66

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00029997 00000002 Folios: 9
Fecha (AMD): 2001-02-12 15:46:39
Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEME
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE INSCRIPCIÓN DE AFECTACIONES
2000-9

1)	
☒ Patente de invención	☐ Marca Colectiva
☐ Patente de Modelo de Utilidad	☐ Marca de certificación
☐ Diseño Industrial	☐ Lema comercial
☐ Esquema de Trazado de Circuitos Integrados	☐ Nombre Comercial
	☐ Enseña Comercial
	☐ Marcas de Productos y Servicios

2) ☐ Trasferencias ☐ Cambio de domicilio ☐ Prendas ☒ Modificación o limitación a reivindicaciones ☐ Cambio de nombre ☐ Cambio de dirección ☐ Embargo

3) SOLICITANTE	Nombre: Lilly Icos LLC Dirección 1209 Orange Street Wilmington, Delaware 19801, Estados Unidos Teléfono: Fax: E. Mail: Domicilio: Wilmington, Delaware, Estados Unidos	**IDENTIFICACIÓN** C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO_____
4) REPRESENTATE O APODERADO	Nombre: DILIA MARÍA RODRÍGUEZ D´ALEMAN Dirección: Carrera 11 N°. 93-43 Of. 404 Santafé de Bogotá D.C. Teléfono: 6350835 Fax: 6350824 E. Mail: clarkemodet@clarkemodet.com.co	**IDENTIFICACIÓN** C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ

5) DATOS DE LA INSCRICPICION
Título de la nueva creación o denominación del signo distintivo:

ARTÍCULOS DE FABRICACIÓN

Clasificación:_____ Número de expediente o certificado: 00029997

Número de expediente o certificado de registro de marca sociada (Si es lema):

Vigencia:

TRANSFERENCIA	CAMBIO DE NOMBRE	CAMBIO DE DOMICILIO
DE: **DOMICILIO:** **A:** **DOMICILIO:**	**DE:** **A:**	**DE:** **A:**

67

Industria y Comercio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00029997 00000002 Folios: 9
Fecha (AMD): 2001-02-12 15:46:39
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NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 01 - 8,429
FECHA : FEBRERO 12 DE 2001

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	3143050	12/02/2001	73,440.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	73,440.00
		TOTAL : $	73,440.00

SON: SETENTA Y TRES MIL CUATROCIENTOS CUARENTA PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 350 5220
e-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C.,Colombia

68 3

TRANSFERENCIA	CAMBIO DE NOMBRE	CAMBIO DE DOMICILIO
DE: DOMICILIO: A: DOMICILIO:	DE: A:	DE: A:

MODIFICACIÓN O LIMITACIÓN A REIVINDICACIONES

Se presenta nuevo capítulo reivindicatorio, el cual reemplaza al inicialmente presentado con la solicitud.

6) **COMPROBANTE DE PAGO N°.** 8429 **FECHA:** Feb 12/01

7) **ANEXOS:**

☒ **Comprobante de pago de la tasa**
☐ **P deres, si fuere el caso**
☐ **Documento que respalde la inscripción según sea el caso**
☐ **D cumentos que acrediten el legítimo interés, si fuere el caso**
☐ **Certificado de Existencia y representación legal de las martes, cuando sean personas jurídicas.**

Nombre: DILIA RODRÍGUEZ D´ALEMAN

FIRMA:

C.C. 41.654.882 de Bogota TP 20824 CSJ

REIVINDICACIONES

1. Un artículo de fabricación para uso farmacéutico humano, que comprende:

(a) una forma de dosificación oral que comprende de 1 a 20 mg de un inhibidor de PDE5 selectivo que tiene

(i) una diferencia de 100 veces en los valores de IC_{50} para la inhibición de PDE5 frente a PDE6,

(ii) una diferencia de 1000 veces en los valores de IC_{50} para la inhibición de PDE5 frente a PDE1c,

(iii) una IC_{50}, para la inhibición de PDE5, menor que 10 nM, y

(iv) una biodisponibilidad suficiente para que sea eficaz en dosificaciones orales unitarias de 1 a 20 mg;

(b) un prospecto dentro del empaque que establece dicho inhibidor de PDE5 es útil para tratar la disfunción sexual en un paciente que lo necesite, y que está libre de contraindicaciones asociadas con la administración del inhibidor de PDE5 a un paciente, que sufra de una condición seleccionada dentro de un grupo que incluye una enfermedad retinal, propensión a oleadas de calor, propensión a anormalidades en la visión, fallo cardiaco o congestivo de clase 1, un infarto del miocardio 90 días o mas, antes del comienzo del tratamiento de la disfunción sexual, y combinaciones de los mismos; y

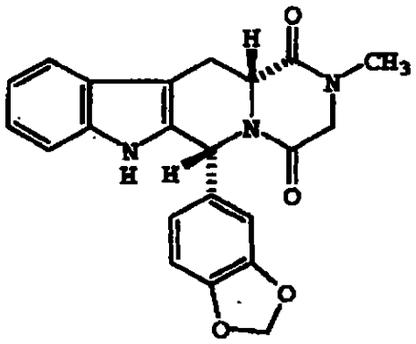
(c) un recipiente.

2. El artículo de acuerdo con la Reivindicación 1, en el que la enfermedad retinal es retinopatía diabética (o retinitis pigmentosa).

3. El artículo de acuerdo con las reivindicaciones 1 y 2, en el que la forma de dosificación oral comprende 5 mg, 10 mg o 20 mg de un inhibidor selectivo de PDE5.

4. El artículo de acuerdo con las reivindicaciones 1 a 3 en el que un prospecto dentro del empaque, establece una dosificación máxima del inhibidor selectivo de PDE5, de 20 mg por periodo de 24 horas.

5. El artículo de acuerdo con las reivindicaciones 1 a 4, en el que el inhibidor selectivo de PDE5 tiene la estructura



6. Un artículo de fabricación fundamente como el descrito anteriormente aquí en la memoria descriptiva.

7. Un método para tratar la disfunción sexual que comprende el uso de un artículo de fabricación de acuerdo con las reivindicaciones 1 a 5.

8. El artículo de acuerdo con la reivindicación 3, en el que la enfermedad retinal es retinitis pigmentosa.

9. Un artículo de fabricación para uso farmacéutico humano, que comprende:

(a) una forma de dosificación oral que comprende de 1 a 20 mg de un inhibidor selectivo de PDE5 que tiene

(i) una diferencia de 100 veces en los valores de IC_{50} para la inhibición de PDE5 frente a PDE6,

(ii) una diferencia de 1000 veces en los valores de IC_{50} para la inhibición de PDE5 frente a PDE1c,

(iii) una IC_{50} para la inhibición de PDE5, menor que 10 nM, y

(iv) una biodisponibilidad suficiente para que sea eficaz en dosificaciones orales unitarias de 1 a 20 mg;

(b) un prospecto dentro del empaque que establece que el inhibidor de PDE5, es útil para tratar la disfunción sexual en un paciente que lo necesite y que un porcentaje menor al 10% de los pacientes, presenten oleadas de calor después del tratamiento con el inhibidor de PDE5; y

(c) un recipiente.

10. Un artículo de fabricación para uso farmacéutico humano, que comprende:

(a) una forma de dosificación oral que comprende de 1 a 20 mg de un inhibidor selectivo de PDE5 que tiene

(i) una diferencia de 100 veces en los valores de IC_{50} para la inhibición de PDE5 frente a PDE6,

(ii) una diferencia de 1000 veces en los valores de IC_{50} para la inhibición de PDE5 frente a PDE1c,

(iii) una IC_{50} para la inhibición de PDE5, menor que 10 nM, y

(iv) una biodisponibilidad suficiente para que sea eficaz en dosificaciones orales unitarias de 1 a 20 mg;

(b) un prospecto dentro del empaque que dispone que el inhibidor de PDE5, es útil para tratar la disfunción sexual en un paciente que lo necesite y que un porcentaje menor al 10% de los pacientes, reporta anormalidades en la visión, después del tratamiento con el inhibidor de PDE5 en el rótulo del sildefanil; y

(c) un recipiente.

11. Un artículo de fabricación para uso farmacéutico humano, que comprende:

(a) una forma de dosificación oral que comprende de 1 a 20 mg de un inhibidor selectivo de PDE5 que tiene

(i) una diferencia de 100 veces en los valores de IC_{50} para la inhibición de PDE5 frente a PDE6,

(ii) una diferencia de 1000 veces en los valores de IC_{50} para la inhibición de PDE5 frente a PDE1c,

(iii) una IC_{50} para la inhibición de PDE5, menor que 10 nM, y

(iv) una biodisponibilidad suficiente para que sea eficaz en dosificaciones orales unitarias de 1 a 20 mg;

(b) un prospecto dentro del empaque que dispone que el inhibidor de PDE5, es útil para tratar la disfunción sexual en un paciente que lo necesite y que un porcentaje menor al 10% de los pacientes, reporta anormalidades en la visión, después del tratamiento con el inhibidor de PDE5 en el rótulo del sildefanil; y

(c) un recipiente.

