Industria y Comercio

SUPERINTENDENCIA

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO"
INVENTARIO

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE Nº** 10-40524

54. **TÍTULO** **Trans-Clomifeno para el síndrome metabólico.**

51.. **CLASIFICACIÓN INTERNACIONAL** A61K 31/138

71. **SOLICITANTE** **REPROS THERAPEUTICS INC.**

DOMICILIO The Woodlands, Texas, Estados Unidos de América.

74. **APODERADO** DILIA MARIA RODRIGUEZ D´ALEMAN

22. **BOGOTÁ, D.C.**

Cap I & II
16-09-2010

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-040524- -00000-0000
Fecha: 2010-04-08 15:24:36 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 176

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

[x] Patente de Invención [ ] Patente de Modelo de Utilidad

[X] Capitulo I. (Solo 190) [x] Capítulo II

2 SOLICITANTE (71)	**Nombre**: **REPROS THERAPEUTICS, INC.** **Dirección**: 2408 Timberloch Place, B-7, The Woodlands, Texas 77380, Estados Unidos de América. **Nacionalidad o domicilio**: The Woodlands, Texas, Estados Unidos de América. **Lugar de Constitución**: Texas, Estados Unidos de América. **Teléfono:** **Fax:** **E-mail**	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Número**
3 REPRESENTANTE O APODERADO (74)	Nombre: DILIA MARÍA RODRÍGUEZ D´ALEMAN Dirección: Carrera 11 No. 86-53, piso 6 Teléfono: 6 181088 Fax: 6350824 E-mail: clarkemodet@clarkemodet.com.co	**IDENTIFICACIÓN** C.C. [x] NIT [ ] C.E. [ ] Otro [ ] Número 41.654.882 TP 20824 CSJ
4 INVENTOR (ES) (72)	Nombre: **VAN AS, Andre** Dirección: 1273 Robynwood Lane, West Chester, Pennsylvania 19380, Estados Unidos de América. Nacionalidad o domicilio: Estadounidense.	

5 PCT (86)

Solicitud Internacional No. **PCT/US2008/075433** Fecha **5 de septiembre de 2008**

Publicación Internacional No. **WO 2009/051908 A1** Fecha **23 de abril de 2009**

6 TITULO (54) **TRANS-CLOMIFENO PARA EL SÍNDROME METABÓLICO.**

7 Clasificación Internacional (51) A61K 31/138 A61P 3/06 A61P 3/10

8 Prioridad SI [x] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	Estados Unidos de América	**16 de octubre de 2007**	**60/980,334**

9 Comprobante de pago No. **10-7,156 // 10-11,065 // 10-24,890 // 10-24,889**
Fecha 29/01/10 // 10/02/10 // 05/04/10 // 05/04/10

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [x] Documento que acredita 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 de 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 deposito del material biológico
- [ ] Arte final 12 X 12 .
- [ ] 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 Reporte de búsqueda internacional.

11 FIGURA CARACTERÍSTICA

12 Solicito la concesión de la patente

NOMBRE : DILIA MARÍA RODRÍGUEZ D´ALEMAN

FIRMA:

C.C. 41.654.882 **T.P. 20824**

As. P-2523

R-2523

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 7,156
FECHA : ENERO 29 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-040524- -00000-0000
Fecha: 2010-04-08 15:24:36 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 176

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBRECIBO DE CAJA				7006	29/01/2010	12,105,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVCIOS ADMINISTRATIVOS	2,000.00
			TOTAL : $	2,000.00

SON: DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 11,065
FECHA : FEBRERO 10 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-040524- -00000-0000

Fecha: 2010-04-08 15:24:36 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 176

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	175684132	10/02/2010	68,215,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS		20,000.00
		TOTAL :	$	20,000.00

SON: VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

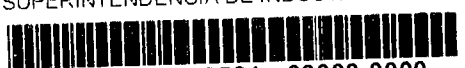
ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 24,890
FECHA : ABRIL 5 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-040524- -00000-0000

Fecha: 2010-04-08 15:24:36 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 176

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLONB	CONSIGNACION	BANCO DE BOGOTA	062754387	353190121	31/03/2010	84,780,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVCIOS ADMINISTRATIVOS	500,000.00
			TOTAL : $	500,000.00

SON: QUINIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 24,989
FECHA : ABRIL 5 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-040524- -00000-0000

Fecha: 2010-04-08 15:24:36 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 176

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	353190121	31/03/2010	04,780,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

