

Q.F.
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCION

21. EXPEDIENTE No.

PCT
04-1222

54. TITULO METODOS Y MATERIALES PARA EL TRATAMIENTO DE DEFICIENCIAS
DE TESTOSTERONA EN VARONES

51. CLASIFICACION INTERNACIONAL A61K 31/225, 31/135

71. SOLICITANTE ZONAGEN, INC.

DOMICILIO THE WOODLANDS, TEXAS, ESTADOS UNIDOS DE AMERICA

74. APODERADO CAMILO ALVAREZ

22. SANTAFE DE BOGOTA, D.C. _____

PETITORIO

Industria y Comercio
SUPERINTENDENCIA



04 001222 00

SUPERINDUSTRIA Y COMERCIO
Radicación: 04001222 00000000 Folios: 73
Fecha (MM): 2004-01-09 12:51:14
Trámite: 011 PCT-PATENTE 379 FASE NACI 411 PRESENTAC
Dependencia: 0200 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

①

SOLICITUD DE:



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

②

SOLICITANTE
(71)

Nombre: ZONAGEN, INC.

2408 Timberloch Place

Dirección:

B-4

The Woodlands, Tx 77380

Estados Unidos de America

Nacionalidad o Domicilio: E.U.A.

Lugar de Constitución: E.U.A.

Teléfono:

Fax:

E-mail:

IDENTIFICACIÓN

C.C.



NT



C.E.



Otro



Cual

Número

③

REPRESENTANTE
O APODERADO

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Dirección:

Calle 69A No. 4 - 64

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Teléfono:

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Fax:

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E-mail:

IDENTIFICACIÓN

C.C.



NT



C.E.



Otro



Cual

Número

19219009

TP20343

④

INVENTOR (ES)
(72)

Nombre: Joseph S. Podolski

3 Pebble Hollow Court

Dirección:

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Estados Unidos de America

Nacionalidad o Domicilio

Estados Unidos de America

⑤ PCT (86)

Solicitud Internacional No.

PCT/US02/21524

Fecha

Julio 9, 2002

Publicación Internacional No.

WO 03/005954 A3

Fecha

Enero 23, 2003

⑥ Título (54)

Metodos y Materiales para el Tratamiento de

Deficiencias de Testosterona en Varones

⑦

Clasificación Internacional (51)

A61K 31/225, 31/135

⑧

Prioridad

(33) Pais de Origen

(32) Fecha

(31) Número de Solicitud

SI



NO



E.U.A.

Julio 9/01

60/304,313

⑨

Comprobante de pago No.

04 001222 00

Fecha

Enero 7/04

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

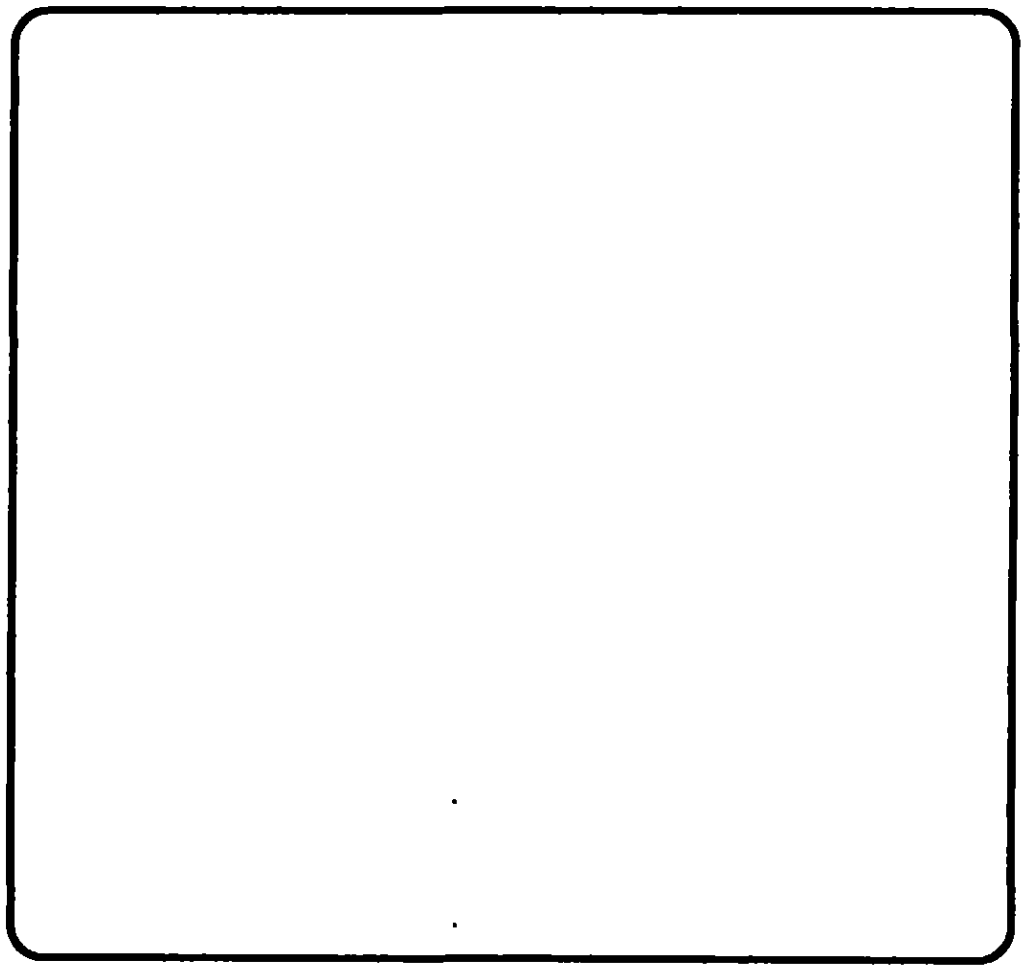
2003-FSC-02-04-047

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☒ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☐ Otros

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente.

NOMBRE: Camilo Alvarez

FIRMA:

C.C. 19.219.005 T.P. 20.243

Instrucciones para la presentación de los anexos, ver reverso de esta página.

3

SUPERINDUSTRIA Y COMERCIO
Radiación : 04001222 00000000 Folio: 13
Fecha (MM): 2004-01-07 12:51:14
Trámite : 011 PCI-PAIEM J/P FASE NACI 411 PRESENTAC
Dependencia: SED DIVISION DE NUEVAS CIERREJONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 1,102
FECHA : ENERO 7 DE 2004

***** CONSIGNACION *****

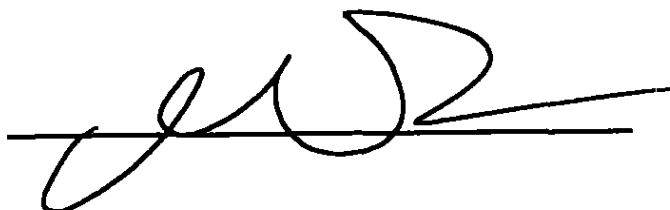
DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAMILO ALVAREZ	CONSIGNACION	BANCO POPULAR	030-00110-6	4536620	07/01/2004	422,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	110 PTC SOLICITUD DE PATENTE DE INVEN	422,000.00
		TOTAL :	\$ 422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE :



RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 212875-00215

Box No. I TITLE OF INVENTION Methods and Materials for the Treatment of Testosterone Deficiency in Men	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) ZONAGEN, INC. 2408 Timberloch Place, B-4 The Woodlands, Texas 77380 United States of America	Telephone No. 281/719-3400 Facsimile No. 281/719-3446 Teleprinter No. Applicant's registration No. with the Office
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) PODOLSKI, Joseph S. 3 Pebble Hollow Court The Woodlands, Texas 77381 United States of America	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) CLOUGH, David W. KATTEN MUCHIN ZAVIS ROSENMAN 525 West Monroe Street Suite 1600 Chicago, IL 60661 United States of America	Telephone No. 312/902-5464 Facsimile No. 312/577-8736 Teleprinter No. Agent's registration No. with the Office 36,107
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☐ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☐ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☐ **EP** European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|--|---|---|
| ☐ AE United Arab Emirates | ☐ GM Gambia | ☐ NZ New Zealand |
| ☐ AG Antigua and Barbuda | ☐ HR Croatia | ☐ OM Oman |
| ☐ AL Albania | ☐ HU Hungary | ☐ PH Philippines |
| ☐ AM Armenia | ☐ ID Indonesia | ☐ PL Poland |
| ☐ AT Austria | ☐ IL Israel | ☐ PT Portugal |
| ☐ AU Australia | ☐ IN India | ☐ RO Romania |
| ☐ AZ Azerbaijan | ☐ IS Iceland | ☐ RU Russian Federation |
| ☐ BA Bosnia and Herzegovina | ☐ JP Japan | |
| ☐ BB Barbados | ☐ KE Kenya | ☐ SD Sudan |
| ☐ BG Bulgaria | ☐ KG Kyrgyzstan | ☐ SE Sweden |
| ☐ BR Brazil | ☐ KP Democratic People's Republic of Korea | ☐ SG Singapore |
| ☐ BY Belarus | ☐ KR Republic of Korea | ☐ SI Slovenia |
| ☐ BZ Belize | ☐ KZ Kazakhstan | ☐ SK Slovakia |
| ☐ CA Canada | ☐ LC Saint Lucia | ☐ SL Sierra Leone |
| ☐ CH & LI Switzerland and Liechtenstein | ☐ LK Sri Lanka | ☐ TJ Tajikistan |
| ☐ CN China | ☐ LR Liberia | ☐ TM Turkmenistan |
| ☐ CO Colombia | ☐ LS Lesotho | ☐ TN Tunisia |
| ☐ CR Costa Rica | ☐ LT Lithuania | ☐ TR Turkey |
| ☐ CU Cuba | ☐ LU Luxembourg | ☐ TT Trinidad and Tobago |
| ☐ CZ Czech Republic | ☐ LV Latvia | |
| ☐ DE Germany | ☐ MA Morocco | ☐ TZ United Republic of Tanzania |
| ☐ DK Denmark | ☐ MD Republic of Moldova | ☐ UA Ukraine |
| ☐ DM Dominica | | ☐ UG Uganda |
| ☐ DZ Algeria | ☐ MG Madagascar | ☐ US United States of America |
| ☐ EC Ecuador | ☐ MK The former Yugoslav Republic of Macedonia | |
| ☐ EE Estonia | ☐ MN Mongolia | ☐ UZ Uzbekistan |
| ☐ ES Spain | ☐ MW Malawi | ☐ VN Viet Nam |
| ☐ FI Finland | ☐ MX Mexico | ☐ YU Yugoslavia |
| ☐ GB United Kingdom | ☐ MZ Mozambique | ☐ ZA South Africa |
| ☐ GD Grenada | ☐ NO Norway | ☐ ZM Zambia |
| ☐ GE Georgia | | ☐ ZW Zimbabwe |
| ☐ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that these additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

6

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 9 July 2001 (09.07.01)	60/304,313	US		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / .. US

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):	Number of declarations
☐ Box No. VIII (i) Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