12. El artículo de acuerdo con la reivindicación 11, en el que el prospecto establece que el porcentaje de pacientes que reportan anormalidades en la visión, después del tratamiento con el inhibidor de PDE5, es casi cero.

13. El uso de un inhibidor selectivo de PDE5, para la fabricación de un medicamento que contiene un prospecto en el que se establece que el inhibidor de PDE5 es útil para tratar la disfunción sexual en un paciente que lo necesite, y que está libre de cualquier contraindicación, referente a la administración del inhibidor de PDE5, a un paciente que sufra de una enfermedad retinal.

14. El uso de un inhibidor selectivo de PDE5, para la fabricación de un medicamento que contiene un prospecto en el que se establece que el inhibidor de PDE5 es útil para tratar la disfunción sexual en un paciente que lo necesite, y que un porcentaje menor al 10% de los pacientes reporta oleadas de calor después del tratamiento con el inhibidor de PDE5.

15. El uso de un inhibidor selectivo de PDE5, para la fabricación de un medicamento que contiene un prospecto en el que se establece que el inhibidor de PDE5 es útil para tratar la disfunción sexual en un paciente que lo necesite, y que el porcentaje de los pacientes que reporta oleadas de calor después del tratamiento con inhibidor de PDE5, es menor que el porcentaje de los pacientes que reportan oleadas de calor, en un rótulo del sildefanil.

16. El uso de un inhibidor selectivo de PDE5, para la fabricación de un medicamento que contiene un prospecto en el que se establece que el inhibidor de PDE5 es útil para tratar la disfunción sexual en un paciente que lo necesite, y que el porcentaje de los pacientes que reporta anormalidades en la visión después del tratamiento con el inhibidor de PDE5, es menor que el porcentaje de los pacientes que reporta anormalidades en la visión, en un rótulo del sildefanil.

17. El uso de un inhibidor selectivo de PDE5, para la fabricación de un medicamento que contiene un prospecto en el que se establece que el inhibidor de PDE5 es útil para tratar la disfunción sexual en un paciente que lo necesite, y que está libre de cualquier contraindicación, referente a la administración del inhibidor de PDE5, a un paciente que sufra una condición seleccionada dentro del grupo en el que se encuentran fallo cardiaco congestivo de clase 1, infarto de miocardio 90 días o más, antes del comienzo del tratamiento de la disfunción sexual y combinación de los anteriores.

18. Un artículo de fabricación para uso farmacéutico humano, que comprende:

(a) una forma de dosificación oral que comprende de 1 a 20 mg de un inhibidor de PDE5 selectivo que tiene

(i) una diferencia de 100 veces en los valores de IC_{50} para la inhibición de PDE5 frente a PDE6,

(ii) una diferencia de 1000 veces en los valores de IC_{50} para la inhibición de PDE5 frente a PDE1c,

(iii) una IC_{50}, para la inhibición de PDE5, menor que 10 nM, y

(iv) una biodisponibilidad suficiente para que sea eficaz en dosificaciones orales unitarias de 1 a 20 mg;

(b) un prospecto dentro del empaque que establece dicho inhibidor de PDE5 es útil para tratar la disfunción sexual en un paciente que lo necesite, y que está libre de cualquier contraindicación referente a la administración del inhibidor de PDE5 a un paciente, que sufra de una condición seleccionada dentro de un grupo en el que se encuentran fallo cardiaco o congestivo de clase 1, un infarto del miocardio 90 días o mas, antes del comienzo del tratamiento de la disfunción sexual, y combinaciones de los anteriores; y

(c) un recipiente.

P. 321 12 A 75

PA 234957

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 17, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/132,036***
FILING DATE: ***April 30, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

L. Edelen

L. EDELEN
Certifying Officer

TRADUCCION OFICIAL No. 2000/136
HILDA ASUNCION DE PIEDRAHITA
INTERPRETE OFI L
RES No 323 DEL MIN DE JUSTICIA

APPROV 48 76

Modified PTO/SB/16 (6-95)
Approved for use through 04/11/98. OMB 0651-0037
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

Docket Number	P-12929	Type a plus sign (+) inside this box -->	+

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE NAME	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Emmick	Jeffrey	Thomas	Plainfield, Indiana
Ferguson	Kenneth	Michael	Bothell, Washington
Pullman	William	Ernest	Carmel, Indiana
Whitaker	John	Steven	Woodinville, Washington

TITLE OF THE INVENTION (280 characters max)

ARTICLES OF MANUFACTURE

CORRESPONDENCE ADDRESS

Lilly ICOS LLC
c/o Eli Lilly and Company
Patent Division/D.C. 1104
Lilly Corporate Center
Indianapolis, Indiana 46285

STATE	IN	ZIP CODE	46285	COUNTRY	USA

ENCLOSED APPLICATION PARTS *(check all that apply)*

X	Specification	Number of pages	38		Small Entity Statement		
	Drawing(s)	Number of Sheets			Other (Specify)		

METHOD OF PAYMENT *(check one)*

	A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT ($)	$150.00
X	The Assistant Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 05-0840		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

X No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,
SIGNATURE _____ Date 04/30/99

TYPED or PRINTED NAME STEVEN P. CALTRIDER

REGISTRATION NO. *(if appropriate)* 36,467

☐ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FOR PATENT FILING ONLY

"Express Mail" mailing label number EM564068463US Date of Deposit April 30, 1999
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C., 20231.

D'Leah R. Sanders _____
Printed Name Signature

TITLE

ARTICLES OF MANUFACTURE

FIELD OF THE INVENTION

The present invention relates to highly selective phosphodiesterase (PDE) enzyme inhibitors and to their use in pharmaceutical articles of manufacture. In particular, the present invention relates to potent inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase type 5 (PDE5) that when incorporated into a pharmaceutical product are useful for the treatment of sexual dysfunction. The articles of manufacture described herein are characterized by selective PDE5 inhibition, and accordingly, provide a benefit in therapeutic areas where inhibition of PDE5 is desired, with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes.

BACKGROUND OF THE INVENTION

The biochemical, physiological, and clinical effects of cyclic guanosine 3',5'-monosphosphate specific phosphodiesterase (cGMP-specific PDE) inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or endocrine function is desired. Type 5 cGMP-specific phosphodiesterase (PDE5) is the major cGMP

hydrolyzing enzyme in vascular smooth muscle, and its expression in penile corpus cavernosum has been reported [Taher et al., J. Urol., 149:285A (1993)]. Thus, PDE5 is an attractive target in the treatment of sexual dysfunction [Murray, DN&P 6(3):150-56 (1993)].

A pharmaceutical product, which provides a PDE5 inhibitor, is currently available and marketed under the trademark VIAGRA®. The active ingrediant in such a product is sildenafil. The product is sold as an article of manufacture including 25, 50, and 100 mg tablets and a package insert. The package insert provides that sildenafil is a more potent inhibitor of PDE5 than other known phosphodiesterases (>80 fold for PDE1, >1,000 fold for PDE2, PDE3, and PDE4). It is described as being 4,000 fold selective for PDE5 versus PDE3, and only 10 fold selective for PDE6. Its relative lack of selectivity for PDE6 is thought to be the basis for abnormalities related to color vision. While sildenafil has obtained significant commercial success, it has fallen short of satisfying the medical need due to its significant side effects including flushing (10% incidence rate). Side effects limit the use of sildenafil in patients suffering from visual abnormalities, hypertension, or, most significantly, in patients who use organic nitrates. Welds et al., The Amer J of Cardiology, 53(5A) 21(c)-28(c) 1999. The use of sildenafil in patients taking organic nitrates is believed to cause a clinically significant drop in blood pressure which could place the patient in danger. Accordingly, the package label for sildenafil provides strict contraindications against its use in combination with organic nitrates. Thus, even with the introduction of sildenafil, there remains a need to identify improved

pharmaceutical products that are useful in treating sexual dysfunction.

The present invention provides an article of manufacture for human pharmaceutical use, comprising a package insert, a container and an oral dosage form comprising a selective PDE5 inhibitor at dosages between 1 and 20 mg/dosage form. This product was obtainable only through Applicants' clinical studies and through the discovery that a selective PDE5 inhibitor meeting the following criteria:

1) at least a 100 fold differential in the IC_{50} for the inhibition of PDE5 versus PDE6;

2) at least a 1000 fold differential in the IC_{50} for the inhibition of PDE5 versus PDE1c; and

3) an IC_{50} less than 10 nM;

allows for the effective administration of 1 to 20 mg/dosage form without contraindications and/or warning generally required for PDE5 inhibitor products such as those directed to visual abnormalities. Significantly, the studies also reveal that an effective product can be prepared that has a reduced tendency to cause flushing. Most unexpectedly, the product can be administered with clinically insignificant interactions with organic nitrates. Thus, the contraindication once believed to be indicative of a product having a PDE5 inhibitor is unnecessary when a selective PDE5 inhibitor is used as described and claimed herein. Thus, the invention provides effective therapy to millions of patients who were previously untreatable, including those who have cardiovascular disease requiring nitrate therapy or suffer from visual abnormalities.

SUMMARY OF THE INVENTION

The present invention provides an article of manufacture for human pharmaceutical use, comprising a package insert, a container and an oral dosage form comprising 1 to 20 mg of a selective PDE5 inhibitor per dosage form.