5

6

P. 965

The State of Texas

Secretary of State

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1. **Country:** **United States of America**

This public document

2. **has been signed by** **TARA F STEWART**

3. **acting in the capacity of** **Notary Public, State of Texas**

4. **and bears the seal/stamp of** **TARA F STEWART, Notary Public, State of Texas, Commission Expires: 02-26-09**

CERTIFIED

5. **at Austin, Texas**

6. **on September 13, 2007**

7. **by the Secretary of State of Texas**

8. **Certificate No. N-607592**

9. **Seal**

10. **Signature:**

TRADUCCION OFICIAL No. 37
JUAN PABLO PEDRAZZINI ACOSTA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2005
DEL MIN. INTERIOR Y DE JUSTICIA

Notaría Once (E) del Círculo de Bogotá, D.C. Hago constar que esta FOTOCOPIA coincide con su Original que he tenido a la vista
07 ABR 2010
Nelson J. Sánchez García
NOTARIO ONCE (E)
BOGOTA D.C.

Phil Wilson
Secretary of State
ST/sjs

6

COLOMBIA

Carrera 11 No 86-53 Piso 6 Bogotá Colombia Tel: (57 1) 6181088 Fax: (57 1) 6350824 Email: info@clarkemodet.com.co

PODER

Yo (nosotros), abajo firmante(s)

en mi (nuestro) carácter de representante(s) legales de
Repros Therapeutics Inc.

una sociedad organizada y existente de acuerdo con las leyes de
Estado de Delaware

y en actual cumplimiento de su objeto social, con domicilio en
2408 Timberloch drive, B-7,
The Woodlands, texas, 77380 USA
por el presente instrumento confiero (conferimos) poder especial a favor de DILIA MARIA RODRIGUEZ D'ALEMAN, con Cédula de Ciudadanía No 41.654.882 de Bogotá, y tp 20824 y CLAUDIA LUCIA CARO RAMIREZ, con Cédula de Ciudadanía No. 40.017.374 de Tunja, y tp. 36448, con domicilio en Bogotá, Colombia, para que actuando en su orden en nombre del (de la) otorgante le (la) representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos:

1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de Propiedad Industrial, tales como: patentes de invención, modelos de utilidad; diseños industriales, variedades vegetales; marcas, lemas, nombres y enseñas comerciales y denominaciones de origen; así como sus renovaciones, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias
2) Solicitar, tramitar, obtener y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la protección de secretos industriales y know-how
3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
4) Ejercer acciones de oposición, observación, reclamos, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrá(n) intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía; en acciones o juicios promovidos por el (la) mandante o en contra el (ella).
5) Registrar nombres de dominio ante la entidad competente.
6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, comprometer en árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir a derechos concedidos o en curso de concesión, admitir los hechos del proceso
7) Ratificar o no la agencia oficiosa.
8) Así mismo faculto (facultamos) a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren.

Dado y firmado en

a los 26 días de Julio, 2007

TRADUCCION OFICIAL No.
JUAN PABLO RIED ARIZA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

POWER OF ATTORNEY

I (we), the undersigned

legal representative(s) of **Repros Therapeutics Inc.**

an organization existing under the laws of **State of Delaware**

and in present execution of its business activity, domiciled at
2408 Timberloch Drive, B-7, The Woodlands, Texas, 77380 USA

do hereby grant POWER OF ATTORNEY to DILIA MARIA RODRIGUEZ D'ALEMAN, identification card No. 41.654.882 of Bogotá, and tp. 20824 and CLAUDIA LUCIA CARO RAMIREZ, tp. 36448, identification card No. 40.017.374 of Tunja, residing in Bogotá, Colombia, to act in the order of their appointment in behalf of grantor before any entity, authority and/or natural or juridical person, specially before those Administrative, Administrative-Contentious, Judicial, arbitration courts, and/or any other, in all matters concerning the following:

1) To apply, process, obtain and/or register any of the modalities of Industrial Property, such as: Patents of Invention, Utility Models; Designs, plant varieties; Marks, Slogans, Trade Names and emblems and appellations of Origin, as well as their renewals, assignments, changes of name and/or domicile, agreements and licenses.
2) To apply, process, obtain and/or register copyrights of any kind as well as protection of industrial secrets or know-how.
3) To apply, process, obtain and/or register sanitary registrations, operating authorizations and/or licenses; as well as their renewals or assignments, changes of name and/or domicile, agreements and licenses.
4) To bring actions of opposition, observations, claims, reconsideration, appeal or legal remedies, cancellations, nullity, protection to the consumer, granting of licenses, protection of trade secrets and other actions related with rights derived from the above- mentioned matters and against the unfair competition, actions resulting from the obtaining or exploitation of licenses, recovering damages actions. They can also intervene or participate in Civil, Commercial, Criminal or Contentious-Administrative Trials; the actions for writ mandamus, police actions; in actions, lawsuits or litigations instituted by the grantor or against him.
5) To register domain names before the competent entity.
6) To the effect of this mandate the above-named proxy are empowered to: conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take possession of the litigation related object and waive or renounce the rights granted or in process of granting, admit the facts of the case.
7) To ratify or not the officious agency.
8) I (we) hereby appoint the above-mentioned proxys with power to receive notifications and to designate judicial and extrajudicial attorneys, substitute this Power of Attorney and revoke the substitutions that they make.

Nelson J. Sánchez García
NOTARIO ONCE (E)
Bogotá D.C.

Copia fotostática tomada de su original que he tenido a la vista

07 ABR 2010

Granted and signed at

on this 26 day of July, 2007

Firma / signature
Joseph S. Podolski, President and Chief Executive Officer

TARA F. STEWART
MY COMMISSION EXPIRES
FEBRUARY 26, 2009

CERTIFICADO NOTARIAL

(Cuando el solicitante es SOCIEDAD)

(Poderes otorgados en: El Salvador, Estados Unidos, México y Venezuela)

A los días del mes de de , el Notario que suscribe DA FE de que:

1. Joseph S.Podolski
(nombre de la persona que firma el poder)

mayor de edad y domiciliado 3 Pebble Hollow Court, The Woodlands, TX 7738 USA firmó de su puño y letra el documento que antecede.

2. Conoce al (a la) otorgante y que este (a) está legalmente capacitado para el otorgamiento.

3. El otorgante ha firmado el referido documento en su carácter de Presidente y Funcionario Jefe Ejecutivo de la persona jurídica Repros Therapeutics Inc.

4. La citada persona jurídica con sede en _____ _____ está legalmente constituida, que tiene actualmente existencia legal y que el acto para el cual se ha otorgado este poder está comprendido entre los que constituyen su objeto social.

5. El otorgante tiene efectivamente la representación que ostenta, que esta es legítima y que está facultado para otorgar este poder.

6. las anteriores certificaciones de los puntos 3, 4 y 5, me constan porque he tenido a la vista los documentos auténticos.

_____
Notario Público

NOTA: A continuación de lo anterior, el Cónsul de Colombia debe autenticar la firma del Notario Público.

CERTIFICADO NOTARIAL (Cuando el solicitante es INDIVIDUO)

A los días del mes de de , el Notario que suscribe DA FE de que:

1. _____
(nombre de la persona que firma el poder)

mayor de edad y domiciliado en _____ _____ firmó en su presencia el documento que antecede, conoce al otorgante y que este está legalmente capacitado para el otorgamiento.

_____
Notario Público

NOTA: A continuación de lo anterior, el Cónsul de Colombia debe autenticar la firma del Notario Público.

Para todos los demás países el Señor Cónsul de Colombia o ante quien se otorgue, debe expedir una certificación dejando constancia 1) de la existencia legal de la sociedad, 2) de que esta ejerce actualmente su objeto social, y 3) de que la persona o personas que otorgan el poder están facultadas para hacerlo, dejando constancia así mismo de que tuvo a la vista las pruebas que acrediten tales circunstancias.

LEGALIZACIÓN POR EL CONSUL DE COLOMBIA O POR APOSTILLA

NOTARIAL CERTIFICATE

(When the applicant is a CORPORATION)

(Powers of attorney granted in: El Salvador, Mexico, U.S.A. and Venezuela)

This 26th day of **July, 2007** , the undersigned Notary CERTIFIES that:

1. **Joseph S. Podolski**
(name of the person who signs the power of attorney)

of legal age and domiciled in **3 Pebble Hollow Court, The Woodlands, Texas, 77381 USA** set his hand on the foregoing document.

2. The grantor is to him personally known and that he/she has legal capacity to execute the document.

3. The grantor has executed the foregoing document in his capacity of **President and Chief Executive Officer** of the juridical person **Repros Therapeutics Inc.**

4. The mentioned juridical person with place of business in **2408 Timberloch Drive, B-7, The Woodlands, Texas, 77380, USA** is duly organized, has actual legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. The grantor has in fact the referred quality and that his/her representation is legal and that he/she is empowered to grant this power of attorney.