7

Box No. IX CHECK LIST; LANGUAGE OF FILING																																											
This international application consists of: (a) the following number of sheets in paper form: <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">request (including declaration sheets)</td> <td style="width: 20%; text-align: right;">4</td> </tr> <tr> <td>description (excluding sequence listing part)</td> <td style="text-align: right;">15</td> </tr> <tr> <td>claims</td> <td style="text-align: right;">1</td> </tr> <tr> <td>abstract</td> <td style="text-align: right;">1</td> </tr> <tr> <td>drawings</td> <td style="text-align: right;">3</td> </tr> <tr> <td>Sub-total number of sheets</td> <td style="text-align: right;">24</td> </tr> <tr> <td colspan="2">sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)</td> </tr> <tr> <td>Total number of sheets</td> <td style="text-align: right;">24</td> </tr> </table> (b) sequence listing part of description filed in computer readable form (i) ☐ only (under Section 801(a)(i)) (ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii)) Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column):	request (including declaration sheets)	4	description (excluding sequence listing part)	15	claims	1	abstract	1	drawings	3	Sub-total number of sheets	24	sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)		Total number of sheets	24	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">1. ☒ fee calculation sheet</td> <td style="width: 20%; text-align: right;">:</td> </tr> <tr> <td>2. ☐ original separate power of attorney</td> <td style="text-align: right;">:</td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td style="text-align: right;">:</td> </tr> <tr> <td>4. ☐ copy of general power of attorney, reference number, if any:</td> <td style="text-align: right;">:</td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td style="text-align: right;">:</td> </tr> <tr> <td>6. ☐ priority document(s) identified in Box No. VI as item(s):</td> <td style="text-align: right;">:</td> </tr> <tr> <td>7. ☐ translation of international application into (language):</td> <td style="text-align: right;">:</td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td style="text-align: right;">:</td> </tr> <tr> <td>9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))</td> <td style="text-align: right;">:</td> </tr> <tr> <td colspan="2">(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)</td> </tr> <tr> <td colspan="2">(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter</td> </tr> <tr> <td colspan="2">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column</td> </tr> <tr> <td>10. ☐ other (specify):</td> <td style="text-align: right;">:</td> </tr> </table>	1. ☒ fee calculation sheet	:	2. ☐ original separate power of attorney	:	3. ☐ original general power of attorney	:	4. ☐ copy of general power of attorney, reference number, if any:	:	5. ☐ statement explaining lack of signature	:	6. ☐ priority document(s) identified in Box No. VI as item(s):	:	7. ☐ translation of international application into (language):	:	8. ☐ separate indications concerning deposited microorganism or other biological material	:	9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	:	(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)		(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column		10. ☐ other (specify):	:
request (including declaration sheets)	4																																										
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claims	1																																										
abstract	1																																										
drawings	3																																										
Sub-total number of sheets	24																																										
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(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column																																											
10. ☐ other (specify):	:																																										
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English																																										

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).
By: David W. Clough, Ph.D. Attorney for Applicant Registration No.: 36,107

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

PC

FEE CALCULATION SHEET
Annex to the Request

Applicant's or agent's file reference 212875-00215 Applicant ZONAGEN, INC. CALCULATION OF PRESCRIBED FEES 1. TRANSMITTAL FEE 240.00 [T] 2. SEARCH FEE 700.00 [S] International search to be carried out by <u>EP</u> (If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.) 3. INTERNATIONAL FEE Basic Fee Where item (b) of Box No. IX applies, enter Sub-total number of sheets } Where item (b) of Box No. IX does not apply, enter Total number of sheets } [b1] first 30 sheets 407.00 [b1] [b2] <u> </u> x <u> </u> = <u> </u> [b2] number of sheets in excess of 30 fee per sheet [b3] additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)): 400 x <u> </u> = <u> </u> [b3] fee per sheet Add amounts entered at b1, b2 and b3 and enter total at B [B] Designation Fees The international application contains <u> </u> designations. <u>5</u> x <u>88.00</u> = <u>440.00</u> [D] number of designation fees payable (maximum 5) amount of designation fee Add amounts entered at B and D and enter total at I 1787.00 [I] (Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.) 4. FEE FOR PRIORITY DOCUMENT (if applicable) 15.00 [P] 5. TOTAL FEES PAYABLE 1802.00 Add amounts entered at T, S, I and P, and enter total in the TOTAL box TOTAL ☐ The designation fees are not paid at this time.	Receiving Office use only International Application No. _____ Date stamp of the receiving Office _____
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MODE OF PAYMENT ☒ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons ☐ cheque ☐ bank draft ☐ revenue stamps ☐ other (specify): _____	
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all receiving Offices) ☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. ☐ Authorization to charge the fee for priority document.	
Receiving Office: RO/ <u>US</u> Deposit Account No.: <u>50-1214</u> Date: <u>9 July 2002</u> Name: <u>David W. Clough, Ph.D.</u> Signature: <u>David W. Clough</u>	

**METHODS AND MATERIALS FOR THE TREATMENT OF TESTOSTERONE
DEFICIENCY IN MEN**

[0001] This application claims the benefit, under 35 U.S.C. § 119(e), of U.S. Provisional Patent Application No. 60/304,313, filed on July 9, 2001.

FIELD OF THE INVENTION

[0002] The present invention relates to the compositions and methods for increasing testosterone levels. More specifically, the present invention relates to a composition comprising clomiphene enriched for trans-clomiphene. The present invention also relates to the use of a composition comprising clomiphene enriched for trans-clomiphene reagents for increasing testosterone levels.

BACKGROUND

[0003] Testosterone is the primary male androgen, playing a vital role in overall male health. Testosterone is essential to the development and maintenance of specific reproductive tissues (testes, prostate, epididymis, seminal vesicle, and penis) and male secondary sex characteristics. It plays a key role in libido and erectile function and is necessary for the initiation and maintenance of spermatogenesis. Testosterone also has important functions not related to reproductive tissues. For example, it positively affects body composition by increasing nitrogen retention, which supports lean body mass, muscle size and strength. It also acts on bone to stimulate bone formation.

[0004] Testosterone secretion is the end product of a series of hormonal processes. Gonadotropin-releasing hormone (GnRH), which is secreted in the hypothalamus, controls the pulsatile secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which are secreted by the anterior pituitary. LH, in turn, regulates the production and

secretion of testosterone in the Leydig cells of the testes, while FSH assists in inducing spermatogenesis.

[0005] Testosterone is most often measured as "total testosterone." This measurement includes testosterone that is bound to sex hormone-binding globulin (SHBG) (~44%) and is therefore not bioavailable and testosterone which either is free (~2%) or loosely bound to other proteins (non-SHBG-bound) (~54%).

[0006] Results from a WHO study indicate that testosterone is normally secreted in a circadian rhythm, with higher levels in the morning and nadir levels occurring around 8 to 10 p.m. See FIG. 1. This variation in testosterone secretion throughout the day becomes much less pronounced in older men (mean age equals 71 years). The importance of this rhythm is not known at this time.

[0007] Samples were obtained from both young and elderly patients every 10 minutes for 24 hours via an indwelling cannula. According to Tenover (1987) the mean 24 hr total serum testosterone levels in healthy young men (age range 22 yrs.-35 yrs. mean 27.3 yrs) was 4.9 ± 0.3 ($\pm$ SEM) mg/ml (17.0 nmol/L) while older men (age range 65yrs – 84 yrs. mean 70.7 yrs.) had a significantly lower mean 24 hrs. total serum testosterone level of 4.1 ± 0.4 mg/ml. ($P < 0.5$; 14.2 nmol/L).

[0008] Total serum testosterone levels obtained from single random samples were also significantly lower in older men (4.0 ± 0.2 mg/ml [13.9 nmol/L]) as compared to 4.8 ± 0.2 mg/ml [16.6 nmol/L] in healthy young men.

[0009] Testosterone deficiency can result from underlying disease or genetic disorders and is also frequently a complication of aging. For example, primary hypogonadism results from primary testicular failure. In this situation, testosterone levels are low and levels of pituitary gonadotropins (LH and FSH) are elevated. Secondary hypogonadism is due to inadequate secretion of the pituitary gonadotropins. In addition to a low testosterone level, LH and FSH

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levels are low or low-normal. Some of the sequelae of adult testosterone deficiency include a wide variety of symptoms including: loss of libido, erectile dysfunction, oligospermia or azoospermia, absence or regression of secondary sexual characteristics, progressive decrease in muscle mass, fatigue, depressed mood and increased risk of osteoporosis.

[0010] Several forms of testosterone therapy exists in the United States today. Recently, transdermal preparations have gained favor in the market. However, a scrotal testosterone patch results in supraphysiologic levels of 5 α -dihydrotestosterone (DHT) due to the high concentration of 5 α -reductase in scrotal skin. It is not known whether these elevated DHT levels have any long-term health consequences. Nonscrotal systems are considered more convenient and most patients achieve average serum concentrations within the normal range and have normal levels of DHT. Oral testosterone therapy is not recommended because doses required for replacement therapy are associated with significant risk of hepatotoxicity.

SUMMARY

[0011] The present invention is directed to compositions useful for increasing testosterone levels in male mammals and for ameliorating or preventing the sequelae of low testosterone levels. In one of its aspects the invention is directed to compositions having active ingredients comprising 0% to 29% weight/weight of (*cis*-, *Z*-, *trans*-clomiphene) (hereinafter "*cis*-clomiphene") and 100% to 71% w/w (*trans*-, *E*-, *cis*-clomiphene) (hereinafter "*trans*-clomiphene") or pharmaceutically acceptable salts thereof. Among the preferred compositions of the present invention which contain both *cis*-clomiphene and *trans*-clomiphene invention are compositions wherein the ratio of *trans*-clomiphene and *cis*-clomiphene is greater than 1. A more preferred composition according to the present invention comprises about 100% w/w of active ingredients of *trans*-clomiphene or a pharmaceutically acceptable salt thereof. All compositions of the present invention may further comprise suitable pharmaceutical excipients diluents, carriers, and the like. Analogs

of the *cis*-clomiphene and *trans*-clomiphene are also contemplated for use in all aspects of the present invention.

[0012] The present invention is also directed to methods for increasing serum testosterone levels in hypogonadal male mammals (and for ameliorating or preventing the sequelae of low testosterone levels), the method comprising administering to a subject male an effective amount of a composition according to the present invention, the compositions having active ingredients comprising 0% to 29% weight/weight of *cis*-clomiphene and 100% to 71% w/w *trans*-clomiphene including any of their pharmaceutically acceptable salts thereof. Among the preferred methods are those in which the administered compositions contain both isomers wherein the ratio of *trans*-clomiphene to *cis*-clomiphene is greater than 1. A more preferred method comprises administering to the male a composition comprising about 100% w/w of *trans*-clomiphene.

BRIEF DESCRIPTION OF THE DRAWING

[0013] FIG. 1 is a graphic representative of the normal secretory total serum testosterone profiles in healthy men (young and old).

[0014] FIG. 2 shows the chemical structure of clomiphene citrate.

[0015] FIG. 3 is a graphic demonstration of the time course of serum testosterone levels with Clomid, Enclomid and Zuclomid.

DETAILED DESCRIPTION

[0016] The present invention provides methods and compositions useful for increasing testosterone levels in male mammals and for ameliorating or preventing the sequelae of low testosterone levels including but not limited to those described above.

[0017] Clomiphene (FIG. 2) is an antiestrogen related to tamoxifen that blocks the normal estrogen feedback on the hypothalamus and subsequent negative feedback on the pituitary. This leads to increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH).

In men, these increased levels of gonadotropins stimulate the Leydig cells of the testes and result in the production of higher testosterone levels. Clomiphene citrate has the following structure:

[0018] Ernst *et al.*, J. Pharmaceut. Sci. 65:148 (1976), have shown that clomiphene is a mixture of two geometric isomers which they refer to as *cis*,-Z-, clomiphene (*cis*-clomiphene or zuclophene) and *trans*,-E-, clomiphene, (*trans*-clomiphene or enclophene).

According to Ernst, *et al.* *trans*-clomiphene HCl has a melting point of 149°C-150.5°C, while *cis*-clomiphene HCl has a melting point of 156.5°C-158°C.