The present invention further provides a method of treating conditions where inhibition of PDE5 is desired, which comprises administering to a patient in need thereof an oral dosage form having 1 to 20 mg of a selective PDE5 inhibitor, as needed up to a total dose of 20 mg/day. The invention further provides the use of an oral dosage form comprising a selective PDE5 inhibitor at a dosage of 1 to 20 mg for the treatment of sexual dysfunction.

Specific conditions claimed include male erectile dysfunction and female sexual dysfunction, particularly female arousal disorder.

DETAILED DESCRIPTION

For purposes of the claimed invention as disclosed and described herein, the following terms and abbreviations have the following meanings.

The term "container" means any receptacle and closure suitable for storing, shipping, dispensing or handling pharmaceutical products.

The term "IC_{50}" is the measure of potency of a compound to inhibit a particular PDE enzyme (e.g., PDE1c, PDE5 or PDE6). The IC_{50} is the concentration of a compound that results in 50% enzyme inhibition in a single dose-response experiment. Determining the IC_{50} for a compound is readily carried out by known *in vitro* methodology generally

described in Y. Cheng et al., Biochem. Pharmacol., 22: 3099-3108 (1973).

The term "package insert" means information accompanying the product that provides a description of how the product is to be administered along with the safety and efficacy data required to allow the physician, pharmacist and patient to make an informed decision regarding the use of the product. The package insert is generally regarded as the "label" for a pharmaceutical product.

The term "oral dosage form" is used in a general sense to reference pharmaceutical products administered orally. Oral dosage forms are recognized by those skilled in the art to include such forms as liquid formulations, tablets, capsules, and gelcaps.

The term "selective PDE5 inhibitor" is a PDE5 inhibitor having:

1) at least a 100 fold differential in the IC_{50} for the inhibition of PDE5 versus PDE6;

2) at least a 1000 fold differential in the IC_{50} for the inhibition of PDE5 versus PDE1c; and

3) an IC_{50} less than 10 nM;

Selective PDE5 inhibitors vary significantly in chemical structure, and their use in the present invention is not dependent on the chemical structure, but rather on the critical parameters outlined herein.

The term "vision abnormalities" means abnormal vision typically characterized by blue-green vision believed to be caused by cross-reactivity to PDE6.

As noted, the present invention is an article of manufacture for human pharmaceutical use, comprising a package insert, a container and a dosage form comprising 1

to 20 mg of a selective PDE5 inhibitor per dosage form. A selective PDE5 inhibitor is a PDE5 inhibitor having:

1) at least a 100 fold differential in the IC_{50} for the inhibition of PDE5 versus PDE6;

2) at least a 1000 fold differential in the IC_{50} for the inhibition of PDE5 versus PDE1c;

3) an IC_{50} less than 10 nM;

and is sufficiently bioavailable to be effective in 1 to 20 mg tablets. The differential is expressed as a PDE6/PDE5 ratio of IC_{50} values, i.e., the ratio of IC_{50} versus PDE6 to the IC_{50} versus PDE5 (PDE6/PDE5) is greater than 100, more preferably greater than 300; and most preferably greater than 500.

Similarly, the ratio of IC_{50} versus PDE1c to IC_{50} versus PDE5 (PDE1c/PDE5) is greater than 1000, preferred PDE5 inhibitors have greater than 3,000 fold differential between the inhibition of PDE5 and PDE1c, more preferably greater than 5,000 fold differential between PDE5 and PDE1c. The potency, as represented by the IC_{50}, of the inhibitor is less than 10nM; preferably less than 5 nM, more preferably less than 2 nM, and most preferably less than 1 nM.

The package insert provides a description of how a pharmaceutical product is to be administered along with the safety and efficacy data required to allow the physician, pharmacist and patient to make an informed decision regarding the use of the product. The package insert is generally regarded as the label of the pharmaceutical product. The package insert incorporated into the present article of manufacture indicates that the selective PDE5 inhibitor is useful to treat conditions wherein the inhibition of PDE5 is desired. The package insert also provides instructions to administer one or more 1 to 20 mg

dosage forms as needed up to a total dose of 20 mg per day. Preferably, the dose administered is 5 to 20 mg/day; more preferably 5 to 15 mg; and most preferably a 10 mg dosage form administered once per day, as needed.

Preferred conditions to be treated include sexual dysfunction (including male erectile dysfunction and female sexual dysfunction and more preferably female arousal disorder (FAD)). The preferred condition to be treated is male erectile dysfunction. Significantly, the package insert supports the use of the product to treat sexual dysfunction in patients suffering from retinitis pigmentosa, or patients who are using organic nitrates. Thus, the package insert is preferably free of contraindications associated with these conditions and particularly the administration of the dosage form with an organic nitrate. More preferably, the package insert is also free of any cautions or warnings associated with these conditions. Preferably, the package insert also reports incidences of flushing below 2%, preferably below 1% and most preferably below 0.5%. The incident rate of flushing demonstrates marked improvement over the prior pharmaceutical products including a PDE5 inhibitor.

The container used in the present article of manufacture is conventional to the pharmaceutical arts. Generally, the container is a blister pack, foil packet, glass or plastic bottle, or other such device suitable for use by the patient or pharmacist. Preferably, the container is sized to accommodate 1000 solid dosage forms, preferably 1 to 500 solid dosage forms, and most preferably, 5 to 30 solid dosage forms.

Oral dosage forms are recognized by those skilled in the art to include such forms as liquid formulations,

tablets, capsules, and gelcaps. Preferably the dosage forms are solid dosage forms, particularly, tablets comprising 1 to 20 mg of selective PDE5 inhibitor. Any pharmaceutically acceptable excipients for oral use are suitable for preparation of such dosage forms. Suitable pharmaceutical dosage forms include those described in WO 96/38131. Preferably, the tablets comprise generally recognized as safe pharmaceutical excipients such as lactose, microcrystalline cellulose, starch, $CaCO_3$, magnesium stearate, stearic acid, talc, colloidal silicon dioxide and are prepared by standard pharmaceutical manufacturing techniques as described in Remington's Pharmaceutical Sciences, 18th Ed. (1990), Easton, PA: Mack Publishing Co. Such techniques include, for example, wet granulation followed by drying, milling and compression into tablets with or without film coating; dry granulation followed by milling, compression into tablets with or without film coating; dry blending followed by compression into tablets, with or with film coating; molded tablets; wet granulation, dried and filled into gelatin capsules; dry blend filled into gelatin capsules; or suspension and solution filled into gelatin capsules. Generally, the solid dosage forms have identifying marks which are debossed or imprinted on the surface.

The present invention is based on Applicants' detailed experiments and clinical trials, and their unexpected observation that the side effects believed to be indicative of PDE5 inhibition could be reduced to clinically insignificant levels by the selection of a selective PDE5 inhibitor having the specific characteristics outlined herein, namely:

1) at least a 100 fold differential in the IC_{50} for the inhibition of PDE5 versus PDE6;

2) at least a 1000 fold differential in the IC_{50} for the inhibition of PDE5 versus PDE1c; and

3) an IC_{50} less than 10 nM.

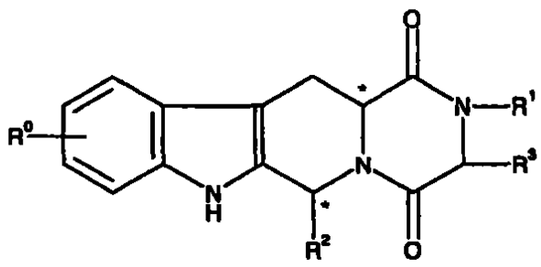
This observation, therefore enabled the development of articles of manufacture that incorporate a selective PDE5 inhibitor in 1 to 20 mg dosage forms that, when administered, do not cause the undesired side effects previously believed unavailable. These side effects include flushing, vision abnormalities, significant decreases in blood pressure alone or in combination when administered with organic nitrate. The minimal effect on PDE6 also allows the administration of a select PDE5 inhibitor to patients suffering from retinitis pigmentosa.

One such inhibitor, (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,4,7,12,12a-hexahydro-2-methyl-pyrazino[1',2':1,6]-pyrido[3,4-b]indole-1,4-dione, was demonstrated in human clinical studies to have minimal impact on systolic blood pressure when administered in conjunction with nitrates. By contrast, sildenafil demonstrates a 4 fold greater decrease in systolic blood pressure over placebo, which leads to the contraindications and warnings in certain patients.

Selective PDE5 inhibitors vary significantly in chemical structure, and the use of a selective PDE5 inhibitor in the present invention is not dependent on a particular chemical structure, but rather on the critical parameters outlined herein. However, preferred compounds having the required selectivity can be readily identified from those described in U.S. patent 5,859,006, WO 95/19978

and WO 97/03985, all of which are herein incorporated by reference.