6. I have based the above certifications 3, 4 and 5, on the authentic documents which for such purpose were exhibited to me.

Tara F. Stewart
Notary Public

NOTA. Then the Colombian Consul must legalize the signature of the Notary Public.

NOTARIAL CERTIFICATE (When the applicant is an INDIVIDUALS)

On this day of the undersigned Notary CERTIFIES that:

1. _____
(name of the person who signs the Power of Attorney)

of legal age and domiciled at _____ _____ signed in his presence the foregoing document, the grantor is to him personally known and that he has legal capacity to execute the document and he obtained con su cédula que ha tenido a la vista.

_____
Notary Public

07 ABR 2010

NOTA. Then the Colombian Consul must legalize the signature of the Notary Public.

Nelson J. Sánchez García

For all other countries the Colombian Consul or before who this is granted must issue a certification stating 1) the legal existence of the corporation, 2) that the corporate purposes are actually being accomplished , 3) that the person or persons who grant this Power of Attorney are empowered to do it. The Consul will certify also that the documents evidencing those circumstances were exhibited to him.

P. 965

TRADUCCIÓN OFICIAL No. 06/406 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Juan Pablo Piedrahita Aguilera, Traductor e Intérprete Oficial debidamente reconocido de conformidad con el Certificado de Idoneidad Profesional No. 0045 expedido por la Universidad Nacional de Colombia, por el *Ministerio de Relaciones Exteriores y autorizado por el Ministerio del Interior y de Justicia, por resolución* número 718 de 2003.

(Se traduce un poder otorgado por la compañía Repros Therapeutics Inc. firmado por Joseph S. Podolski, certificado notarial y Apostilla No. II-607592, escritos en inglés.)

Clarke, Modet & Co.

COLOMBIA

(Dirección en español)

PODER

Yo (nosotros), Joseph S. Podoski, representantes legales de Repros Therapeutics Inc., sociedad constituida y existente bajo las leyes de el Estado de Delaware, Estados Unidos de América, y en actual cumplimiento de su objeto social, con domicilio en 2408 Timberloch Drive, B-7,The Woodlands Texas, 77380, Estados Unidos de América, por el presente por el presente confiero (conferimos) poder especial a favor de a DILIA MARÍA RODRÍGUEZ D'ALEMÁN, identificada con cédula de ciudadanía No. 41.654.882 de Bogotá y Tarjeta Profesional 20824 y CLAUDIA LUCIA CARO RAMIREZ, identificada con Tarjeta Profesional 36448 y cédula de ciudadanía No 40.017.374 de Tunja, con domicilio en Bogotá, Colombia, para que actuando en su orden en nombre de la otorgante la representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a la siguiente:

1) Solicitar, tramitar, obtener y/o registrar cualesquiera de las modalidades de

Como Notario Once (E) del Circulo de Bogotá D.C. certifica que la copia es fiel y coincide con su original que he tenido a la vista.
07 ABR 2010
NOTARIO ONCE (E)
BOGOTA, D.C.

07/406

TRADUCCION OFICIAL No._____
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

Propiedad Industrial, tales como: Patentes de Invención, Modelos de Utilidad; Diseños Industriales, variedades vegetales, Marcas, Lemas, Nombres y Enseñas Comerciales y Denominaciones de Origen; así como sus renovaciones, prórrogas, traspasos, cambios de nombre y/o domicilio, contratos y licencias.

2) Solicitar, tramitar, obtener, y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la protección de secretos industriales y know-how.

3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, cesiones, traspasos, cambios de nombre y/o domicilio, contratos y licencias.

4) Ejercer acciones de oposición, observación, reclamos, reivindicaciones, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrán intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía; acciones o juicios promovidos por el mandante o contra el.

Como Notario Once (E) del Círculo de ... hago constar que esta ... que he tenido a la vista.
07 ABR 2010
Nelson J. Sánchez García
NOTARIO ONCE (E)
BOGOTÁ D.C.
11

5) Registrar nombres de dominio ante la entidad competente.

6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan

TRADUCCION OFICIAL No. 07...
JUAN PABLO PIEDRAHITA AGUI...
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

10

facultados para: conciliar, cancelar, transigir, aceptar cláusulas compromisorias, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir derechos concedidos o en curso de concesión, admitir los hechos del proceso.

7) Ratificar o no la agencia oficiosa.

8) Así mismo facultamos a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren.

Dado y firmado en (en blanco) hoy día 26 de Julio, 2007.