[0019] Ernst *et al.* have also noted that (the *trans*-isomer) is antiestrogenic (AE) while the *cis*-isomer is the more potent and more estrogenic form and has also been reported to have anti-estrogenic activity. The authors attribute the effect of the drug on ovulatory activity to both forms stating that the mixture is more effective than *trans*-clomiphene alone. The *trans*-isomer aids ovulation at the level of the hypothalamus. The estrogenic isomer *cis*-clomiphene contributes to enhanced ovulation elsewhere in the physiologic pathway leading to ovulation. The isomers are also reported to have different *in vivo* half-life. Furthermore the *cis* form has been reported to leave residual blood levels for in excess of one month following a single dose.

[0020] Vandekerckhove, *et al.* (Cochrane Database Syst Rev 2000;(2):CD000151 (2000)) noted that ten studies involving 738 men have suggested that anti-estrogens appear to have a beneficial effect on endocrinal outcomes, *i.e.* testosterone, but there is not enough evidence to evaluate fertility effects. Nevertheless should clomiphene administration enhance testosterone levels then one could easily conclude that the drug should positively impact the side effects of testosterone deprivation as long as the testes still retain the ability to respond to gonadotropin stimulation.

[0021] Clomiphene is currently approved as a mixture of both cis- and trans-isomers, the cis-isomer being present as about 30% to 50% (Merck Manual) for fertility enhancement in the anovulatory patient. Clomiphene improves ovulation by initiating a series of endocrine events culminating in a preovulatory gonadotropin surge and subsequent follicular rupture. The drug is recommended to be administered for 5 days at a dose of up to 100 mg daily. Clomiphene has also been associated with numerous side effects including: blurred vision, abdominal discomfort, gynecomastia, testicular tumors, vasomotor flushes, nausea, and headaches. Furthermore, other studies suggest that clomiphene possesses both genotoxic and tumor enhancement effects. The net outcome of these observations is that clomiphene in its current format, having between 30% and 50% of the cis isomer, would be unacceptable for chronic therapy in men for the treatment of testosterone deficiency.

[0022] Clomiphene has also been used for therapeutic intervention in men with low testosterone levels. Tenover *et al.*, *J. Clin. Endocrinol. Metab.* 64:1103, (1987) and Tenover *et al.*, *J. Clin. Endocrinol. Metab.* 64:1118 (1987) found increased in FSH, LH in both young and old men after treatment with clomiphene. They also found increases in free and total testosterone in men with young men showing significant increases

[0023] Studies were also conducted to determine whether or not clomiphene could be used to improve fertility in men by improving semen quality. Homonnai *et al.* *Fertil. and Steril* 50:801 (1988) saw increases in sperm concentration and count but others have not. (See e.g., Sokel, *et al.*, *Fertil. and Steril.* 49:865 (1988); Check, *et al.*, *Int. J. Fertil.* 34:120 (1989); Purvis, *et al.*, *Int. J. Androl* 21:109 (1989); and Breznik, *Arch. Androl.* 21:109 (1993).) One group saw a deterioration in the percentage of normal sperm with long-term treatment. Shamia, *et al.*, *Arch. Androl* 21:109 (1991). A WHO study showed no changes in semen quality or fertility after 6 months of treatment. (Anonymous *Androl.* 15:299 (1992).) A meta-analysis seems to confirm that testosterone levels go up in men with poor quality sperm

but not fertility. (Vanderkerckhove, *et al.*, 2000). Studies have also suggested that long term treatment with clomiphene does not seem to have a drastic deleterious effect on health, although it did show that treatment resulted in poorer sperm quality after 4 months. Studies have kept men on clomiphene for as long as 18 months and at levels of 25 mg per day or 100 mg every other day.

[0024] In 1991, Guay *et al* (Urology 38:377 (1991)) suggested that clomiphene could treat sexual dysfunction in men. Their hypothesis seems to be that sexual function follows testosterone levels. This was supported by early studies showing positive influence of androgens and sexual function, Davidson, *et al.*, J. Clin. Endocrinol. Metab. 48:955 (1979), and studies that rated sleep-related erections as a strong response to T, Cunningham, *et al.*, J. Clin. Endocrinol. Metab. 70:792 (1990). However, in 1995, Guay *et al.* (Gray, *et al.*, J. Clin. Endocrinol. Metab. 80:3546 (1995)) published a study in which they saw increase in LH, FSH, and testosterone after 2 months of clomiphene but no effects on erectile dysfunction. There might be some advantage for young men and specific groups of older men, but it seems that just raising the testosterone level is not enough. Effects of testosterone on sleep-related erections may have been taken too seriously (Herskowitz, *et al.*, J. Psychosomat. Res. 42:541 (1997)).

[0025] According to the present invention, a composition comprising of one isomer preferably *trans*-clomiphene or a predefined blend of the isomers of clomiphene as described below differing from the normally produced mixture are used to enhance testosterone levels while reducing the side effects of the drug. Thus, the present invention provides an oral therapy for increasing testosterone levels, which lacks or has diminished side effects connected with the existing clomiphene formulations.

[0026] In one embodiment of the present invention, a patient who has a need or desire to increase their serum testosterone levels are administered one or more dosages of an effective

amount of composition comprising *trans*-clomiphene at a dosage between one mg to about 200 mg (although the determination of optimal dosages is with the level of ordinary skill in the art). *Cis*-clomiphene may also be present in the composition so long as the ratio of *trans*-clomiphene to *cis*-clomiphene is greater than 1. Analogs of the *trans*- and *cis*- isomers of clomiphene such as those described in Ernst, *et al. supra* are also useful in the practice of the present invention.

[0027] Dosages are preferably (but not necessarily) administered as part of a dosage regimen designed to give rise to serum testosterone levels that mimic or correspond to the normal secretory total serum testosterone profile described in FIG. 1. For example, according to FIG. 1 a dosage of the preferred composition may be administered in a pharmaceutical formulation that would give rise to peak serum testosterone levels at around 8 a.m. Such pharmaceutical formulations may be in the form of sustained release formulations prepared as described for example in U.S. Patent No. 6,221,399, Japanese patent 4-312522, Meshali *et al.*, *Int. J. Phar.* 89:177-181 (1993), Kharenko *et al.*, *Intern. Symp. Control Rel. Bioact. Mater.* 22:232-233 (1995), WO 95/35093, Dangprasit *et al.*, *Drug. Devel. and Incl. Pharm.* 21 (20):2323-2337 (1995); U.S. Patent Nos. 6,143,353, 6,190,591, 6,096,338, 6,129,933, 6,126,969, 6,248,363 and other sustained release formulations well known in the art.

[0028] Suitable pharmaceutical compositions or unit dosage form may be in the form of solids, such as tablets or filled capsules or liquids such as solutions suspensions, emulsions, elixirs or capsules filled with the same, all for oral use. The compositions may also be in the form of sterile injectable solutions or emulsions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions.

[0029] Compositions according to the present invention may also be administered by the intravenous, subcutaneous, buccal, transmucosal, intrathecal, intradermal, intracisternal or

other routes of administration. After administration of the composition serum testosterone levels may be measured as described above and dosages may be altered to achieve a sufficient increase in the serum testosterone levels to achieve the desired physiological results associated with normal testosterone described above.

[0030] All of the references discussed herein are incorporated by reference in their entirety.

[0031] The following Example is meant to be illustrative of the invention and is not intended to limit the scope of the invention as set out in the appended claims.

EXAMPLE 1

Effects of Clomids on Serum Testosterone in Male Baboons

[0032] Adult, male, Baboons were given 1.5 mg/kg of Clomid, Enclomid (*trans*-Clomid) or Zucloimid (*cis*-Clomid) for 12 consecutive days. The samples analyzed were sera taken on the day of first treatment before being given test article (day 0), after 12 days of treatment (day 12) and 7 days after the last treatment (end or wash-out).

1. Effects on Body Weight and Serum LH, FSH, PRL and Testosterone

[0033] There were significant increases in total serum testosterone in the group receiving Enclomid. See Table 1. There were no differences among groups in the baseline period or at day 0. There were also no differences among the three groups 7 days after treatment (the washout period). However, Enclomid produced higher levels of testosterone compared to Clomid and Zucloimid on day 6 ($p = 0.03$ and $p = 0.00002$ respectively) and compared to Zucloimid on day 12 ($p = 0.047$). Zucloimid clearly did not raise total serum testosterone to any extent. Compared to the animals receiving Enclomid, the animals receiving Clomid exhibited more variable total testosterone levels on day 6 and later as judged by their coefficients of variations. When we looked at the time course of the effects (FIG. 3), we determined that only Enclomid significantly and statistically raised total serum testosterone

on days 6 and 12 compared with either baseline or day 0 values. Moreover, cessation of Enclomid treatment, resulted in a significant drop in the level of total serum testosterone between day 12 and day 18 (washout). This indicates that Enclomid is readily cleared from the circulation consistent with the metabolic clearance seen for Enclomid in humans. Enclomid was clearly better and more consistent than Clomid itself and Zucloamid was ineffective.

Table 1 - Serum Testosterone Levels (ng/dl)

Group	ID	baseline 12/3/01	0 day 12/7/01	6 days 12/13/01	12 days 12/20/01	wash-out 12/26/01
CLO	7500	79.01	76.15	940.97	891.5	150.9
	9012	97.55	305.24	585.92	555.6	316.3
	9097	158.06	102.94	151.12	318.9	143.6
	mean	111.5	161.4	559.3	588.7	203.6
	SD	41.3	125.2	395.6	287.7	97.7
ENCLO	7223	64.57	74.96	1223.8	633.6	307.2
	8021	166.86	133.59	1128.2	1466	399.2
	8369	170.45	106.47	1081.1	1166	271
	mean	134.0	105.0	1144.4	1088.5	325.8
	SD	60.1	29.3	72.7	421.6	66.1
ZUCLO	7438	124.84	210.4	137.51	314.5	359.7
	8292	104.66	67.37	169.98	406.1	860.5
	10098	282.29	904.82	227.95	353.0	274.1
	mean	170.6	394.2	178.5	357.9	498.1
	SD	97.3	448.0	45.8	46.0	316.8
ANOVA		p = 0.61	p = 0.43	p = 0.007	p = 0.57	p = 0.256
K-W		p = 0.56	p = 0.84	p = 0.051	p = 0.079	p = 0.252

[0034] There were no changes in serum LH or FSH. The ratio of total serum testosterone to LH followed the same pattern as total serum testosterone, suggesting a lack of dependence (data not shown). There was also no change in body weight during the 12 day study. There was a decrease in serum prolactin (PRL) during the study in the group receiving Enclomid, suggesting an effect of antiestrogen that has been described in part (Ben-Jonathan and

Hnasko, 2001) and expected on the basis of the fact that as men age, testosterone declines and Prolactin increase (Feldman *et al.*, 2002).

2. Effects on Clinical Chemistry Parameters

[0035] The mean values for each parameter did not differ among the three groups for any test parameter at the beginning of the study as determined by ANOVA or by the Kruskal-Wallis test. All groups exhibited normal values at each parameter except for (1) serum sodium; a related calculated parameter, anionic gap, which were low for all nine baboons throughout the trial; (2) serum glucose; and (3) BUN which were high on day 0 for the group which would be treated with Enclomid. On day 12 of treatment and 7 days after treatment (washout), there were no differences among groups for any parameter except anionic gap that showed that the Clomid and Zucloimid groups had lower values than the Enclomid group. The values of serum sodium and anionic gap appear to be anomalies associated with this group of baboons.

[0036] There were substantive effects on the red blood cell population with Enclomid and Zucloimid and on hematocrit with Zucloimid. All the compounds lower the mean cell hemoglobin concentration (MCHC) either at day 0 or at the endpoint. With no change in mean cell hemoglobin (MCH) and an increase in the mean cell volume (MCV), the lowering of MCHC is predictable. Although testosterone might be expected to raise hematocrit, only Zucloimid treatment, which did not increase total serum testosterone, demonstrated a statistical difference. Clearly, men in a clinical trial that uses Zucloimid should be monitored for the characteristics of their red blood cell population. Enclomid would be predicted to have less of an effect.