Preferred compounds of U.S. patent 5,859,006 are represented by Formula (I):

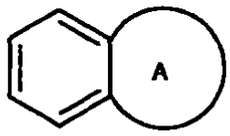


(I)

R^0 represents hydrogen, halogen or C_{1-6}alkyl;

R_1 represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl, wherein aryl is phenyl or phenyl substituted with one to three substituents selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkoxy, methylenedioxy, and mixtures thereof, or heteroarylC_{1-3}alkyl, wherein heteroaryl is thienyl, furyl, or pyridyl, each optionally substituted with one to three substituents selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkoxy, and mixtures thereof;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine or an optionally substituted bicyclic ring



attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-

membered ring which can be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen;

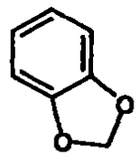
R^3 represents hydrogen or C_{1-3}alkyl, or R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain; and salts and solvates thereof.

Other preferred compounds are those of formula (I) wherein:

R_0 is hydrogen, halogen or C_{1-6}alkyl;

R_1 is hydrogen or C_{1-6}alkyl;

R_2 is the bicyclic ring



which may be optionally substituted by one or more groups selected from halogen and C_{1-3}alkyl;

and

R_3 is hydrogen or C_{1-3}alkyl.

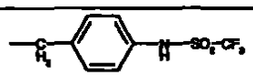
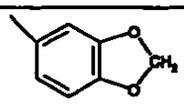
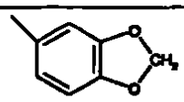
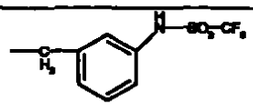
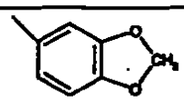
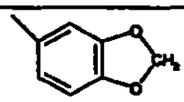
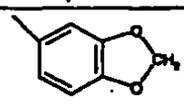
The following Table 1 illustrates for PDE5 and PDE6 IC_{50} values for representative selective PDE5 inhibitors within U.S. Patent 5,859,006 as determined by the procedures described herein.

Table 1

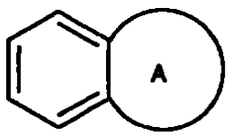
Compound	PDE5 IC_{50} (nM)	PDE6 IC_{50} (nM)	PDE6/PDE5
1	5	663	133
2	2	937	469
3	2	420	210
4	5	729	146
5	2.5	3400	1360

Compound 5 additionally demonstrates an IC_{50} against PDE1c of 10,000 and a ratio of PDE1c/PDE5 of 4,000.

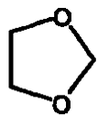
The structures of Compound Nos. 1-5 in Table 1 are as in Formula I wherein R^0, R^1, R^2, and R^3 are as follows:

Compound	R^0	R^1	R^2	R^3
1	H			H
2	H	CH_3		CH_3
3	H			H
4	H	CH_3		H
5	H	H		CH_3

The data in Table 1 indicate that a compound of Formula (I), wherein R^1 is hydrogen or C_{1-6}alkyl, R^2 is



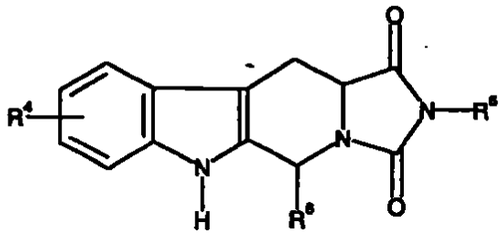
and R^3 is hydrogen; is especially preferred. Preferably A is



Preferred compounds are selected from the group consisting of:

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2-methyl-pyrazino [2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-pyrazino[2',1':6,1] pyrido [3,4-b]indole-1,4-dione;
(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-3-methyl-pyrazino[2',1':6,1]pyrido [3,4-b]indole-1,4-dione;
(3S,6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2,3-dimethyl-pyrazino[2'1':6,1]pyrido [3,4-b]indole-1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2-isopropyl-pyrazino [2',1':6,1]pyrido [3,4-b]indole-1,4-dione;
and physiologically acceptable solvates thereof.

Other exemplary compounds useful in the present invention are those disclosed in WO 96/32003, and include those within the Formula (II):



(II)

and salts and solvates thereof, wherein

R^4 represents hydrogen, halogen, or C_{1-6}alkyl;

R^5 is selected from the group consisting of:

hydrogen, C_{1-6}alkyl, optionally substituted with one or more substituents selected from phenyl, halogen, $-CO_2R^a$, and $-NR^aR^b$,

C_{3-6}cycloalkyl,

phenyl, and

a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected form oxygen, nitrogen, and

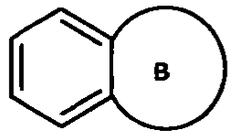
sulfur and being optionally substituted by one or more C_{1-6}alkyl, and optionally linked the nitrogen atom to which R^5 is attached via C_{1-6}alkyl;

R^6 is selected from the group consisting of:

C_{3-6}cycloakyl, phenyl, optionally substituted by one or more substituents selected from $-OR^c$, $-NR^cR^d$, halogen, hydroxy, trifluoromethyl, cyano, and nitro,

a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from oxygen, nitrogen, and sulfur, and

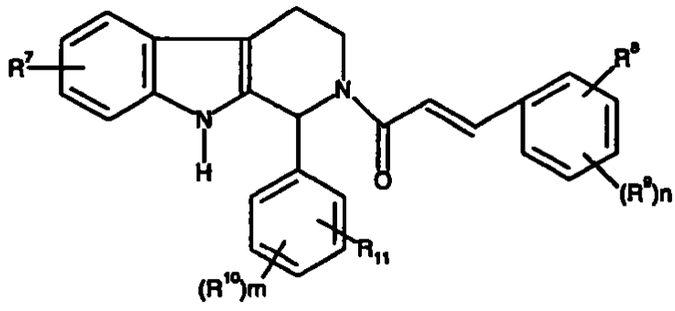
a bicyclic ring



attached to the rest of the molecule via one of the benzene ring carbon atoms and B is a 5- or 6-membered heterocyclic ring as defined in point (h); and

R^c and R^d independently represent hydrogen or C_{1-6}alkyl.

Additional exemplary compounds are from the class of compounds disclosed in WO 97/43287, which is specifically incorporated herein by reference. This class of compounds has the structural formula (III):



(III)

and salts and solvates (e.g., hydrates) thereof, wherein

R^7 represents hydrogen or halogen;

R^8 is selected from the group consisting of:

hydrogen,

NO_2,

trifluoromethyl,

trifluoromethoxy,

halogen,

cyano,

a 5- or 6-membered heterocyclic group containing at least one heteroatom selected from oxygen, nitrogen and sulphur, and is optionally substituted by $C(=O)OR^e$ or C_{1-4}alkyl,

C_{1-6}alkyl optionally substituted by OR^e,

C_{1-3}alkoxy,

$C(=O)R^e$,

$O-C(=O)R^e$,

$C(=O)OR^e$,

C_{1-4}alkylene $C(=O)OR^e$,

$O-C_{1-4}$alkylene-$C(=O)OR^e$,

C_{1-4}alkylene-$O-C_{1-4}$alkylene-$C(=O)OR^e$,

$C(=O)NR^eSO_2R^g$,

$C(=O)C_{1-4}$alkyleneHet,

C_{1-4}alkyleneNR^eR^f,

C_{2-6}alkenyleneNR^eR^f,

$C(=O)NR^eR^f$,

$C(=O)NR^eR^g$,

$C(=O)NR^eC_{1-4}$alkyleneOR^f,

$C(=O)NR^eC_{1-4}$alkyleneHet,

OR^e,

OC_{2-4}alkyleneNR^eR^f,

OC_{1-4}alkylene-$CH(OR^e)CH_2NR^eR^f$,

$O-C_{1-4}$alkyleneHet,

$O\text{-}C_{2-4}$alkylene-OR^e,

$O\text{-}C_{2-4}$alkylen-$NR^e\text{-}C(=O)\text{-}OR^f$,

NR^eR^f,

NR^eC_{1-4}alkyleneNR^eR^f,

$NR^rC(=O)R^g$,

$NR^eC(=O)NR^eR^f$,

$N(SO_2C_{1-4}alkyl)_2$,

$NR^e(SO_2C_{1-4}alkyl)$,

$SO_2NR^eR^f$, and

OSO_2trifluoromethyl;

R^9 is selected from the group consisting of:

hydrogen,

halogen,

OR^e,

C_{1-6}alkyl,

NO_2, and

NR^eR^f,

or R^8 and R^9 are taken together to form a 3- or 4-membered alkylene or alkenylene chain component of a 5- or 6-membered ring, optionally containing at least one heteroatom;

R^{10} is selected from the group consisting of:

hydrogen,

halogen,

NO_2,

trifluoromethoxy,

C_{1-6}alkyl, and

$C(=O)OR^e$;

R^{11} is hydrogen or halogen,

or R^{10} or R^{11} are taken together to form a 3- or 4-membered alkylene or alkenylene chain component of a 5- or

6-membered ring, optionally containing at least one heteroatom;

Het represents a 5- or 6-membered heterocyclic group containing at least one heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur and is optionally substituted with C_{1-4}alkyl;

R^e and R^f can be the same or different, and are independently selected from hydrogen and C_{1-6}alkyl;

R^g represents phenyl or C_{4-6}cycloalkyl, wherein the phenyl or C_{4-6}cycloalkyl can be optionally substituted by one or more halogen atoms, one or more $C(=O)OR^e$, or one or more OR^e;

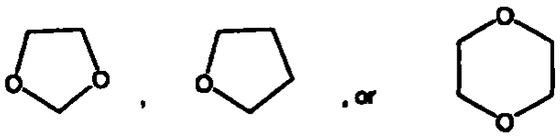
n is an integer selected from 1, 2 and 3;

and

m is an integer selected from 1 and 2.