Por: (Firmado) Joseph S. Podolski, Presidente y Funcionario jefe Ejecutivo

---

CERTIFICADO NOTARIAL (Cuando el solicitante es una SOCIEDAD)

(*Poderes otorgados en El Salvador, México, Estados Unidos de América y* Venezuela)

Expedido hoy día 26 de Julio, 2007, el suscrito Notario CERTIFICA que:

1). Joseph S. Podolski, (nombre de quien firma el poder), mayor de edad y domiciliado en 3 Pebble Hollow Court, The Wodlands, Texas, 77381, Estados Unidos de América, suscribió el anterior documento.

2) El otorgante le es conocido personalmente y tiene capacidad para firmar el documento.

3) El otorgante ha suscrito el anterior documento en su calidad de Presidente y Funcionario jefe Ejecutivo de la persona jurídica Repros Therapeutics Inc.

Notaría Única (E) del Círculo de Bogotá, D.C. Hace constar que esta FOTOCOPIA coincide con su Original que he tenido a la vista

07 ABR 2010

Nohora Sánchez García
BOGOTA D.C.

TRADUCCION OFICIAL No.
JUAN PABLO [illegible] AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

11

4) La mencionada persona jurídica con domicilio comercial en 2408, Timberloch Drive, B-7, The Woodlands, Texas, 77380, Estados Unidos de América, está debidamente constituida, tiene actualmente existencia legal y el fin para el cual se otorga este poder se encuentra dentro de su objeto social.

5) El otorgante tiene en efecto la capacidad referida y su representación es legal y está autorizado para otorgar este poder.

6) Fundamento las certificaciones 3), 4) y 5) en los documentos auténticos que para tal fin me fueron exhibidos.

(Firmado) Tara F. Stewart, Notario Público

Notario Público

(Sello Notarial a tinta: TARA F. STEWART, mi comisión vence Febrero 26, 2009)

Nota: El Consulado de Colombia debe autenticar la firma del Notario Público.

Para todos los demás países el Señor Cónsul de Colombia o ante quien se otorgue, debe expedir una certificación dejando constancia de: 1) la existencia legal de la sociedad, 2) que cumple actualmente con su objeto social, y 3) que la persona o personas que otorgan este poder están facultadas para hacerlo. El Cónsul también certificará que los tuvo a la vista los documentos que prueban y acreditan tales circunstancias.

LEGALIZACIÓN POR EL CÓNSUL DE COLOMBIA O POR APOSTILLA

Cónsul Notario Cmpt. (E) del Circulo de Bogotá D.C. que ha tenido a la vista

07 ABR 2010

Nelson J. Sánchez García
NOTARIO ONCE (E)
BOGOTÁ D.C.

TRADUCCIÓN OFICIAL No. 17

JUAN PABLO PICO SARMIENTA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

12

(Sello Pre-impreso del Estado de Texas)

El Estado de Texas

Secretario de Estado

APOSTILLA

(Convención de la Haya de Octubre 5 de 1961)

1. País: Estados Unidos de América
   Este documento público
2. Ha sido firmado por TARA F. STEWART
3. Obrando en calidad de Notario Público, Estado de Texas
4. Lleva el sello/estampilla de TARA F. STEWART, Notario Público, Estado de Texas, Comisión vence 02-26-09

CERTIFICADA

5. En Austin, Texas 6. Hoy 13 de Septiembre, 2007
7. Por el Secretario de Estado de Texas
8. Certificado Número **N-607592**
9. (Sello) (Sello Pre-impreso del Estado de Texas)
10. (Firma) Firmado
    (Firmado) Phil Wilson, Secretario de Estado
    ST/sjs

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

Bogotá, Octubre 16, 2007.

Como Notario Once (E) del Círculo de Bogotá, D.C., hago constar que esta FOTOCOPIA coincide con su Original que he tenido a la vista.

07 ABR 2010

NOTARIA ONCE (E) BOGOTA, D.C.

TRADUCCION OFICIAL No. _____
JUAN PABLO PIC[illegible] AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

13

Como Notario Once (E) del Circulo de Bogotá, D.C., hago constar que esta FOTOCOPIA coincide con su Original que he tenido a la vista.

07 ABR 2010

Nelson J. Sánchez García
NOTARIO ONCE (E)
BOGOTÁ, D.C.

MINISTERIO DE
RELACIONES EXTERIORES

2007 OCT 16 P 1:25

JEFE DE LEGALIZACIONES
BOGOTA D.C.

