: LAFRANCOL GUATEMALA S.A.
DOMICILIO: GUATEMALA
NACIONALIDAD: GUATEMALTECA
ACTIVIDAD: PRODUCCION, FABRICACION, EXPORTACION Y DISTRIBUCION DE PRODUCTOS FARMACEUTICOS Y/O ALIMENTICIOS Y NATURALES DE CONSUMO HUMANO Y LA COMERCIALIZACION DE TODA CLASE DE MERCANCIAS POR CUENTA PROPIA O EN NOMBRE DE TERCEROS.

PRESUPUESTO DE CONTROL: ABBOTT INVESTMENTS LUXEMBOURG S.A. R.L ADQUIRIÓ EL 26 DE SEPTIEMBRE DE 2014 UNA PARTICIPACIÓN INDIRECTA DE MAS DEL 50% DEL CAPITAL DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL SAS.
UNA PARTICIPACIÓN INDIRECTA EN EL CAPITAL DE LAS SOCIEDADES ACTUALMENTE REGISTRADAS COMO SUBORDINADAS DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S EN COLOMBIA Y EN EL EXTERIOR (LAS SOCIEDADES SUBORDINADAS A SABER: AMERICAN GENERICS S A S, LABORATORIOS NATURMEDIK S.A.S., LABORATORIOS PAULY PHARMACEUTICAL S.A.S., DISTRIBUCIONES UQUIFA S.A.S., FOCUS PHARMACEUTICAL S.A.S. LAFRANCOL PERU SRL, LAFRANCOL DOMINICANA S.A.S, LAFRANCOL GUATEMALA S.A.)
UNA PARTICIPACIÓN INDIRECTA DE MAS DEL 50% DEL CAPITAL DE LABORATORIOS SYNTHESIS S.A.S, CON DOMICILIO EN BOGOTA E IDENTIFICADA CON NIT: 860000760-1
ABBOTT INVESTMENTE LUXEMBOURG S.A.R.L. TIENE UNA PARTICIPACIÓN DIRECTA DEL MAS DEL 50% EN EL CAPITAL DE ABBOT LABORATORIES DE COLOMBIA S.A SITUACION DE CONTROL QUE FUE REGISTRADA MEDIANTE DOCUMENTO PRIVADO DEL 15 DE OCTUBRE DE 2013, INSCRITO EL 22 DE OCTUBRE DEL MISMO AÑO.
ADEMÁS DEL VÍNCULO DE SUBORDINACIÓN POR PARTICIPACIÓN QUE EXISTE ENTRE ABBOTT INVESTMENTS LUXEMBOURG S.A. R.L. (SOCIEDAD CONTROLANTE) Y LAS SOCIEDADES COLOMBIANAS ABBOTT LABORATORIES DE COLOMBIA S.A., LABORATORIOS SYNTHESIS S.A.S., LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S, Y LAS SOCIEDADES SUBORDINADAS, EN LOS TÉRMINOS DEL NUMERAL 1 DEL ARTÍCULO 261 DEL CÓDIGO DE COMERCIO; EXISTE ENTRE DICHAS SOCIEDADES UNIDAD DE PROPÓSITO Y DIRECCIÓN, SEGÚN LO DISPUESTO EN EL ARTÍCULO 28 DE LA LEY 222 DE 1995. POR LO TANTO, SE CONFIGURA UN GRUPO EMPRESARIAL A PARTIR DEL 26 DE SEPTIEMBRE DE 2014.

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.5234-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL UBICADO EN: ---K 1 46 84 DE CALI
RENOVO : POR EL AÑO 2015

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.870576-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS FRANCO COLOMBIANO LAFRANCOL SAS UBICADO EN: CL. 36 A NRO. 4 03 DE CALI
FECHA MATRICULA : 02 DE MAYO DE 2013
RENOVO : POR EL AÑO 2015

CERT FICA

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 27 DE MARZO DE 2015

Cámara de Comercio de Cali

CODIGO DE VERIFICACION: 08159ZS8JS
NUMERO DE RADICACION: 20150846719-INT
FECHA DE IMPRESION: VIERNES 27 NOVIEMBRE 2015 08:46:43
PAGINAS: 9 - 9

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CERTIFICA

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL PRESENTE CERTIFICADO.
LOS ACTOS ADMINISTRATIVOS DE REGISTRO QUEDAN EN FIRME DIEZ (10) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS.

LA PERSONA O ENTIDAD A LA QUE USTED LE VA A ENTREGAR EL CERTIFICADO PUEDE VERIFICAR, POR UNA SOLA VEZ, SU CONTENIDO INGRESANDO A http://www.ccc.org.co/registraya/ Y DIGITANDO EL CODIGO DE VERIFICACION QUE SE ENCUENTRA EN EL ENCABEZADO DEL PRESENTE DOCUMENTO.
EL CERTIFICADO A VALIDAR CORRESPONDE A LA IMAGEN Y CONTENIDO DEL CERTIFICADO CREADO EN EL MOMENTO EN QUE SE GENERO EN LAS SEDES O A TRAVES DE LA PLATAFORMA VIRTUAL DE LA CAMARA.

ESTE CERTIFICADO CUENTA CON PLENA VALIDEZ JURIDICA SEGUN LO DISPUESTO EN LA LEY 527 DE 1999. EN EL SE INCORPORAN TANTO LA FIRMA MECANICA QUE ES UNA REPRESENTACION GRAFICA DE LA FIRMA DEL SECRETARIO DE LA CAMARA DE COMERCIO DE CALI, COMO LA FIRMA DIGITAL , LAS CUALES PODRA VERIFICAR A TRAVES DE SU APLICATIVO VISOR DE DOCUMENTOS PDF.
LA PERSONA O ENTIDAD A LA QUE USTED LE VA A ENTREGAR EL CERTIFICADO PUEDE VERIFICAR, POR UNA SOLA VEZ, SU CONTENIDO INGRESANDO A http://www.ccc.org.co/registraya/ Y DIGITANDO EL CODIGO DE VERIFICACION QUE SE ENCUENTRA EN EL ENCABEZADO DEL PRESENTE DOCUMENTO.
EL CERTIFICADO A VALIDAR CORRESPONDE A LA IMAGEN Y CONTENIDO DEL CERTIFICADO CREADO EN EL MOMENTO EN QUE SE GENERO EN LAS SEDES O A TRAVES DE LA PLATAFORMA VIRTUAL DE LA CAMARA.
DADO EN CALI A LOS 27 DIAS DEL MES DE NOVIEMBRE DEL AÑO 2015 HORA: 08:46:43 AM