Preferred compounds are those of Formula (III), wherein R^9 is hydrogen, halogen, or piperazyl; R^8 is hydrogen, NO_2, trifluoromethyl, halogen, C_{1-4}alkyleneC(=O)OH, $NR^eC(=O)NR^eR^f$, $C(=C)R^e$, OC_{2-4}alkylene-NR^eR^f, CO_2H, OR^e, OH, NR^eR^f, CHO, $NR^c(C=O)R^f$, or OSO_2CF_3;

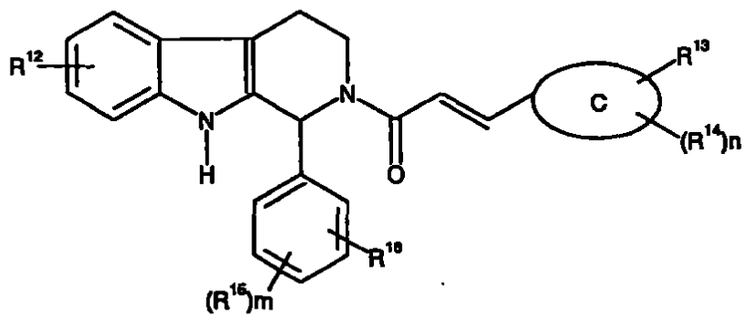
and R^{10} and R^{11} are taken together as



or individually as R^{11} is H or halogen, and R^{10} is hydrogen, halogen, or C_{1-6}alkyl.

Further exemplary compounds for use in the present invention are disclosed PCT application PCT/EP98/06050, which designates the U.S., entitled "Chemical Compounds," inventors A. Bombrun and F. Gellibert, the disclosures of

which are specifically incorporated by reference herein. This class of compounds has the structural formula (IV):



(IV)

and salts and solvates (e.g., hydrates) wherein

C represents a 5- or 6-membered heteroaryl group containing at least one heteroatom selected from the group consisting of oxygen, nitrogen, and sulphur;

R^{12} represents hydrogen or halogen;

R^{13} is selected from the group consisting of

hydrogen,

nitro (NO_2),

trifluoromethyl,

trifluoromethoxy,

halogen,

cyano (CN),

a 5- or 6-membered heterocyclic group containing at least one heteroatom selected from the group consisting of oxygen, nitrogen, and sulphur, optionally substituted with $C(=O)OR^a$ or C_{1-4}alkyl,

C_{1-6}alkyl, optionally substituted with OR^a,

C_{1-3}alkoxy,

$C(=O)R^h$,

$O\text{-}C(=O)OR^h$,

$C(=O)OR^h$,

C_{1-4}alkyleneHet,
C_{1-4}alkyleneC(=O)OR^h,
O-C_{1-4}alkylene-C(=O)OR^h,
C_{1-4}alkylene-O-C_{1-4}alkylene-C(=O)OR^h,
$C(=O)NR^iSO_2R^j$,
$C(=O)C_{1-4}$alkyleneHet,
C_{1-4}alkyleneNR^{h}R^i,
C_{2-6}alkyleneNR^{h}R^i,
C(=O)NR^{h}R^i,
C(=O)NR^{h}R^i,
$C(=O)NR^hC_{1-4}$alkyleneOR^i,
$C(=O)NR^hC_{1-4}$alkyleneHet,
OR^i,
OC_{2-4}alkylene NR^{h}R^i,
OC_{1-4}alkylene-CH(OR^h)CH_2-NR^{h}R^i,
O-C_{1-4}alkyleneHet,
O-C_{2-4}alkylene-OR^h,
O-C_{2-4}alkylene-NR^h-C(=O)-OR^i,
NR^{h}R^i,
NR^hC_{1-4}alkyleneNR^{h}R^i,
NR^{h}C(=O)R^i,
NR^{h}C(=O)NR^{h}R^i,
$N(SO_2C_{1-4}alyl)_2$,
NR^h(SO_2C_{1-4}alkyl),
$SO_2NR^hR^i$,
and OSO_2trifluoromethyl;

R^{14} is selected from the group consisting of hydrogen, halogen, OR^h, C_{1-6}alkyl, NO_2, and NR^{h}R^i;

or R^{13} and R^{14} are taken together to form a 3- or 4-membered alkylene or alkenylene chain component of a 5- or 6-membered ring, optionally containing at least one heteroatom;

R^{15} is selected from the group consisting of hydrogen, halogen, NO_2, trifluoromethoxy, C_{1-6}alkyl, OC_{1-6}alkyl, and $C(=O)OR^h$;

R^{16} is hydrogen,

or R^{15} and R^{16} are taken together to form a 3- or 4-membered alkylene or alkenylene chain component of a 5- or 6-membered ring, optionally containing at least one heteroatom;

Het represents a 5- or 6-membered heterocyclic group containing at least one heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur, and is optionally substituted with C_{1-4}alkyl;

R^h and R^i can be the same or different, and are independently selected from hydrogen and C_{1-6}alkyl;

R^j represents phenyl or C_{4-6}cycloalkyl, wherein the phenyl or C_{4-6}cycloalkyl can be optionally substituted with one or more halogen atoms, one or more $C(=O)OR^a$, or one or more OR^h;

n is an integer 1, 2, or 3; and

m is an integer 1 or 2.

Preferred compounds of Formula (IV) are those wherein C is a heteroaryl group containing at least one nitrogen or sulfur, R14 is hydrogen, and R13 is selected from the group consisting of NR^aR^b and a 5- or 6-membered heterocyclic group containing at least one nitrogen optionally substituted with C_{1-4} alkyl.

Preparations

A. Human PDE5 Preparation

Recombinant production of human PDE5 was carried out essentially as described in Example 7 of U.S. Patent No.

5,702,936, except that the yeast transformation vector employed which is derived from the basic ADH2 plasmid described in V. Price et al., Methods in Enzymology, 1985, pages 308-318 (1990) incorporated yeast ADH2 promoter and terminator sequences rather than ADH1 promoter and terminator sequences and the *Saccharomyces cerevisiase* host was the protease-deficient strain BJ2-54 deposited on August 31, 1998 with the American Type Culture Collection, Manassas, Virginia, under accession number ATCC 74465. Transformed host cells were grown in 2X SC-leu medium, pH 6.2, with trace metals, and vitamins. After 24 hours, YEP medium containing glycerol was added to a final concentration of 2X YEP/3% glycerol. Approximately 24 hours later, cells were harvested, washed, and stored at -70° C.

Cell pellets (29 g) were thawed on ice with an equal volume of lysis buffer (25 mM Tris-Cl, pH 8, 5 mM $MgCl_2$, 0.25 mM dithiothreitol, 1 mM benzamidine, and 10 µM $ZnSO_4$). Cells were lysed in a microfluidizer with N_2 at 20,000 psi. The lysate was centrifuged and filtered through 0.45 µm disposable filters. The filtrate was applied to a 150 mL column of Q Sepharose Fast Flow (Pharmacia). The column was washed with 1.5 volumes of Buffer A (20 mM Bis-Tris Propane, pH 6.8, 1 mM $MgCl_2$, 0.25 mM dithiothreitol, 10 µM $ZnSO_4$) and eluted with a step gradient of 125 mM NaCl in Buffer A followed by a linear gradient of 125-1000 mM NaCl in Buffer A.

Active fractions from the linear gradient were applied to a 180 mL hydroxyapatite column in Buffer B (20 mM Bis-Tris Propane (pH 6.8), 1 mM $MgCl_2$, 0.25 mM dithiothreitol, 10 µM $ZnSO_4$, and 250 mM KCl. After loading, the column was washed with 2 volumes of Buffer B and eluted with a linear gradient of 0-125 mM potassium phosphate in Buffer B.

Active fractions were pooled, precipitated with 60% ammonium sulfate, and resuspended in Buffer C (20 mM Bis-Tris Propane, pH 6.8, 125 mM NaCl, 0.5 mM dithiothreitol, and 10 μM $ZnSO_4$). The pool was applied to a 140 mL column of Sephacryl S-300 HR and eluted with Buffer C. Active fractions were diluted to 50% glycerol and stored at -20° C. The resultant preparations were about 85% pure by SDS-PAGE.