DIRECCION
RESPONSABILIDAD
DEL TESTA

672144

[illegible]
[illegible]
[illegible]
[illegible]
LAS FUNCIONES INDICADAS

TRANS-CLOMIFENO PARA EL SÍNDROME METABÓLICO

RESUMEN

Administración de composiciones que comprenden un antiestrógeno, preferentemente *trans*-clomifeno, para el tratamiento del síndrome metabólico en un sujeto. La invención también se refiere a métodos para reducir los niveles de glucosa en ayunas en un sujeto mediante la administración de una composición que comprende un antiestrógeno, preferentemente *trans*-clomifeno.

TRANS-CLOMIFENO PARA EL SÍNDROME METABÓLICO

CAMPO DE LA INVENCIÓN.

[0001] La presente invención se relaciona con composiciones y con métodos para tratar el síndrome metabólico y las condiciones asociadas con el mismo. Más específicamente, la presente invención se relaciona con el uso de composiciones que comprenden clomifeno enriquecidas en *trans*-clomifeno para el tratamiento del síndrome metabólico y las condiciones asociadas con el mismo en sujetos con niveles bajos o normales bajos de testosterona.

ANTECEDENTES

[0003] El síndrome metabólico se caracteriza por un grupo de factores de riesgo metabólico en una persona incluyendo obesidad abdominal, resistencia a insulina o intolerancia glucosa, dislipidemia aterogénica, estado protrombótico, estado proinflamatorio e hipertensión. El Panel de Tratamiento de Adultos define al síndrome metabólico como presente si un paciente manifiesta al menos tres de los siguientes síntomas: un contorno de cintura de al menos 40 pulgadas para hombres, 35 pulgadas para mujeres; niveles de triglicéridos en suero de al menos 150 mg/dl; niveles de colesterol HDL menores que 40 mg/dl en hombres, menores que 50 mg/dl en mujeres, presión sanguínea de al menos 135/80 mm de Hg y azúcar en sangre (glucosa sérica) de al menos 110 mg/dl. Se ha estimado que hasta un 25% de la población en los EE.UU. está afectado por el síndrome metabólico.

[0004] Se considera que una causa subyacente del síndrome metabólico es la resistencia a la insulina en donde está atenuada la capacidad de la insulina para tomar glucosa de la sangre. Esto hace que los niveles de glucosa permanezcan elevados después de ingerir alimento a lo cual el páncreas

responde con excreción de insulina. Si no se trata, el síndrome metabólico incrementa significativamente el riesgo de diabetes tipo II, enfermedad cardiovascular y otras enfermedades relacionadas con la acumulación de placas en las paredes arteriales.

[0005] Distintos estudios han demostrado una correlación inversa entre los niveles de insulina en ayunas y la testosterona en suero en hombres. Más aún, la testosterona en suero es significativamente más baja en hombres con síndrome metabólico y otros estados resistentes a insulina tales como obesidad y diabetes mellitus tipo 2 en comparación con los controles. Sin embargo, no se ha dilucidado aún el mecanismo que fundamenta estas observaciones.

[0006] Un estudio reciente ha sugerido que la relación entre testosterona e insulina puede estar mediada por cambios en el índice de masa corporal (BMI) en donde los niveles bajos de testosterona conducen a obesidad y desregulación del metabolismo de ácidos grasos que a su vez promueve la resistencia a insulina. A diferencia de la testosterona, no se encontró una relación significativa entre los niveles de estrógenos y la sensibilidad a la insulina en dicho estudio.

[0007] Otro estudio reciente evaluó al eje hipotalámico-pituitario-gonadal en hombres con un amplio espectro de sensibilidad a la insulina. En este estudio, se observó una relación positiva entre la sensibilidad a la insulina y la testosterona, no obstante lo cual no se observó relación alguna entre la sensibilidad a la insulina y los parámetros de secreción de la hormona luteinizante (LH) lo cual sugiere que un nivel bajo de testosterona asociado con resistencia a insulina no es el resultado de un defecto en el hipotálamo o la pituitaria, sino más bien se debe a una alteración en la función de las células de

16

Leydig. En este sentido, está bien establecido que la esteroidogénesis en las células de Leydig, al menos *in vitro*, no solo es modulada por una secreción pulsátil de LH sino también por hormonas, factores de crecimiento, citoquinas e insulina.