[0037] There appears to be a clear effect of 12-day Enclomid treatment on platelets although the values found stayed within the normal range. One thing to consider here is the sexual dimorphism in platelet counts between male and female baboons (279 for males vs. 348 for

EO

females). This is likely to be due to hormones. Since the Enclomid group demonstrated increased testosterone, the lowering of the platelet count could be secondary to the change in testosterone in this group. Moreover, treatment with Enclomid pushed the platelet count to its normal male level from a day 0 level that was the high end of the normal range for this group. Enclomid would not necessarily predict a deleterious effect on platelets.

[0038] All the Clomids tested had effects on the white blood cell (WBC) population, the most striking was that of Enclomid on raising the counts of lymphocytes and eosinophiles. The effects are not as straightforward as they would seem to be. There appears to be a strong effect of Enclomid on lowering the per cent of granulocytes in the blood. The effects are very strong after the 7-day washout period when the values are decreased below the normal range. (This time course could reflect the relatively long time required to affect change the WBC population.) There is little sexual dimorphism in baboons with respect to the white blood cell populations, so the effects are more likely to be due to the compound itself than changes in testosterone. However, when we look at the calculated count of granulocytes using the WBC count, we find no differences in granulocyte count due to any compound. Concomitantly, it is the lymphocyte story that is the most interesting. Both the count and per cent lymphocytes in the population increase with Enclomid treatment. Whereas the mean values of per cent lymphocytes remain in the normal range, given the trend for an increase in WBC count, the net effect is an increase in lymphocyte count with Enclomid. This eosinophil result is analogous. There is a clear implication for treating men who have low lymphocytes, such as men who are HIV-positive. Since Enclomid is unlikely to lower lymphocytes based on this result, a case could be made for its use in the population of men with AIDS. These individuals are often treated with agents that are intended to raise testosterone due to the wasting effects of disease. Low liver and kidney toxicity and favorable effects on cholesterol

and lipids are also highly favored attributes for any medication intended for use HIV-positive men who are already compromised by their disease.

[0039] The increase in serum glucose with Clomid or Zucloamid was within the normal range. In the case of Enclomid where the mean serum glucose values were high on day 0, there were no increases with treatment. There was no evidence that Enclomid would have a deleterious effect on blood glucose.

[0040] No clearly adverse effects on liver function are apparent as judged by the enzymes AST and ALT. The trend in these values was a decrease with treatment. An increase in the level of enzymes in the serum would indicate liver damage. ALT/SGPT was out of range low at the end of the study for the Clomid group although the differences over the treatment period were not statistically significant. The changes with Enclomid and Zucloamid were within the normal range. AST is depressed in pregnancy; thus the action of an estrogen agonist such as Zucloamid in lowering the marginal AST level could be rationalized. Alkaline phosphatase (ALP) is also found in the liver and is elevated various disease states. The lowering of ALP argues further against hepatic damage. There were no changes in serum albumin, also a liver product. A strong suppression of serum albumin over an extended time period could contribute to free serum steroid hormone levels in humans although a more important role is played by sex hormone binding globulin. As a bottom line, none of the compounds could be linked to liver damage on the basis of the parameters assayed.

[0041] Osteoblastic activity and diseases of the bone are accompanied by high serum ALP values. ALP was not elevated following Zucloamid treatment and was decreased in value following Enclomid treatment. The trends would predict a more benign result for the use of Enclomid compared to Zucloamid.

[0042] Although BUN and BUN/creatinine were altered during the study in the Clomid and Enclomid groups, the lack of a definitive change in creatinine argues against renal

dysfunction. A loss of glomerular filtration capacity would result in an increase in BUN. Decreased BUN occurs in humans due to poor nutrition (not likely in a controlled setting), or high fluid intake (presumably accompanied by edema). Also, despite an increase in total serum testosterone between day 0 and Day 12 with Enclomid, there were no differences between serum creatinine values, arguing against an increase in muscle mass over this short time interval.

[0043] Serum sodium levels were lower than reference values for all animals throughout the study. Serum carbon dioxide was higher than reference values on day 12 for the Clomid and Zuclomid groups. Serum anion gap was lower for all animals throughout the study, paralleling the sodium results. Enclomid raised this parameter towards normal values. The electrolyte imbalances detected in the test animals throughout all treatment periods remains elusive but might be part of the same fluid derangement phenomenon suggested by the BUN results.

[0044] Treatment with Enclomid tended to decrease serum cholesterol and Zuclomid tended to increase the same parameter although neither change reached statistical significance. Those changes were within the normal range although the trend for the two isomers to demonstrate opposite effects over a short period of time merits the further monitoring and might not be unexpected given that the isomers have, alternatively, estrogen agonist or antagonist activity. Enclomid might be expected to be more benign than Zuclomid with respect to serum cholesterol if used chronically.

[0045] The foregoing results indicate that Enclomid is more effective than Clomid or Zuclomid at enhancing total serum testosterone. Zuclomid is clearly not effective and that deficiency limits any use of Clomid for hypogonadism, particularly since the Zuclomid component of Clomid would predominate in the circulation over time given its longer half-life.

[0046] Enclomid appeared to be relatively benign in all aspects when compared to Zuclomid and, often, even Clomid. This is particularly true when consideration is given to the trend of Enclomid to lower cholesterol, and liver enzymes as opposed to Zuclomid's trend to raise the same parameters. The surprising trend for Enclomid to raise the lymphocyte count may be useful for men with AIDS if it can be shown the CD4+ subpopulation of lymphocytes is not lowered or is enhanced.

EXAMPLE 2

Method for Increasing Testosterone Level in Men Using *Trans*-clomiphene and Mixtures of *Trans*-clomiphene and *Cis*-clomiphene at Ratios Greater Than 1

[0047] Prior to administration of *trans*-clomiphene, blood samples are taken from subject males and testosterone levels are measured using methodologies described for example in Matsumoto, *et al.* Clin. Endocrinol. Metab. 56; 720 (1983) (incorporated herein by reference). Sex hormone binding globulin (SHBG), both free and bound to testosterone, may also be measured as described for example in Tenover *et al.* J. Clin. Endocrinol. Metab. 65:1118 (1987) which describe measurement of SHBG by both a [³H] dihydrotestosterone saturation analysis and by radioimmunoassay. Non-SHBG-bound testosterone levels (bioavailable testosterone) are also measured for example according to Tenover *et al.* J. Clin. Endocrinol and Metab. 65:1118 (1987). See also Soderguard *et al.* J. Steroid Biochem 16:801 (1982) incorporated herein by reference.

[0048] Patients are given daily dosages of 1.5 mg/kg clomiphene, wherein the ratio of *trans*-clomiphene to *cis*-clomiphene is greater than 1. Patients are monitored for testosterone levels such that the dosage amount and dosage frequency may be adjusted to achieve therapeutic levels of testosterone in the patient.

CLAIMS

I Claim:

1. A method for increasing serum levels of testosterone in a male mammal, the method comprising administering to the mammal an effective amount of a compound comprising *cis*-clomiphene and *trans*-clomiphene or analogs thereof or pharmaceutically acceptable salts or solvates thereof and optionally one or more pharmaceutically acceptable diluents, adjuvants, carriers or excipients and wherein the ratio of *trans*-clomiphene and *cis*-clomiphene is greater than 1 w/w.

2. The method of claim 1 wherein the composition consists essentially of an effective amount of *trans*-clomiphene or an analog thereof or a pharmaceutically effective salt or solvate thereof and optionally one or more pharmaceutically acceptable diluents, adjuvants, carriers or excipients.

3. A composition comprising 0% to about 29% w/w of *cis*-clomiphene and about 100% to about 71% *trans*-clomiphene or analogs thereof or pharmaceutically acceptable salts or solvates thereof and optionally one or more pharmaceutically acceptable diluents, adjuvants, carriers or excipients.

4. A composition comprising *cis*-clomiphene and *trans*-clomiphene or analogs thereof or pharmaceutically acceptable salts or solvates thereof and optionally one or more pharmaceutically acceptable diluents, adjuvants, carriers or excipients and wherein the ratio of *trans*-clomiphene and *cis*-clomiphene is greater than 1.

ABSTRACT

[0049] The present invention relates to the use of compositions comprising *trans*-clomiphene for treating men with hypogonadism. The invention is also directed to methods for treating males with hypogonadism.

FIG. 1

Normal Secretory Total Serum Testosterone Profiles in Healthy Young and Older Men

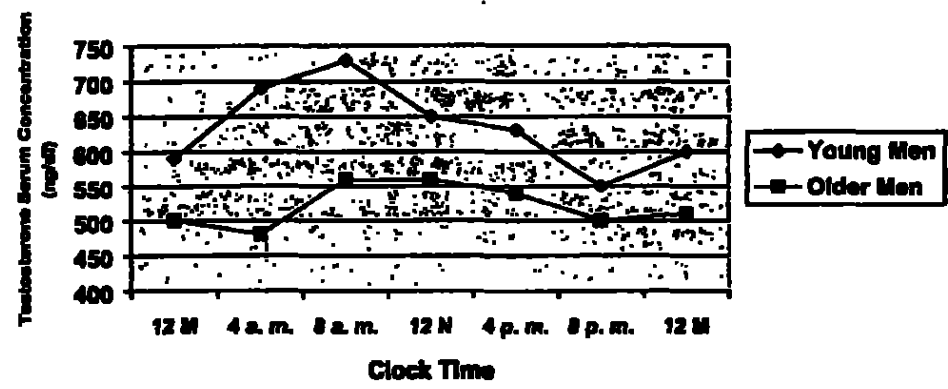


FIG. 2

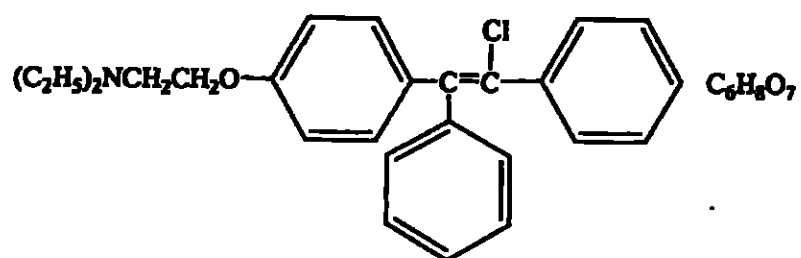
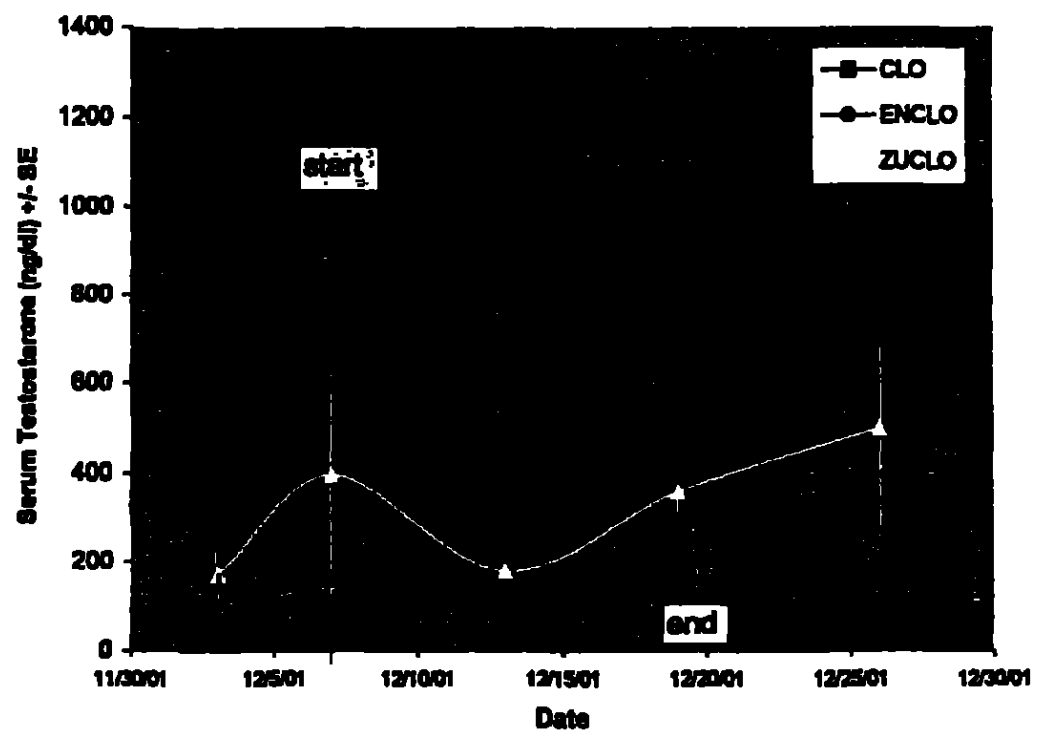


FIG. 3



MÉTODOS Y MATERIALES PARA EL TRATAMIENTO DE DEFICIENCIAS
DE TESTOSTERONA EN VARONES

Esta solicitud reclama el beneficio, de acuerdo con
5 el 35 USC § 119(e) de la solicitud de patente provisional
US No. 60/304,313, presentada el 9 de julio de 2001.