Specific activity of the preparations was determined as follows. PDE assays utilizing a charcoal separation technique were performed essentially as described in Loughney et al., (1996), The Journal of Biological Chemistry, 271:796-806. In this assay, PDE5 activity converts [^{32}P]cGMP to [^{32}P]5'GMP in proportion to the amount of PDE5 activity present. The [^{32}P]5'GMP is then quantitatively converted to free [^{32}P] phosphate and unlabeled adenosine by the action of snake venom 5'-nucleotidase. Hence, the amount of [^{32}P] phosphate liberated is proportional to enzyme activity. The assay is performed at 30° C in a 100 μL reaction mixture containing (final concentrations) 40 mM Tris-Cl (pH 8.0), 1 μM $ZnSO_4$, 5 mM $MgCl_2$, and 0.1 mg/mL bovine serium albumin. PDE5 is present in quantities that yield <30% total hydrolysis of substrate (linear assay conditions). The assay is initiated by addition of substrate (1 mM [^{32}P]cGMP), and the mixture is incubated for 12 minutes. Seventy-five (75) μg of *Crotalus atrox* venom is then added, and the incubation is continued for 3 more minutes (15 minutes total). The reaction is stopped by addition of 200 mL of activated charcoal (25 mg/mL suspension in 0.1 M NaH_2PO_4, pH 4). After centrifugation (750 x g for 3 minutes) to sediment the charcoal, a sample of the supernatant is taken for radioactivity determination in a scintillation counter and

the PDE5 activity is calculated. The preparations had specific activities of about 3 µmoles cGMP hydrolyzed per minute per milligram protein.

B. Bovine PDE6 Preparation

Bovine PDE6 was supplied by Dr. N. Virmaux, INSERM U338, Strasbourg. Bovine retinas were prepared as described by Virmaux et al., FEBS Letters, 12(6): 325-328 (1971) and see also, A. Sitaramayya et al., Exp. Eye Res., 25:163-169 (1977). Briefly, unless stated otherwise, all operations were done in the cold and in dim red light. Eyes were kept in the cold and in the dark for up to four hours after slaughtering.

Preparation of bovine retinal outer segment (ROS) basically followed procedures described by Schichi et al., J. Biol. Chem., 224:529 (1969). In a typical experiment, 35 bovine retinas were ground in a mortar with 35 mL 0.066 M phosphate buffer, pH 7.0, made up to 40% with sucrose, followed by homogenization in a Potter homogenizer (20 up and down strokes). The suspension was centrifuged at 25,000 x g for 20 minutes. The pellet was homogenized in 7.5 mL 0.006 M phosphate buffer (40% in sucrose), and carefully layered under 7.5 mL of phosphate buffer (containing no sucrose). Centrifugation was conducted in a swing-out rotor at 45,000 x g for 20 minutes, and produced a pellet which is black at the bottom, and also a red band at the interface 0.066 M. phosphate—40% sucrose/0.066 M phosphate (crude ROS). The red material at the interface was removed, diluted with phosphate buffer, spun down to a pellet, and redistributed in buffered 40% sucrose as described above. This procedure was repeated 2 or 3 times until no pellet was formed. The purified ROS was washed in phosphate buffer and

finally spun down to a pellet at 25,000 x g for 20 minutes. All materials were then kept frozen until used.

Hypotonic extracts were prepared by suspending isolated ROS in 10 mM Tris-Cl pH 7.5, 1 mM EDTA, and 1 mM dithioerythritol, followed by centrifugation at 100,000 x g for 30 minutes.

The preparation was reported to have a specific activity of about 35 nmoles cGMP hydrolyzed per minute per milligram protein.

C. PDE1c Preparation from *Spodoptera fugiperda* Cells (Sf9)

Cell pellets (5g) were thawed on ice with 20ml of Lysis Buffer (50mM MOPS pH 7.4, 10μM $ZnSo_4$, 0.1mM $CaCl_2$, 1mM DTT, 2mM benzamidine HCl, 5μg/ml each of pepstatin, leupeptin, and aprotenin). Cells were lysed by passage through a French pressure cell (SLM-Aminco) while temperatures were maintained below 10°C. The resultant cell homogenate was centrifuged at 36,000 rpm at 4°C for 45 minutes in a Beckman ultracentrifuge using a Type TI45 rotor. The supernatant was discarded and the resultant pellet was resuspended with 40ml of Solubilization Buffer (Lysis Buffer containing 1M NaCl, 0.1M $MgCl_2$, 1mM $CaCl_2$, 20μg/ml calmodulin, and 1% Sulfobetaine SB12 (Z3-12) by sonicating using a VibraCell tuner with a microtip for 3 x 30 seconds. This was performed in a crushed ice/salt mix for cooling. Following sonication, the mixture was slowly mixed for 30 minutes at 4°C to finish solubilizing membrane bound proteins. This mixture was centrifuged in a Beckman ultracentrifuge using a type TI45 rotor at 36,000 rpm for 45 minutes. The supernatant was diluted with Lysis Buffer containing 10μg/ml calpain inhibitor I and II. The precipitated protein was

centrifuged for 20 minutes at 9,000 rpm in a Beckman JA-10 rotor. The recovered supernatant then was subjected to Mimetic Blue AP Agarose Chromatography.

In order to run the Mimetic Blue AP Agarose Column, the resin initially was shielded by the application of 10 bed volumes of 1 % polyvinylpyrrolidine (i.e., MW of 40,000) to block nonspecific binding sites. The loosely bound PVP-40 was removed by washing with 10 bed volumes of 2M NaCl, and 10mM sodium citrate pH 3.4. Just prior to addition of the solubilized PDE1c3 sample, the column was equilibrated with 5 bed volumes of Column Buffer A (50mM MOPS pH 7.4, 10μM $ZnSO_4$, 5mM $MgCl_2$, 0.1mM $CaCl_2$, 1mM DTT, 2mM benzamidine HCl).

The solubilized sample was applied to the column at a flow rate of 2ml/min with recycling such that the total sample was applied 4 to 5 times in 12 hours. After loading was completed, the column was washed with 10 column volumes of Column Buffer A, followed by 5 column volumes of Column Buffer B (Column Buffer A containing 20mM 5'-AMP), and followed by 5 column volumes of Column Buffer C (50mM MOPS pH 7.4, 10μM $ZnSO_4$, 0.1mM $CaCl_2$, 1mM dithiothreitol, and 2mM benzamidine HCl). The enzyme was eluted into three successive pools. The first pool consisted of enzyme from a 5 bed volume wash with Column Buffer C containing 1mM cAMP. The second pool consisted of enzyme from a 10 bed volume wash with Column Buffer C containing 1M NaCl. The final pool of enzyme consisted of a 5 bed volume wash with Column Buffer C containing 1M NaCl and 20mM cAMP.

The active pools of enzyme were collected and the cyclic nucleotide removed via conventional gel filtration chromatography or chromatography on hydroxy-apatite resins. Following removal of cyclic nucleotides, the enzyme pools were dialyzed against Dialysis Buffer containing 25mM MOPS

pH 7.4, 10μM $ZnSO_4$, 500mM NaCl, 1mM $CaCl_2$, 1mM dithiothreitol, 1mM benzamidine HCl, followed by dialysis against Dialysis buffer containing 50% glycerol. The enzyme was quick frozen with the aid of dry ice and stored at -70°C.

The resultant preparations were about >90% pure by SDS-PAGE. These preparations had specific activities of about 0.1 to 1.0μmol cAMP hydrolyzed per minute per milligram protein.

C. IC_{50} Determinations

The parameter of interest in evaluating the potency of a competitive enzyme inhibitor of PDE5 and/or PDE1c and PDE6 is the inhibition constant, i.e., Ki. This parameter can be approximated by determining the IC_{50}, which is the inhibitor concentration that results in 50% enzyme inhibition, in a single dose-response experiment under the following conditions.

1) The concentration of inhibitor is always much greater than the concentration of enzyme, so that free inhibitor concentration (which is unknown) is approximated by total inhibitor concentration (which is known).

2) A suitable range of inhibitor concentrations is chosen (i.e., inhibitor concentrations at least several fold greater and several fold less than the Ki are present in the experiment). Typically, inhibitor concentrations ranged from 10 nM to 10 μM.

3) The concentrations of enzyme and substrate are chosen such that less than 20% of the substrate is consumed in the absence of inhibitor (providing, e.g., maximum substrate hydrolysis of from 10 to 15%), so that enzyme activity is approximately constant throughout the assay.

4) The concentration of substrate is less than one-tenth the Michaelis constant (Km). Under these conditions, the IC_{50} will closely approximate the Ki. This is because of the Cheng-Prusoff equation relating these two parameters:

$IC_{50}=Ki(1+S/Km)$, with $(1+S/Km)$ approximately 1 at low values of S/Km.

5) The IC_{50} value is estimated from the data points by fitting the data to a suitable model of the enzyme inhibitor interaction. When this interaction is known to involve simple competition of the inhibitor with the substrate, a two-parameter model can be used:

$$Y=A/(1+x/B)$$

where the y is the enzyme activity measured at an inhibitor concentration of x, A is the activity in the absence of inhibitor and B is the IC_{50}. See Y. Cheng et al., Biochem. Pharmacol., 22:3099-3108 (1973).