[0008] Los datos sobre el impacto de suplementos con andrógenos sobre la sensibilidad a la insulina en hombres son conflictivos. En un estudio, los hombres con diabetes tipo 2 no mostraron mejoras en el control de la glucemia con reemplazo de testosterona, en tanto un estudio más amplio mostró una reducción significativa en la hemoglobina glicosilada.

[0009] La testosterona es el andrógeno masculino primario, que cumple un rol vital en la salud general de los hombres. La testosterona es esencial para el desarrollo y el mantenimiento de tejidos reproductores específicos (testículos, próstata, epidídimo, vesícula seminal y pene) y las características sexuales secundarias masculinas. Cumple una función clave en la líbido y la función eréctil y es necesaria para el inicio y mantenimiento de la espermatogénesis.

[0010] La secreción de testosterona es el producto final de una serie de procesos hormonales. La hormona liberadora de gonadotrofina (GnRH), que es secretada en el hipotálamo, controla la secreción pulsátil de la hormona luteinizante (LH) y de la hormona folículoestimulante (FSH), que es secretada por la pituitaria anterior. La LH, a su vez, regula la producción y secreción de testosterona en las células de Leydig en testículos, en tanto la FSH ayuda a inducir la espermatogénesis.

[0011] Una deficiencia de testosterona puede deberse a una enfermedad subyacente o a trastornos genéticos y con frecuencia también es una

17

complicación del envejecimiento. Por ejemplo, el hipogonadismo primario es el resultado de una falla testicular primaria. En esta situación, los niveles de testosterona son bajos y los niveles de de gonadotropinas pituitarias (LH y FSH) son elevados. El hipogonadismo secundario o hipogonadotrófico se debe a una secreción inadecuada de las gonadotropinas pituitarias. Además de un nivel bajo de testosterona, los niveles de LH y FSH son bajos o normales bajos. Algunas de las secuelas de una deficiencia de testosterona en adultos incluyen una amplia variedad de síntomas incluyendo: pérdida de la líbido, disfunción eréctil, oligospermia o azoospermia, ausencia o regresión de las características sexuales secundarias, disminución progresiva de la masa muscular, fatiga, humor deprimido y mayor riesgo de osteoporosis. Muchos de estos trastornos se denominan genéricamente como menopausia masculina.

[0012]El clomifeno (FIG. 2), que es un antiestrógeno relacionado con el tamoxifeno, también se ha usado en el tratamiento de hombres con niveles bajos de testosterona. El clomifeno bloquea la retroalimentación normal de estrógenos en el hipotálamo y la subsiguiente retroalimentación negativa en la pituitaria. Esto conduce a incrementos en la hormona luteinizante (LH) y en la hormona folículoestimulante (FSH). En hombres, estos mayors niveles de gonadotropinas estimulan las células de Leydig en testículos y dan como resultado la producción de mayores niveles de testosterona.

[0013]Tenover *et al.*, *J. Clin. Endocrinol. Metab.* *64*:1103, (1987) y Tenover *et al.*, *J. Clin. Endocrinol. Metab.* *64*:1113 (1987) encontraron incrementos en FSH, LH en hombres jóvenes y de edad después del tratamiento con clomifeno. También encontraron incrementos en la testosterona libre y total en hombres, con incrementos significativos en

18

hombres jóvenes.

[0014]Ernst *et al.*, *J. Pharmaceut. Sci. 65*:148 (1976), han mostrado que el clomifeno es una mezcla de dos isómeros geométricos a los que hacen referencia como *cis*,-Z-, clomifeno (*cis*-clomifeno o zuclomifeno) y *trans*-,E-, clomifeno, (*trans*-clomifeno o enclomifeno). De acuerdo con Ernst, *et al.* el *trans*-clomifeno HCl tiene un punto de fusión de 149°C-150,5°C, en tanto el *cis*-clomifeno HCl tiene un punto de fusión de 156,5°C-158°C. Ernst *et al.* también notaron que (el isómero *trans*) es antiestrogénico (AE) en tanto el isómero *cis* es la forma más potente y más estrogénica y también se ha informado que presenta actividad anti-estrogénica. Los autores atribuyen el efecto de la droga sobre la actividad ovulatoria a ambas formas aseverando que la mezcla es más eficaz que el *trans*-clomifeno solo. El isómero *trans* ayuda en la ovulación a nivel del hipotálamo. El isómero estrogénico *cis*-clomifeno contribuye en una mejora en la ovulación en otra parte de la vía fisiológica que conduce a la ovulación. También se ha informado que los isómeros tienen una vida media diferente *in vivo*. Aún más, se ha informado que la forma *cis* deja niveles residuales en sangre en exceso por un mes después de una sola dosis.