CAMPO DE LA INVENCION

La presente invención se refiere a las composiciones
10 y los métodos para aumentar los niveles de testosterona.
Más específicamente, la presente invención se refiere a
una composición que contiene clomifeno enriquecido para
trans-clomifeno. La presente invención también se refiere
al uso de una composición que contiene clomifeno
15 enriquecido para reactivos trans-clomifeno, para aumentar
los niveles de testosterona.

ANTECEDENTES

La testosterona es el andrógeno masculino primordial,
20 desempeña una función vital en la salud masculina general.
La testosterona es esencial para el desarrollo y
mantenimiento de los tejidos reproductores específicos
(testículos, próstata, epidídimo, vesícula seminal y pene)
y los caracteres sexuales secundarios masculinos.
25 Desempeña una función primordial en la libido y la función

eréctil y es necesaria para el inicio y mantenimiento de la espermatogénesis. La testosterona también tiene funciones importantes no relacionadas con los tejidos reproductivos. Por ejemplo, afecta positivamente la composición corporal aumentando la retención de nitrógeno, lo cual da soporte a la masa corporal magra, el tamaño y la resistencia muscular. También actúa sobre hueso para estimular la formación ósea.

10 La secreción de testosterona es el producto final de una serie de procesos hormonales. La hormona liberadora de gonadotropina (GnRH), que es secretada en el hipotálamo, regula la secreción pulsátil de la hormona luteinizante (LH) y la hormona estimuladora del folículo (FSH), que es secretada por la hipófisis anterior. La LH, a su vez, regula la producción y secreción de testosterona en las células de Leydig de los testículos, mientras que la FSH ayuda a inducir la espermatogénesis.

20 Con mucha frecuencia la testosterona se mide como "testosterona total". Esta medición incluye la testosterona que se une a la globulina de unión a la hormona sexual (SHBG) (~44%) y por tanto no está biodisponible, y testosterona libre (~2%) o débilmente unida a otras proteínas (no unida a SHBG) (~54%).

Los resultados de un estudio de la OMS indican que la testosterona normalmente se secreta en un ritmo circadiano, con mayores niveles por la mañana y niveles nadir alrededor de las 8 a 10 p.m. Véase la Figura 1.

5 Esta variación en la secreción de testosterona a lo largo del día se hace mucho más evidente en varones mayores (en edad promedio de 71 años). La importancia de este ritmo se desconoce hasta el momento.

10 Se obtuvieron muestras de pacientes jóvenes y mayores cada 10 minutos durante 24 horas a través de una cánula residente. De acuerdo con Tenover (1987), los niveles promedio de testosterona sérica total en 24 horas en varones jóvenes sanos (intervalo de edades de 22 a 35 años, promedio
15 27.3 años) fue de 4.9 ± 0.3 ($\pm$ ETM) mg/mL (17.0 nmol/L) mientras que los varones mayores (intervalo de edad 65 años - 84 años, promedio 70.7 años) tuvieron un nivel promedio de testosterona sérica total en 24 horas significativamente menor de 4.1 ± 0.4 mg/mL ($p < 0.5$; 14.2 nmol/L).

20

Los niveles de testosterona sérica total obtenidos de muestras individuales aleatorias también fueron significativamente menores en varones mayores (4.0 ± 0.2 mg/mL [13.9 nmol/L]) en comparación con 4.0 ± 0.2 mg/mL
25 [16.6 nmol/L] en varones jóvenes sanos.

La deficiencia de testosterona puede resultar de una enfermedad subyacente o alteraciones genéticas y con frecuencia también es una complicación del envejecimiento. Por ejemplo, el hipogonadismo primario resulta de la deficiencia testicular primaria. En este caso, los niveles de testosterona son bajos y se elevan los niveles de gonadotropinas hipofisiarias (LH y FSH). El hipogonadismo secundario se debe a la secreción inadecuada de las gonadotropinas hipofisiarias. Además de un bajo nivel de testosterona, los niveles de LH y FSH son bajos o de bajos a normales. Algunas de las secuelas de la deficiencia de testosterona en adultos incluye una amplia variedad de síntomas como: pérdida de la libido, disfunción eréctil, oligospermia o azoospermia, ausencia o regresión de los caracteres sexuales secundarios, disminución progresiva en la masa muscular, fatiga, estado de ánimo deprimido y mayor riesgo de osteoporosis.

En la actualidad, en Estados Unidos se practican algunas formas de terapia de testosterona. En fechas recientes, en el mercado se pueden encontrar preparaciones transdérmicas. No obstante, un parche escrotal de testosterona conduce a niveles suprafisiológicos de 5 alfa-dihidrotestosterona (DHT) debido a una elevada concentración de la 5 alfa-reductasa

en la piel escrotal. No se sabe si estos niveles elevados de DHT tienen alguna consecuencia para la salud a largo plazo. Se considera que los sistemas no escrotales son más convenientes y la mayoría de los pacientes logran 5 concentraciones séricas promedio dentro del intervalo normal y tienen niveles normales de DHT. No se recomienda el tratamiento de testosterona oral porque las dosis necesarias para terapia de reemplazo están asociadas con un riesgo importante de hepatotoxicidad.

10

COMPENDIO

La presente invención se dirige a las composiciones útiles para aumentar las concentraciones de testosterona en mamíferos machos y para aminorar o prevenir las 15 secuelas de las bajas concentraciones de testosterona. En uno de sus aspectos, la invención se dirige a las composiciones que tienen ingredientes activos que comprenden de 0% a 29% en peso/peso de (cis, -Z-, trans-clomifeno) (en adelante "cis-clomifeno") y de 100% a 71% 20 p/p de (trans-, E-, cis-clomifeno) (en adelante "trans-clomifeno") o las sales aceptables para uso farmacéutico de estos. Entre las composiciones preferidas de la presente invención que contienen cis-clomifeno y trans-clomifeno de la invención están las composiciones en 25 donde la relación de trans-clomifeno y cis-clomifeno es

mayor que 1. Una composición más preferida de conformidad con la presente invención contiene aproximadamente 100% p/p de los ingredientes activos de *trans*-clomifeno o una sal aceptable para uso farmacéutico de éste. Todas las composiciones de la presente invención pueden además
5 contener los excipientes, diluyentes, portadores y similares, farmacéuticos, convenientes. Los análogos de *cis*-clomifeno y *trans*-clomifeno también están contemplados para utilizarlos en todos los aspectos de la
10 presente invención.

La presente invención también se dirige a los métodos para aumentar las concentraciones de testosterona sérica en mamíferos machos hipogonadales
15 (y para aminorar o prevenir las secuelas de las bajas concentraciones de testosterona), el método consiste en administrar a un individuo o macho una cantidad eficaz de una composición de conformidad con la presente invención, las composiciones con los ingredientes
20 activos que contienen de 0% a 29% en peso/peso de *cis*-clomifeno y 100% a 71% en peso/peso de *trans*-clomifeno, incluida cualquiera de las sales aceptables para uso farmacéutico de estos. Entre los métodos más preferidos están aquellos en los que las composiciones
25 administradas contienen ambos isómeros, en donde la

relación de *trans*-clomifeno a *cis*-clomifeno es mayor que 1. Un método más preferido consiste en administrar al macho una composición que contenga aproximadamente 100% p/p de *trans*-clomifeno.

5

BREVE DESCRIPCIÓN DEL DIBUJO

La Figura 1 es una gráfica que representa los perfiles normales de testosterona sérica total secretora en varones sanos (jóvenes y mayores).

10

La Figura 2 muestra la estructura química de citrato de clomifeno.

La Figura 3 es una demostración gráfica del transcurso de las concentraciones de testosterona sérica con Clomid, Enclomid y Zucloimid.

15

DESCRIPCIÓN DETALLADA

La presente invención proporciona los métodos y las composiciones útiles para elevar las concentraciones de testosterona en mamíferos machos y para aminorar o prevenir las secuelas de las bajas concentraciones de testosterona que incluyen, pero no se limitan a, las descritas en lo anterior.

20

25

El clomifeno (Figura 2) es un antiestrógeno relacionado con tamoxifeno que bloquea la retroalimentación normal de estrógenos sobre el hipotálamo y la retroalimentación negativa subsiguiente en la hipófisis. Esto da origen a aumentos en la hormona luteinizante (LH) y la hormona estimuladora del folículo (FSH). En los varones, estos niveles aumentados de gonadotropinas estimulan las células de Leydig de los testículos y conduce a la producción de mayores concentraciones de testosterona. El citrato de clomifeno tiene la siguiente estructura:

[lacuna]

Ernst y col., J. Pharmaceut. Sci. 65: 148 (1976), han demostrado que el clomifeno es una mezcla de dos isómeros geométricos a los que se refieren como *cis*-, *-Z*-, clomifeno (*cis*-clomifeno o zuclofifeno) y *trans*-, *E*-, clomifeno (*trans*-clomifeno o enclomifeno).

De acuerdo con Ernst y col., el *trans*-clomifeno HCl tiene un punto de fusión de 149°C-150.5°C, mientras que *cis*-clomifeno HCl tiene un punto de fusión de 156.5°C-158°C.

Ernst y col., también han indicado que el isómero *trans* es antiestrógeno (AE) mientras que el isómero *cis*

es la forma más estrógena y más potente, y también se ha informado que tiene actividad antiestrógena. Los autores atribuyen el efecto del medicamento sobre la actividad ovulatoria a ambas formas, estableciendo que la mezcla es
5 más eficaz que el isómero trans-clomifeno solo. El isómero trans ayuda a la ovulación a nivel del hipotálamo. El isómero estrógeno cis-clomifeno contribuye a mejorar la ovulación en cualquier parte de la vía fisiológica que conduce a la ovulación. También se ha
10 informado que los isómeros tienen diferentes vidas medias *in vivo*. Además, se ha reportado que la forma cis da origen a concentraciones sanguíneas residuales durante más de un mes después de una sola dosis.