Effects of inhibitors of the present invention on enzymatic activity of PDE5 and PDE6 preparations as described above were assessed in either of two assays which differed from each other principally on the basis of scale and provided essentially the same results in terms of IC_{50} values. Both assays involved modification of the procedure of Wells et al., Biochim. Biophys. Acta, 384: 430 (1975). The first of the assays was performed in a total volume of 200 µl containing 50 mM Tris pH 7.5, 3 mM Mg acetate, 1 mM EDTA, 50 µg/mL snake venom nucleotidase and 50 nM [^{3}H]-cGMP (Amersham). Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The assays were incubated for 30 minutes at 30° C and stopped by addition of 800 µl of 10 mM Tris pH 7.5, 10 mM EDTA, 10 mM theophylline, 0.1 mM adenosine, and 0.1 mM guanosine. The mixtures were loaded on to 0.5 mL QAE Sephadex columns, and eluted with 2

mL of 0.1 M formate (pH 7.4). The eluted radioactivity was measured by scintillation counting in Optiphase Hisafe 3.

A second, microplate, PDE assay was developed using Multiscreen plates and a vacuum manifold. The assay (100 µl) contained 50 mM Tris pH 7.5, 5 mM Mg acetate, 1 mM EDTA and 250 µg/mL snake venom nucleotidase. The other components of the reaction mixture were as described above. At the end of the incubation, the total volume of the assays were loaded on a QAE Sephadex microcolumn plate by filtration. Free radioactivity was eluted with 200 µl of water from which 50 µl aliquots were analyzed by scintillation counting as described above.

The following examples are presented to further illustrate the preparation of the claimed invention. The scope of the present invention is not to be construed as merely consisting of the following examples.

Example 1

Compound was prepared as described in U.S. patent 5,859,006 and formulated in tablets using wet granulation. Povidone was dissolved in water to make a 10% solution. The active compound, microcrystalline cellulose, Croscarmellose sodium and sodium lauryl sulphate were added to a high shear mixer and mixed for 2 minutes. The powders were wet granulated with the povidone solution and extra water as required to complete the granulation. The resultant mixture was dried in a fluid bed drier with inlet air at 70° C ± 5° C until the loss on drying was below 2.5%. The granules were passed through a Comil with a suitable screen (or a sieve) and added to a suitable mixer. The extragranular Croscarmellose sodium and sodium lauryl sulphate, and the Colloidal anhydrous silica were passed through a suitable sieve (e.g., 500 micron) and added to the mixer and blended

5 minutes. Magnesium stearate was added and blended for 2 minutes. The blend was compressed to a target compression/weight of 250 mg using 9 mm round normal concave tooling.

The core tablets were coated with an aqueous suspension of Opadry OY-S-7322 using an Accelacota (or similar coating pan) using inlet air at 50° C to 70° C until the tablet weight was increased by approximately 8 mg.

Component	Formulations (mg per tablet)	
Selective PDE5 inhibitor	1	5
Hydroxypropylmethyl-cellulose phthalate	1	5
Microcrystalline cellulose	221.87	213.87
Croscarmellose Sodium	5.00	5.00
Sodium Lauryl Sulphate	2.50	2.50
Povidone K30	9.38	9.38
Purified Water, USP (water for irrigation)	q.s.	q.s.
Croscarmellose Sodium	5.00	5.00
Sodium Lauryl Sulphate	2.50	2.50
Colloidal Anhydrous Silica	0.50	0.50
Magnesium Stearate	1.25	1.25
Total core subtotal	250.00	250.00
(Film coat Opadry OY-S-7322)	~8 mg	~8 mg

Opadry OY-S-7322 contains methylhydroxypropylcellulose Ph.Eur., titanium dioxide Ph.Eur., Triacetin USP. Opadry increases the weight of each tablet to about 258 mg. The amount of film coat applied per tablet may be less than that stated depending on the process efficiency.

The tablets are filled into blister packs and accompanied by package insert describing the safety and efficacy of the compound.

Example 2

The following formula is used in preparing the finished dosage form.

Ingredient	Quantity (mg)
Granulation	
Selective PDE5 inhibitor	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (Spray Dried)	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
	35.00
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (Vegetable)	1.25
Total	250 mg
Film coat (approximately)	11.25

Purified Water, USP is used in the manufacture of these tablets. This solvent is removed during processing and minimal levels remain in the finished product.

Tablets are manufactured using a wet granulation process. A step by step description of the process follows: The drug and excipients to be granulated are security sieved. The selective PDE5 inhibitor is dry blended with lactose monohydrate (spray dried), hydroxypropyl cellulose ,

croscarmellulose sodium, and lactose monohydrate. The resulting powder blend is granulated with an aqueous solution of hydroxypropyl cellulose and sodium lauryl sulfate using a Powerex or other suitable high shear granulator. Additional water may be added to reach the desired endpoint. A mill may be used to delump the wet granulation and facilitate drying. The wet granulation is dried using either a fluid bed dryer or a drying oven. Once the material is dried, it may be sized to eliminate any large agglomerates. Microcrystalline cellulose, croscarmellose sodium, and magnesium stearate are security sieved and added to the dry sized granules. These excipients and the dry granulation are mixed until uniform using a tumble bin, ribbon mixer, or other suitable mixing equipment. The mixing process may be separated into two phases; the microcrystalline cellulose, croscarmellose sodium and the dried granulation are added to the mixer and blended during the first phase, followed by the addition of the magnesium stearate to this granulation and a second mixing phase.

The mixed granulation is then compressed into tablets using a rotary compression machine. The core tablets are film coated with an aqueous suspension of the appropriate color mixture in a coating pan (e.g., Accela Cota). The coated tablets may be lightly dusted with talc to improve tablet handling characteristics.

The tablets are filled into plastic containers (30 tablets/container) and accompanied by package insert describing the safety and efficacy of the compound.

<u>Example 3</u>

Solution Capsule

Ingredient	mg/Capsule	Percent (%)
Selective PDE5 inhibitor	10	2
PEG400 NF	490	98
Fill Weight	500	100

The gelatin capsules are precisely filled by pumping an accurate fill volume of pre-dissolved drug formulation into the partially sealed cavity of a capsule. Immediately following injection fill of the drug solution formulation, the capsule is completely heat sealed.

The capsules are filled into plastic containers and accompanied by a package insert.

<u>Example 4</u>

This study was a randomized, double-blind, placebo-controlled, two-way crossover design clinical pharmacology drug interaction study that evaluated the effects of concomitant administration of a selective PDE5 inhibitor (Study drug) and short-acting nitrates on hemodynamic parameters in healthy male volunteers. In this study, subjects received either Study drug at a dose of 10 mg or placebo daily for 7 days. On the sixth or seventh day, subjects received sublingual nitroglycerin (0.4 mg) while supine on a tilt table. The nitroglycerin was administered 3 hours after drug dosing and all subjects kept the tablet under their tongue until it had completely dissolved. Subjects were tilted to 70° head-up every 5 minutes for a total of 30 minutes with measurement of blood pressure and heart rate. There were no discontinuations among the 22 healthy male subjects (ages 19 to 60 years old) that entered

this study. In a preliminary analysis of this study, the study drug was well tolerated and there were no serious adverse events. There were no study drug-associated changes in laboratory safety assessments or 12-lead ECGs. The most common adverse events were headache, dyspepsia, and myalgia. The mean systolic blood pressure was approximately 4 mmHg lower after 7 days of study drug (10 mg) than after 7 days of placebo, forming the baseline systolic blood pressure for subsequent nitrate administration. The mean maximal nitroglycerin-induced decrease in systolic blood pressure over the 30 minutes was 19 mmHg for placebo and 20 mmHg for Study Drug. The maximal nitroglycerin-induced decrease in systolic blood pressure amongst all patients was 44 mmHg for placebo and 37 mmHg for study drug. There appeared to be a compensatory increase in heart rate of approximately 12 beats per minute (study drug compared to placebo).

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention that is intended to be protected herein, however, is not construed to be limited to the particular forms disclosed, because they are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention.

Example 5

In randomized, double-blinded placebo controlled studies a selective PDE5 inhibitor at a range of doses in both daily dosing and for on demand therapy for sexual encounters and intercourse in the home setting was administered to patients in need thereof.

Doses from 5 to 20 mg of Compound 5 were efficacious and demonstrated <1% flushing and no reports of vision abnormalities.

In a second study (10 mg to 100 mg daily) Applicants found 10 mg of Compound 5 was fully efficacious and demonstrated minimal side effects (<1% flushing and no reports of blue-vision). Enhanced erectile function was determined by the International Index of Erectile Function (IIEF) (Rosen et al., Urology, 49:822-830, 1997), diaries of sexual attempts, and a global satisfaction question. The compound significantly improved the percentage of successful intercourse attempts including the ability to attain and maintain an erection in both "on demand" and daily dosing regimens. Treatment improved patient erections was significantly improved in both studies.

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We claim:

1. An article of manufacture for human pharmaceutical use, comprising a package insert, a container and an oral dosage form comprising 1 to 20 mg of a selective PDE5 inhibitor per dosage.

2. The article of manufacture of Claim 1, wherein said package insert indicates such selective PDE5 inhibitor is useful to treat sexual dysfunction in patients who are using organic nitrates.

3. The article of manufacture of Claim 1, wherein said package insert which indicates such selective PDE5 inhibitor is useful to treat sexual dysfunction in patients in need thereof and which is free of contraindications associated with administration with an organic nitrates.