15 Vandekerckhove y col. (Cochrane Database Syst Rev 2000; (2): CD000151 (2000)) indicaron que 10 estudios que involucraban 738 varones han indicado que los antiestrógenos parecen tener un efecto benéfico sobre los productos endocrinos, es decir, la testosterona, pero no
20 existe suficiente evidencia para evaluar los efectos sobre la fertilidad. No obstante, si la administración de clomifeno mejora las concentraciones de testosterona, entonces se podría concluir que el medicamento debe afectar positivamente los efectos colaterales de la
25 privación de testosterona siempre que los testículos

todavía conserven la capacidad para responder a la estimulación con gonadotropinas.

El clomifeno actualmente está aprobado como una
5 mezcla de isómeros *cis* y *trans*, el isómero *cis* estando presente como aproximadamente 30% a 50% (manual Merck) para mejorar la fertilidad en la paciente anovulatoria. El clomifeno favorece la ovulación iniciando una serie de sucesos endocrinos que culminan en una marejada de
10 gonadotropina preovulatoria y la ruptura folicular ulterior. Se recomienda administrar el medicamento durante 5 días con una dosis de hasta 100 mg diario. También se ha asociado el clomifeno con numerosos efectos colaterales que incluyen: visión borrosa, incomodidad
15 abdominal, ginecomastia, tumores testiculares, bochornos vasomotores, náusea y cefaleas. Además, otros estudios sugieren que clomifeno tiene efectos genotóxicos y de mejoramiento de tumores. El resultado cabal de estas observaciones es que clomifeno en su forma actual, con un
20 contenido de entre 30% y 50% del isómero *cis*, sería inaceptable para tratamiento crónico en varones contra deficiencia de testosterona.

También se ha utilizado clomifeno para intervención
25 terapéutica en varones con bajas concentraciones de

testosterona. Tenover y col., J. Clin. Endocrinol. Metab. 64: 1103 (1987) y Tenover y col., J. Clin. Endocrinol. Metab. 64: 1118 (1987) encontraron aumentos en FSH, LH en varones jóvenes y mayores después del tratamiento con
5 clomifeno. También encontraron aumentos en testosterona libre y total en varones, con aumentos importantes en varones jóvenes.

También se realizaron estudios para determinar si se
10 podía utilizar o no clomifeno para mejorar la fertilidad en varones aumentando la calidad del semen. Hommonai y col. Fertil. and Steril. 50: 801 (1988) observaron aumentos en la concentración y cuenta de esperma, pero otros investigadores no. (Véase, por ejemplo, Sokel y
15 col., Fertil. and Steril. 49: 865 (1988); Check, y col., Int. J. Fertil. 34: 120 (1989); Purvis y col., Int. J. Androl 21: 109 (1989); y Breznik, Arch. Androl. 21: 109 (1993).) Un grupo observó deterioro en el porcentaje de esperma normal con tratamiento de largo plazo. Shamis y
20 col., Arch. Androl 21: 109 (1991). Un estudio de la OMS no observó cambios en la calidad del semen o la fertilidad después de 6 meses de tratamiento. (Anónimo, Androl. 15: 299 (1992).) Parece ser que un meta análisis confirma que las concentraciones de testosterona aumentan
25 en varones con esperma de calidad deficiente, pero no la

fertilidad. (Vanderkerckhove y col. 2000). Los estudios también han sugerido que el tratamiento de largo plazo con clomifeno no parece tener un efecto perjudicial drástico sobre la salud, aunque demostró que el
5 tratamiento condujo a una deficiente calidad del esperma después de 4 meses. Los estudios han tenido a los varones en tratamiento con clomifeno durante tanto como 18 meses y en concentraciones de 25 mg por día ó 100 mg cada tercer día.

10

En 1991, Guay y col. (Urology 38: 377 (1991)) sugirieron que clomifeno podría tratar disfunción sexual en varones. Su hipótesis parece ser que la función sexual se relaciona con las concentraciones de testosterona.
15 Esta hipótesis fue soportada por los primeros estudios que mostraron la influencia positiva de los andrógenos y la función sexual, Davidson y col., J. Clin. Endocrinol. Metab. 48: 955 (1979), y estudios que clasificaron las erecciones relacionadas con el sueño como una fuerte
20 respuesta a T. Cunningham y col., J. Clin. Endocrinol. Metab. 70: 792 (1990). No obstante, en 1995, Guay y col., (Gray y col. J. Clin. Endocrinol. Metab. 80: 3546 (1995)) publicaron un estudio en el que observaron aumento en la LH, FSH y testosterona después de 2 meses de clomifeno
25 pero sin efectos sobre la disfunción eréctil. Podría

haber alguna ventaja para varones jóvenes y grupos
específicos de varones mayores, pero parece que no es
suficiente solo el aumento de la concentración de
testosterona. Puede ser que los efectos de la
5 testosterona sobre las erecciones relacionadas con el
sueño se tomaron con demasiada seriedad (Herskowitz y
col., J. Psychosomat. Res. 42: 541 (1997)).

De acuerdo con la presente invención, una
10 composición compuesta de un isómero, preferentemente
trans-clomifeno, o una mezcla predefinida de isómeros de
clomifeno, como se describe más adelante, diferente de la
mezcla producida normalmente, se utiliza para mejorar las
concentraciones de testosterona reduciendo al mismo
15 tiempo los efectos colaterales del medicamento. Así pues,
la presente invención proporciona un tratamiento oral
para aumentar las concentraciones de testosterona, el
cual carece o tiene efectos colaterales disminuidos
relacionados con las formulaciones de clomifeno
20 existentes.

En una modalidad de la presente invención, a un
paciente que tenga la necesidad o desee aumentar sus
concentraciones de testosterona sérica se administra una
25 o más dosis de una cantidad eficaz de composición que

contenga *trans*-clomifeno en una dosis entre 1 mg hasta aproximadamente 200 mg (aunque la determinación de las dosis óptimas está dentro del conocimiento ordinario en la técnica). El *cis*-clomifeno también puede estar
5 presente en la composición siempre que la relación de *trans*-clomifeno a *cis*-clomifeno sea mayor que 1. Durante la práctica de la presente invención también son útiles los análogos de los isómeros *trans* y *cis* de clomifeno como los descritos en Ernst, y col., supra.

10

Preferentemente (pero no es necesario) las dosis se administran como parte de un esquema de dosificación diseñado para dar origen a las concentraciones de testosterona sérica que imiten o correspondan con el
15 perfil normal de testosterona sérica total secretora, descrito en la Figura 1. Por ejemplo, de acuerdo con la Figura 1, es posible administrar una dosis de la composición preferida en una formulación farmacéutica que pueda dar origen a las concentraciones máximas de
20 testosterona sérica alrededor de las 8 a.m. Estas formulaciones farmacéuticas pueden estar en forma de formulaciones de liberación sostenida preparadas como se describe por ejemplo en la Patente US No. 6,221,399, la Patente Japonesa 4-312522, Meshali y col. Int. J. Phar.
25 89: 177-181 (1993), Kharenko y col., Intern. Symp.

Control Rel. Bioact. Mater. 22: 232-233 (1995), WO 95/35093, Dangprasit y col. Drug. Devel. And Incl. Pharm. 21 (20): 2323-2337 (1995); Patentes US Nos. 6,143,353, 6,190,591, 6,096,338, 6,129,933, 6,126,969, 6,248,363 y
5 otras formulaciones de liberación prolongada bien conocidas en la técnica.

Las composiciones farmacéuticas convenientes y las formas de dosificación unitaria pueden ser en forma de
10 sólidos como tabletas o cápsulas llenas o líquidos como soluciones, suspensiones, emulsiones, elíxires o cápsulas llenas con estos, todos para uso oral. Las composiciones también pueden estar en forma de soluciones o emulsiones estériles inyectables para uso parenteral (incluido el
15 uso subcutáneo). Estas composiciones farmacéuticas y las formas de dosificación unitaria de estas pueden contener los ingredientes en las proporciones habituales.

Las composiciones de conformidad con la presente
20 invención también pueden administrarse por las vías de administración intravenosa, subcutánea, bucal, transmucosa, intratecal, intradérmica, intracisternal u otras. Después de la administración de la composición, pueden medirse las concentraciones de testosterona sérica
25 como ya se describió y pueden modificarse las dosis para

lograr un aumento suficiente de las concentraciones de testosterona sérica para lograr los resultados fisiológicos deseados asociados con la testosterona normal antes descritos.

5

Todas las referencias que se muestran en la presente se incorporan como referencia en sus enterezas.

El siguiente ejemplo es para mostrar la invención y no se pretende limitar el alcance de la invención como se establece en las reivindicaciones anexas.

EJEMPLO 1

Efectos de los clómidos sobre testosterona sérica en mandriles machos

15

A mandriles machos, adultos, se les administró 1.5 mg/kg del clómido Enclomid (*trans*-Clomid) o Zuclomid (*cis*-Clomid) durante 12 días consecutivos. Las muestras analizadas fueron sueros tomados durante el primer día de tratamiento antes de recibir el producto de prueba (día 0), después de 12 días de tratamiento (día 12) y 7 días después del último tratamiento (final o lavado).

1. Efectos sobre el peso corporal y LH, FSH, PRL y testosterona séricas

25

Hubo aumentos importantes en la testosterona sérica total en el grupo que recibía Enclomid. Véase la Tabla 1. No hubo diferencias entre los grupos durante el periodo de la línea base o durante el día 0. Tampoco hubo
5 diferencias entre los tres grupos 7 días después del tratamiento (el periodo de lavado). No obstante, Enclomid produjo mayores concentraciones de testosterona es comparación con Clomid y Zuclomid durante el día 6 ($p = 0.03$ y $p = 0.00002$, respectivamente) y en comparación con
10 Zuclomid durante el día 12 ($p = 0.047$). Como se observa, Zuclomid no aumentó la testosterona sérica total en ninguna forma. Comparados con los animales que recibían Enclomid, los animales que recibieron Clomid mostraron concentraciones de testosterona total más variables
15 durante el día 6 y después como se observa por sus coeficientes de variación. Cuando se observa el transcurso de los efectos (Figura 3), se puede determinar que solo Enclomid aumentó en forma importante y estadística la testosterona sérica total en los días 6 y
20 12 en comparación con los valores de la línea base o el día 0. Además, la interrupción del tratamiento con Enclomid condujo a una caída importante en la concentración de testosterona sérica total entre el día 12 y el día 18 (lavado). Esto indica que Enclomid se
25 eliminó fácilmente de la circulación consistente con el

aclaramiento metabólico observado para Enclomid en humanos. Enclomid fue evidentemente mejor y más consistente que el propio Clomid, y Zuclomid fue ineficaz.

5

Tabla 1 - Concentraciones de testosterona sérica (ng/dL)

Grupo	ID	Línea base 12/3/01	Día 0 12/7/01	Día 6 12/13/01	Día 12 12/20/01	Lavado 12/26/01
CLO	7500	79.01	76.15	940.97	891.5	150.9
	9012	97.55	305.24	585.92	555.6	316.3
	9097	158.06	102.94	151.12	318.9	143.6
	promedio	111.5	161.4	559.3	588.7	203.6
	DE	41.3	125.2	395.6	287.7	97.7
	7223	64.57	74.96	1223.8	633.6	307.2
	8021	166.86	133.59	1128.2	1466	399.2
	8369	170.45	106.47	1081.1	1166	271
	promedio	134.0	105.0	1144.4	1088.5	325.8
	DE	60.1	29.3	72.7	421.6	66.1
	7438	124.84	210.4	137.51	314.5	359.7
	8292	104.66	67.37	169.98	406.1	860.5
	10098	282.29	904.82	227.95	353.0	274.1
	promedio	170.6	394.2	178.5	357.9	498.1
	DE	97.3	448.0	45.8	46.0	316.8

ANOVA p = 0.61 p = 0.43 p = 0.007 p = 0.57 p = 0.256
K-W p = 0.56 p = 0.84 p = 0.051 p = 0.079 p = 0.252

No hubo cambios en LH ó FSH séricas. La relación de
10 testosterona sérica total a LH siguió el mismo modelo que

la testosterona sérica total, sugiriendo una ausencia de dependencia (no se muestran los datos). Tampoco hubo cambios en el peso corporal durante el estudio de 12 días. Hubo una disminución en prolactina sérica (PRL) durante el estudio en el grupo que recibía Enclomid, sugiriendo un efecto del antiestrógeno que se había descrito en parte (Ben-Jonathan y Hnasko, 2001) y se esperaba con base en el hecho de que a medida que el hombre envejece, la testosterona declina y aumenta a prolactina (Feldman y col., 2002).