4. The article of manufacture of Claim 1, wherein said package insert indicates such selective PDE5 inhibitor is useful to treat sexual dysfunction in patients and which is free of contraindications associated with vision abnormalities.

5. The article of manufacture of Claim 1, wherein said package insert indicates such selective PDE5 inhibitor is useful to treat sexual dysfunction in patients and reports that incidences of flushing are below 2%.

6. The article of manufacture of Claims 1-4, wherein the selective PDE5 inhibitor has an IC_{50} ratio of PDE6 to PDE5 greater than 200 and a potency from 0.1 to less than 5 nM.

7. The article of manufacture of Claim 6, wherein the selective PDE5 inhibitor is selected from the group consisting of :

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2-methyl-pyrazino [2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-pyrazino[2',1':6,1] pyrido [3,4-b]indole-1,4-dione;

(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-3-methyl-pyrazino[2',1':6,1]pyrido [3,4-b]indole-1,4-dione;

(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2,3-dimethyl-pyrazino[2'1':6,1]pyrido [3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2-isopropyl-pyrazino [2',1':6,1]pyrido [3,4-b]indole-1,4-dione;

and physiologically acceptable solvates thereof.

8. The article of manufacture of Claim 8, wherein the selective PDE5 inhibitor wherein the dosages are 5, 10, or 20 mg/Tablet.

9. A method of treating sexual dysfunction in patients in need thereof, which comprises administering to a patient in need thereof, a selective PDE5 inhibitor at a dose of 1 to 20 mg per day.

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10. The method of claim 10, wherein the patient is inflicted with cardiovascular disease.

11. An article of manufacture as substantially herebefore described in the specification.

12. The use of an oral dosage form comprising a selective PDE5 inhibitor at a dosage of 1 to 20 mg for the treatment of sexual dysfunction.

ABSTRACT

The present invention relates to highly selective phosphodiesterase (PDE) enzyme inhibitors and to their use in pharmaceutical articles of manufacture. In particular, the present invention relates to potent inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase type 5 (PDE5) that when incorporated into a pharmaceutical product are useful for the treatment of sexual dysfunction. The articles of manufacture described herein are characterized by selective PDE5 inhibition, and accordingly, provide a benefit in therapeutic areas where inhibition of PDE5 is desired, with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes.

TRADUCCIÓN OFICIAL No.2000/136 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho, por resolución número 323 de 1980.

(Se traduce el certificado de la Oficina de Patentes y Marcas de los Estados Unidos de América, correspondiente a la solicitud 60/132,036 y el capítulo reivindicatorio, escritos en inglés.)

ESTADOS UNIDOS DE AMÉRICA

A TODOS A QUIENES ESTOS PRESENTES LLEGAREN:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS

Abril 17, 2000

POR EL PRESENTE CERTIFICO QUE ADJUNTA SE ENCUENTRA UNA COPIA FIEL DE LOS ARCHIVOS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA DE AQUELLOS PAPELES DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO Y QUE CUMPLIERON CON LOS REQUISITOS PARA QUE SE LES OTORGARA UNA FECHA DE SOLICITUD BAJO EL CÓDIGO DE COMERCIO DE LOS ESTADOS UNIDOS DE AMÉRICA

115

TÍTULO 35 SECCIÓN 111.

NUMERO DE SOLICITUD: ***60/132,036***

FECHA DE PRESENTACIÓN: ***Abril 30, 1999***

Por autoridad del

COMISARIO DE PATENTES Y MARCAS

(Firmado.) **L. EDELEN**

Funcionario que Certifica

(SELLO DE OBLEA DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA)

(Nota: al margen aparece un sello a tinta en todas las páginas: 60132036.043099)

Reivindicamos:

1. Un artículo de fabricación para uso farmacéutico humano, que incluye un paquete insertado, un contenedor y una forma de dosificación oral incluyendo de 1 a 20 mg de un inhibidor PDE5 selectivo por dosis.

2. El artículo de fabricación de la reivindicación 1 donde tal paquete insertado indica que dicho inhibidor PDE5 selectivo es útil para tratar la disfunción sexual en pacientes que estén usando nitratos orgánicos.

3. El artículo de fabricación de la reivindicación 1 donde tal paquete insertado

indica que dicho inhibidor PDE5 selectivo es útil para tratar la disfunción sexual en pacientes que lo necesiten y que no tiene contraindicaciones asociadas con su administración con nitratos orgánicos.

4. El artículo de fabricación de la reivindicación 1 donde tal paquete insertado indica que dicho inhibidor PDE5 selectivo es útil para tratar la disfunción sexual en pacientes y que no tiene contraindicaciones asociadas con anormalidades de la visión.

5. El artículo de fabricación de la reivindicación 1 donde tal paquete insertado indica que dicho inhibidor PDE5 selectivo es útil para tratar la disfunción sexual en pacientes y reporta que las incidencias de acaloramiento son menores al 2%.

6. El artículo de fabricación de las reivindicaciones 1-4 donde el inhibidor PDE5 selectivo tiene una relación IC_{50} de PDE6 a PDE5 mayor a 200 y una potencia de 0.1 a menos de 5nM.

7. El artículo de fabricación de la reivindicación 6 donde el inhibidor PDE5 se selecciona del grupo consistente de:

(6R,12aR)-2,3,6,7,12,12a-hexahidro-6-(5-benzofuranil)-2-metil-pirazino [2',1': 6,1] pyrido[3,4-b]indole-1,4-diona;

(6R,12aR)-2,3,6,7,12,12a-hexahidro-6-(5-benzofuranil)-pirazino [2',1': 6,1] pyrido[3,4-b]indole-1,4-diona;

(3S,6R,12aR)-2,3,6,7,12,12a-hexahidro-6-(5-benzofuranil)-3-metil-pirazino [2',1': 6,1] pyrido[3,4-b]indole-1,4-diona;

(3S,6R,12aR)-2,3,6,7,12,12a-hexahidro-6-(5-benzofuranil)-2,3-dimetil-pirazino[2'1': 6,1] pyrido[3,4-b]indole-1,4-diona;

(6R,12aR)-2,3,6,7,12,12a-hexahidro-6-(5-benzofuranil)-2-isopropil-pirazino [2',1': 6,1] pyrido[3,4-b]indole-1,4-diona;

y solvatos fisiológicamente aceptables de ellos.

8. El artículo de fabricación de la reivindicación 8, donde el inhibidor PDE5 selectivo se dosifica en 5, 10, o 20 mg/Tableta.

9. Un método para el tratamiento de la disfunción sexual en pacientes que lo necesiten, que incluye la administración a un paciente que lo necesite, de un inhibidor PDE5 selectivo en una dosis de 1 a 20 mg por día.

10. El método de la reivindicación 10 donde el paciente sufre una enfermedad cardiovascular.

11. Un artículo de fabricación como se ha descrito sustancialmente aquí anteriormente en la especificación.

12. El uso de una forma de dosificación oral que incluye un inhibidor PDE5 selectivo en dosis de 1 a 20 mg para el tratamiento de disfunción sexual.

ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Santafé de Bogotá, 30 de Junio del 2000.

TRADUCCION OFICIAL No. 2000/136
HILDA AGUILERA DE FIELD
INTERPRETE OFICIAL
DEC No. 223 DEL MIN. DE JUSTICIA

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 126

Radicación no 00-29997

Concepto Técnico no 516 Clasificación Internacional de Patentes A 61 K 31/505

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de Patente de Invención:

SI [X]	NO [ ]	Contiene un resumen de la invención (Art.26-e).
SI [X]	NO [ ]	Contiene el título o nombre de la invención (Art.27-d).
SI [X]	NO [ ]	Contiene la descripción de la invención (Art.26-b).
SI [ ]	NO [ ]	NO ES APLICABLE [X] Contiene los dibujos necesarios para comprender la invención (Art.26-d)
SI [X]	NO [ ]	Contiene una o más reivindicaciones. (Art.26-c).
SI [ ]	NO [ ]	NO ES APLICABLE [X] Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
SI [ ]	NO [ ]	NO ES APLICABLE [X] Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-i).
SI [ ]	NO [X]	La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
SI [X]	NO [ ]	La prioridad coincide con la materia reivindicada.
SI [X]	**NO [ ]**	**CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI [ ] NO [ ] ver hoja(s) anexa(s)

1. Se modifica el título de la solicitud (Folio 54).
2. Se presenta nuevo capítulo reivindicatorio (Folio 55 a 58), nuevo Extracto para Publicación y nuevos tarjetas, tanto de archivo temático como de propietarios.

EXAMINADOR TÉCNICO
202038

Bogotá D. C., Marzo 20, 2002.

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Industria y Comercio
SUPERINTENDENCIA

Folio 127

2020
Bogotá DC

0 768

Doctora
DILIA MARIA RODRIGUEZ
Apoderado

REFERENCIA:	Radicación No.	00-29997
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	-
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá DC, a los 23 ABR. 2002

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Bogotá, DC, Enero - 2003 El extracto de esta solicitud fue publicado en el número 517 de la Gaceta de Propiedad Industrial, de fecha 27-06-2002 . El término hábil señalado por la ley expiró el 24-sept-2002 y SI ___ NO X se presentaron oposiciones por parte de terceros.

202027

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