2. Efectos sobre los parámetros químico clínicos

Los valores promedio para cada parámetro no difirieron entre los tres grupos en ninguno de los parámetros de las pruebas al principio del estudio como se determinó por ANOVA o por la prueba de Kruskal-Wallis. Todos los grupos mostraron los valores normales en cada parámetro excepto para el sodio en suero (1); un parámetro que se calcula relacionado, el espacio aniónico, los cuales fueron bajos para los nueve mandriles a lo largo del estudio; (2) glucosa en suero; y (3) BUN (NUS) que fueron altos durante el día 0 para el grupo que sería tratado con Enclomid. Durante el día 12 del tratamiento y 7 días después del tratamiento (lavado), no hubo diferencias entre los grupos para

ningún parámetro excepto el espacio aniónico que mostró que los grupos con Clomid y Zuclomid tuvieron menores valores que el grupo con Enclomid. Los valores de sodio sérico y el espacio aniónico parecen ser anormalidades asociadas con este grupo de mandriles.

Hubo efectos sustanciales sobre la población de células sanguíneas rojas con Enclomid y Zuclomid y sobre el hematocrito con Zuclomid. Todos los compuestos reducen la concentración celular media de hemoglobina (MCHC) en el día 0 o en el punto final. Sin cambios en la hemoglobina celular media (MCH) y un aumento en el volumen celular medio (MCV), se puede predecir el descenso de MCHC. Aunque se podría esperar que la testosterona aumente el hematocrito, solo el tratamiento con Zuclomid, que no aumentó la testosterona sérica total, demostró una diferencia estadística. Como es evidente, los varones en un estudio clínico que utilice Zuclomid deben ser supervisados en cuanto a las características de su población de células sanguíneas rojas. Se podría predecir que Enclomid tiene menos de un efecto.

Parece haber un efecto claro del tratamiento con Enclomid durante 12 días sobre las plaquetas, aunque los

valores encontrados permanecieron dentro del intervalo normal. Algo que debe considerarse es el dimorfismo sexual en las cuentas de plaquetas entre mandriles macho y hembra (279 para machos en comparación con 348 para hembras). Esto tal vez se deba a las hormonas. Dado que el grupo con Enclomid demostró aumento de testosterona, la disminución de la cuenta de plaquetas podría ser secundaria al cambio en la testosterona en este grupo. Más aún, el tratamiento con Enclomid empujó la cuenta de plaquetas a su nivel normal en machos desde un nivel del día 0 que fue el límite superior del intervalo normal para este grupo. Enclomid no necesariamente ocasionaría un efecto perjudicial sobre plaquetas.

15 Todos los clómidos probados tuvieron efectos sobre la población de células sanguíneas blancas (WBC), el más notable fue el de Enclomid sobre la elevación de las cuentas de linfocitos y eosinófilos. Los efectos no son tan directos como parecen ser. Parece haber un fuerte efecto de Enclomid sobre la reducción del porcentaje de granulocitos en la sangre. Los efectos son muy fuertes después del periodo de lavado de 7 días cuando los valores disminuyeron por debajo del intervalo normal (este tiempo puede manifestar el tiempo relativamente prolongado necesario para afectar cambios en la población

de WBC.) Hay poco dimorfismo sexual en mandriles con respecto a las poblaciones de células sanguíneas blancas, de modo que es más probable que los efectos se deban al propio compuesto que a los cambios en la testosterona. No obstante, cuando observamos la cuenta calculada de granulocitos utilizando a cuenta de WBC, no encontramos diferencias en la cuenta de granulocitos debida a ningún compuesto. Al mismo tiempo, es más interesante el aspecto de los linfocitos. La cuenta y el porcentaje de linfocitos en la población aumentan con el tratamiento con Enclomid. Aunque los valores promedio del porcentaje de linfocitos permanecen en el intervalo normal, dada la tendencia de un aumento en la cuenta de WBC, el efecto neto es un aumento en la cuenta de linfocitos con Enclomid. Este resultado es el mismo en eosinófilos. Hay una relación clara para tratar a los varones que tienen linfocitos bajos, como los varones que son positivos al VIH. Dado que es muy poco probable que Enclomid reduzca los linfocitos con base en este resultado, se podría utilizar en la población de varones con SIDA. Es frecuente tratar a estos individuos con agentes propuestos para elevar la testosterona por los efectos devastadores de la enfermedad. La toxicidad baja en hígado y riñón y los efectos favorables sobre colesterol y lípidos también son atributos muy favorables para

cualquier medicación propuesta para uso en varones con VIH positivo que ya estén comprometidos por su enfermedad. El aumento en glucosa sérica con Clomid o Zuclomid estuvo dentro del intervalo normal. En el caso
5 de Enclomid donde los valores de glucosa sérica promedio fueron elevados durante el día 0, no hubo aumentos con el tratamiento. No hubo evidencia de que Enclomid tenga un efecto perjudicial sobre la glucosa en sangre.

10 Ninguno de los efectos claramente adversos sobre la función hepática es evidente según se observó por las enzimas AST y ALT. La tendencia en estos fue una disminución con el tratamiento. Un aumento en la concentración de las enzimas en el suero indicaría daño
15 hepático. La relación ALT/SGPT estuvo fuera del intervalo bajo al término del estudio para el grupo de Clomid, aunque las diferencia sobre el periodo de tratamiento no tuvieron importancia estadística. Los cambios con Enclomid y Zuclomid estuvieron dentro del intervalo
20 normal. La AST se deprimió en embarazo; así pues, se podría tomar en cuenta la acción de un agonista estrogénico como Zuclomid en la reducción de la concentración de AST marginal. La fosfatasa alcalina (ALP) también se encontró en el hígado y se eleva en
25 algunos estados de enfermedad. La reducción de ALP es una

prueba más contra daño hepático. No hubo cambios en la albúmina sérica, también un producto hepático. Una fuerte supresión de albúmina sérica durante un periodo prolongado podría contribuir a los niveles de la hormona
5 esteroide sérica libre en humanos, aunque una función más importante la desempeña la globulina de unión a las hormonas sexuales. Como una base, ninguno de los compuestos podría estar vinculado al daño hepático, con base en los parámetros ensayados.

10

La actividad osteoblástica y las enfermedades del hueso son acompañadas por valores elevados de ALP sérica. La ALP no se elevó después del tratamiento con Zuclomid y disminuyó su valor después del tratamiento con Enclomid.
15 Las tendencias podrían predecir un resultado más benigno para el uso de Enclomid en comparación con Zuclomid.

Aunque se alteró el BUN y BUN/creatinina durante el estudio en los grupos con Clomid y Enclomid, la ausencia
20 de un cambio definitivo en creatinina es una prueba contra disfunción renal. La pérdida en la capacidad de filtración glomerular daría origen a un aumento en el BUN. El BUN disminuido se observa en humanos por mala nutrición (tal vez no en un ambiente controlado) o
25 elevada ingesta de líquidos (tal vez acompañado por

edema). Asimismo, a pesar de un aumento en la testosterona sérica total entre el día 0 y el día 12 con Enclomid, no hubo diferencias entre los valores de creatinina sérica, siendo prueba contra un aumento en la
5 masa muscular durante este breve periodo.

Las concentraciones de sodio sérico fueron menores que los valores de referencia para todos los animales a lo largo del estudio. El dióxido de carbono sérico fue
10 mayor que los valores de referencia durante el día 12 para los grupos de Clomid y Zuclomid. El espacio aniónico sérico fue menor para todos los animales a lo largo del estudio, igualando los resultados del sodio. Enclomid aumentó este parámetro hacia los valores normales. Los
15 desequilibrios de electrolitos detectados en los animales de prueba a lo largo de todos los periodos de tratamiento siguen siendo evasivos pero podrían ser parte del mismo fenómeno de desarreglo de líquidos sugerido por los resultados de BUN.

20

El tratamiento con Enclomid tendió a disminuir el colesterol sérico y Zuclomid tendió a elevar el mismo parámetro aunque ningún cambio alcanzó importancia estadística. Estos cambios estuvieron dentro del
25 intervalo normal, aunque la tendencia de los dos isómeros

para demostrar efectos opuestos durante un periodo breve merece más supervisión y podría no ser inesperado dado que los isómeros tienen, alternativamente, actividad agonista o antagonista de los estrógenos. Se podría
5 esperar que Enclomid sea más benigno que Zuclomid con respecto al colesterol sérico si se utiliza en forma crónica.

Los resultados anteriores indican que Enclomid es
10 más eficaz que Clomid o Zuclomid mejorando la testosterona sérica total. Evidentemente, Zuclomid no es eficaz y esta deficiencia limita cualquier uso de Clomid para hipogonadismo, en particular, dado que el componente Zuclomid de Clomid predominaría en la
15 circulación durante el tiempo de acuerdo con su vida media más prolongada,

Parece ser que Enclomid es relativamente benigno en todos los aspectos en comparación con Zuclomid y, con
20 frecuencia, incluso con Clomid. Esto es particularmente cierto cuando se considera la tendencia de Enclomid a reducir el colesterol, y las enzimas hepáticas, contrario a la tendencia de Zuclomid a elevar los mismos parámetros. La tendencia sorprendente de Enclomid para
25 elevar la cuenta de linfocitos puede ser útil para

varones con SIDA si se puede demostrar que la subpoblación CD4+ de linfocitos no se reduce o se mejora.

EJEMPLO 2

5 **Método para aumentar la concentración de testosterona en varones utilizando trans-clomifeno y mezclas de trans-clomifeno y cis-clomifeno en proporciones mayores que 1**

Antes de la administración de trans-clomifeno, se tomaron muestras de sangre de individuos machos y se
10 midieron las concentraciones de testosterona utilizando los métodos descritos por ejemplo en Matsumoto y col. Clin. Endocrinol, Metab. 56: 720 (1983) (incorporada en la presente como referencia). La globulina de unión a la hormona sexual (SHBG), libre y unida a la testosterona,
15 también se puede medir como está descrito por ejemplo en Tenover y col. J. Clin. Endocrinol. Metab. 65: 1118 (1987) que describe la medición de SHBG por un análisis de saturación de [³H] dihidrotestosterona y por un radioinmunoensayo. Las concentraciones de testosterona no
20 unida a SHBG (testosterona biodisponible) también se miden por ejemplo de acuerdo con Tenover y col. J. Clin. Endocrinol and Metab. 65: 1118 (1987). Véase también Sodergard y col. J. Steroid Biochem 16: 801 (1982) que se incorpora en la presente como referencia.

Se administra a los pacientes dosis diarias de 1.5 mg/kg de clomifeno, en donde la relación de trans-clomifeno a cis-clomifeno es mayor que 1. Se supervisa a los pacientes en cuanto a las concentraciones de 5 testosterona de modo que se pueda ajustar la cantidad y frecuencia de las dosis para obtener concentraciones terapéuticas de testosterona en el paciente.

REIVINDICACIONES

1. Un método para aumentar las concentraciones séricas de testosterona en mamíferos machos, el método
5 consiste en administrar al mamífero una cantidad eficaz de un compuesto que contenga *cis*-clomifeno y *trans*-clomifeno o análogos de estos o sales o solvatos aceptables para uso farmacéutico de estos y, como una opción, uno o más diluyentes, adyuvantes, portadores o
10 excipientes aceptables para uso farmacéutico y, en donde la relación de *trans*-clomifeno y *cis*-clomifeno es mayor que 1 p/p.

2. El método de la reivindicación 1, caracterizado
15 porque la composición consiste principalmente en una cantidad eficaz de *trans*-clomifeno o un análogo de éste o una sal o solvato farmacéuticamente eficaz de estos y, como una opción, uno o más diluyentes, adyuvantes, portadores o excipientes aceptables para uso
20 farmacéutico.

3. Una composición que contiene de 0% a aproximadamente 29% p/p de *cis*-clomifeno y aproximadamente 100% hasta aproximadamente 71% de *trans*-
25 clomifeno o análogos de estos o las sales o solvatos

aceptables para uso farmacéutico de estos y, como una opción, uno o más diluyentes, adyuvantes, portadores o excipientes aceptables para uso farmacéutico.

- 5 4. Una composición que contiene *cis*-clomifeno y *trans*-clomifeno o análogos de estos o las sales o solvatos aceptables para uso farmacéutico de estos y, como una opción, uno o más diluyentes, adyuvantes, portadores o excipientes aceptables para uso farmacéutico
- 10 y, en donde la relación de *trans*-clomifeno y *cis*-clomifeno es mayor que 1.

RESUMEN DE LA INVENCION

La presente invención se refiere al uso de las composiciones que contienen *trans*-clomifeno para tratar a
5 varones con hipogonadismo. La invención también se refiere a los métodos para tratar a varones con hipogonadismo. La invención también se dirige a los métodos para tratar machos con hipogonadismo.

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MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
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ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
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WO 03/005954 A2

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(57) Abstract: The present invention relates to the use of compositions comprising *trans*-clomiphene for treating men with hypogonadism. The invention is also directed to methods for treating males with hypogonadism.

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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,
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52

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/21524

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/225, 31/135
US CL : 514/648, 651
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)
U.S. : 514/648, 651
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)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 6,391,920 B1 (FISCH) 21 May 2002 (21.05.2002) see entire documents, especially page column 2, lines 9-12 and lines 48-62; column 3, lines 6-8.	1-2, 4
X,P	US 2002/0120012 A1 (FISCH) 29 August 2002 (29.08.2002), see entire documents, especially abstract and page 2, para. 23.	1-2, 4
Y	US 4,061,733 A (GUNJIKAR) 06 December 1977 (06.12.1977), see abstract and column 2, lines 5-23.	4
X	EP 0 888 775 A2 (MEDICAL COLLEGE OF HAMPTON ROADS) 01 July 1999 (07.01.1999), see abstract and page 5, line 35.	4

☐ Further documents are listed in the continuation of Box C.	☐ See patent family annex.
* Special categories of cited documents:	* Four documents published after the international filing date or priority date and not in conflict with the application but cited to substantiate the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"A" document member of the same patent family
"O" documents referring to an oral disclosure, use, exhibition or other means	
"P" documents published prior to the international filing date but later than the priority date claimed	

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Name and mailing address of the ISA/US Combinator of Patents and Trademarks Box PCT Washington, D.C. 20531 Facsimile No. (703)305-3230	Authorized officer: Zahra Feyz Telephone No. 703-308-1235

INTERNATIONAL SEARCH REPORT

PCT/US02/21574

Continuation of B. FIELDS SEARCHED Item 3:

STN ONLINE

search term: cis-clomiphene, trans-clomiphene, raclophene, zuclophene

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AMENDED CLAIMS

[Received by the International Bureau on 12 August 2003 (12.08.03)]

1. A method for increasing serum levels of testosterone in a male mammal, the method comprising administering to the mammal an effective amount of a composition comprising *cis*-clomiphene and *trans*-clomiphene or analogs thereof or pharmaceutically acceptable salts or solvates thereof and optionally one or more pharmaceutically acceptable diluents, adjuvants, carriers or excipients, wherein the ratio of *trans*-clomiphene to *cis*-clomiphene is greater than 71/29 w/w.
2. The method of claim 1 wherein the composition consists essentially of an effective amount of *trans*-clomiphene or an analog thereof or a pharmaceutically effective salt or solvate thereof and optionally one or more pharmaceutically acceptable diluents, adjuvants, carriers or excipients.
3. A composition comprising 0% to about 29% w/w of *cis*-clomiphene and about 100% to about 71% *trans*-clomiphene or analogs thereof or pharmaceutically acceptable salts or solvates thereof and optionally one or more pharmaceutically acceptable diluents, adjuvants, carriers or excipients.
4. A composition comprising *cis*-clomiphene and *trans*-clomiphene or analogs thereof or pharmaceutically acceptable salts or solvates thereof and optionally one or more pharmaceutically acceptable diluents, adjuvants, carriers or excipients and wherein the ratio of *trans*-clomiphene to *cis*-clomiphene is greater than 71/29.

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STATEMENT UNDER ARTICLE 19 (1)

The amendments as hereby requested do not go beyond the disclosure in the international application as filed. Support for the amendments may be found at paragraph [0011] of the international application as filed.

REIVINDICACIONES MODIFICADAS

(Recibidas por la Oficina Internacional el 12 de agosto

2003 (12.08.03))

1. Un método para aumentar las concentraciones séricas de testosterona en mamíferos machos, el método consiste en administrar al mamífero una cantidad eficaz de un compuesto que contenga *cis*-clomifeno y *trans*-clomifeno o análogos de estos o sales o solvatos aceptables para uso farmacéutico de estos y, como una opción, uno o más diluyentes, adyuvantes, portadores o excipientes aceptables para uso farmacéutico, en donde la relación de *trans*-clomifeno y *cis*-clomifeno es mayor que 71/29 p/p.

2. El método de la reivindicación 1, caracterizado porque la composición consiste principalmente en una cantidad eficaz de *trans*-clomifeno o un análogo de éste o una sal o solvato farmacéuticamente eficaz de estos y, como una opción, uno o más diluyentes, adyuvantes, portadores o excipientes aceptables para uso farmacéutico.

3. Una composición que contiene de 0% a aproximadamente 29% p/p de *cis*-clomifeno y aproximadamente 100% hasta aproximadamente 71% de *trans*-clomifeno o análogos de estos o las sales o solvatos aceptables para uso farmacéutico de estos y, como una opción, uno o más diluyentes, adyuvantes, portadores o excipientes aceptables para uso farmacéutico.

4. Una composición que contiene *cis*-clomifeno y *trans*-clomifeno o análogos de estos o las sales o solvatos aceptables para uso farmacéutico de estos y, como una opción, uno o más diluyentes, adyuvantes, portadores o excipientes aceptables para uso farmacéutico y, en donde la relación de *trans*-clomifeno y *cis*-clomifeno es mayor que 71/29.

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DECLARACION BAJO EL ARTICULO 19 (1)

Las modificaciones según solicitadas en este no van mas alla a las revelaciones de la solicitud internacional conforme ha sido presentada. El apoyo a las modificaciones puede ser encontrado en el paragrafo (0011) de la solicitud internacional conforme ha sido presentada.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only		
Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 212875-00215
International application No. PCT/US02/21524	International filing date (day/month/year) July 9, 2002	(Earliest) Priority date (day/month/year) July 9, 2001
Title of invention METHODS AND MATERIALS FOR THE TREATMENT OF TESTOSTERONE DEFICIENCY IN MEN		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ZONAGEN, INC. 2408 Timberloch Place, B-4 The Woodlands, Texas 77380		Telephone No. 281-367-5882
		Facsimile No. 281-363-6798
		Teleprinter No.
		Applicant's registration No. with the Office
State (that is, country) of nationality: US		State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)		
State (that is, country) of nationality:		State (that is, country) of residence:
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)		
State (that is, country) of nationality:		State (that is, country) of residence:
☐ Further applicants are indicated on a continuation sheet.		

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)CLOUGH, David W.
SCOTT, Teddy C.
KATTEN MUCHIN ZAVIS ROSENMAN
525 W. Monroe Street, Suite 1800
Chicago, IL 60661

Telephone No.

312/802-5200

Facsimile No.

312/577-1081

Teleprinter No.

Agent's registration No. with the Office

36,107

☐ Address for correspondence: Mark this check-box when no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☒ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☒ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only
received not received

- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
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| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☒ other (specify): Associate Power of Attorney |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

By: 
Teddy C. Scott, Jr., Ph.D.
Registration No. P-53,573
Attorney for Applicant

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

- | | |
|--|---|
| 3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. | ☐ The applicant has been informed accordingly. |
| 4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5. | |
| 5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | |

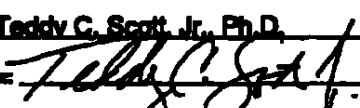
For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US02/21524 Applicant's or agent's file reference 212875-00215 Applicant ZONAGEN, INC.	For International Preliminary Examining Authority use only Date stamp of the IPEA								
CALCULATION OF PRESCRIBED FEES 1. Preliminary examination fee 490.00 P 2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered as H is 25% of the handling fee.) 148.00 H 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box 636.00 TOTAL									
MODE OF PAYMENT <table style="width: 100%;"> <tr> <td>☐ authorization to charge deposit account with the IPEA (see below)</td> <td>☐ cash</td> </tr> <tr> <td>☒ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table>		☐ authorization to charge deposit account with the IPEA (see below)	☐ cash	☒ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☐ authorization to charge deposit account with the IPEA (see below)	☐ cash								
☒ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs) ☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA are met.) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. IPEA/ <u>US</u> Deposit Account No.: <u>50-1214</u> Date: <u>10 February 2003</u> Name: <u>Teddy C. Scott, Jr., Ph.D.</u> Signature: 									

REQUISITOS NECESARIOS PARA PRESENTAR TRAMITE

Superintendencia y Control

Radicación: 00000000 00000000

Folios: 75

Fecha (MM): 2004-01-09 12:51:14

Tramite: 001 PCI-PATENTE 3/9 1984 0002 411 PATENTE
Dependencia: 2000 DIVISION DE MARCAS Y DISEÑOS

PATENTE DE INVENCION

MODELO DE UTILIDAD

USUARIO RADICADOR

() ()

- Indicación de que se solicita la concesión de una patente.
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.
- Descripción de la invención.
- Dibujos de ser estos pertinentes.
- Comprobante de Pago de las tasas establecidas

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INCOMPLETA

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DISEÑO INDUSTRIAL

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- Indicación de que se solicita el registro de Diseño Industrial
- Datos de identificación del solicitante o de la persona que presenta la solicitud.
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.
- Comprobante de pago de las tasas establecidas

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COMPLETA

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INCOMPLETA

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ESQUEMA DE TRAZADO

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- Indicación de que solicita el registro de un Esquema de trazado.
- Datos de identificación del solicitante o de la persona que presenta la solicitud.
- Representación gráfica del esquema de trazado
- Comprobante de pago de las tasas establecidas.

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COMPLETA

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INCOMPLETA

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Firma Responsable:

Fecha:



2020
Bogotá, D.C.,

Doctor:
CAMILO ALVAREZ
Apoderado
ZONAGEN INC.

Oficio N° 01711

ASUNTO:	Radicación N°	04-1222
	Solicitud Internacional	PCT/US2002/21524
	Fecha inicio fase nacional	09/02/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).
- ☐ La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

13 FEB. 2004

El anterior requerimiento fue notificado por fijación en lista de fecha _____.