[0015]Actualmente, el clomifeno está aprobado como una mezcla de ambos isómeros *cis* y *trans*, donde el isómero *cis* constituye aproximadamente entre un 30% y un 50% (Merck Manual), para el aumento de la fertilidad en pacientes anovulatorios. El clomifeno mejora la ovulación porque inicia una serie de eventos endócrinos que culminan en un pico de gonadotrofina preovulatorio y la subsiguiente ruptura folicular. Se recomienda administrar la droga durante 5 días a una dosis de hasta 100 mg por día. El clomifeno también se ha asociado con numerosos efectos secundarios que incluyen:

visión borrosa, molestia abdominal, ginecomastia, tumores testiculares, síntomas vasomotores, náuseas y cefaleas. Aún más, otros estudios sugieren que el clomifeno posee tanto efectos genotóxicos como de aumento de tumores. El resultado neto de estas observaciones es que el clomifeno en su formato actual, que tiene entre un 30% y 50% del isómero *cis*, sería inacceptable para una terapia crónica en hombres para el tratamiento de deficiencia de testosterona.

RESUMEN

[0016]La presente invención se relaciona con un método de tratamiento del síndrome metabólico que comprende administrarle a un sujeto que lo necesita, una composición que comprende una cantidad eficaz de un antiestrógeno o una sal aceptable para uso farmacéutico del mismo. El sujeto puede ser de sexo masculino o femenino. El sujeto también pueden sufrir de hipogonadismo hipogonadotrófico idiopático o secundario.

[0017]La presente invención también se relaciona con un método de tratamiento del síndrome metabólico en un sujeto que comprende administrarle a un sujeto que lo necesita, una cantidad eficaz de una composición que comprende entre 0% y 29% peso/peso de (*cis*, -Z-, *trans*-clomifeno) (de aquí en adelante "*cis*-clomifeno") y entre 100% y 71% p/p de (*trans*-, E-, *cis*-clomifeno) (de aquí en adelante "*trans*-clomifeno") o una sal aceptable para uso farmacéutico del mismo. La composición puede consistir esencialmente de *trans*-clomifeno o una sal del mismo. La composición también puede consistir de *trans*-clomifeno o un análogo del mismo. El sujeto puede ser de sexo masculino o femenino. El sujeto también pueden sufrir de hipogonadismo hipogonadotrófico idiopático o secundario.

20

[0018]La presente invención también se relaciona con un método de tratamiento de uno o más síntomas del síndrome metabólico que comprende administrarle a un sujeto que lo necesita, una composición que comprende una cantidad eficaz de un antiestrógeno o una sal aceptable para uso farmacéutico del mismo. El sujeto puede ser de sexo masculino o femenino. El sujeto también pueden sufrir de hipogonadismo hipogonadotrófico idiopático o secundario.

[0019]La presente invención también se relaciona con un método de tratamiento de glucosa en ayunas deteriorada en un sujeto que comprende administrarle a un sujeto una composición que comprende una cantidad eficaz de un antiestrógeno o una sal aceptable para uso farmacéutico del mismo. El sujeto puede ser de sexo masculino o femenino. El sujeto puede ser un individuo de sexo masculino o femenino que tiene el deseo o la necesidad de reducir los niveles de glucosa en ayunas. El sujeto también pueden sufrir de hipogonadismo hipogonadotrófico idiopático o secundario.

[0020]La presente invención también se relaciona con un método de tratamiento de glucosa en ayunas deteriorada en un sujeto que comprende administrarle a dicho sujeto una composición que comprende entre 0% y 29% peso/peso de (*cis*, -Z-, *trans*-clomifeno) (de aquí en adelante "*cis*-clomifeno") y entre 100% y 71% p/p (*trans*-, E-, *cis*-clomifeno) (de aquí en adelante "*trans*-clomifeno") o una sal aceptable para uso farmacéutico del mismo. La composición puede consistir esencialmente de *trans*-clomifeno o una sal del mismo. La composición también puede consistir de *trans*-clomifeno o un análogo del mismo. El sujeto puede ser un individuo de sexo masculino o femenino que tiene el deseo o la necesidad de reducir los niveles de glucosa

21

en suero. El sujeto también pueden sufrir de hipogonadismo hipogonadotrófico idiopático o secundario.

DESCRIPCIÓN BREVE DE LAS FIGURAS

[0021]La FIG. 1 es un gráfico representativo de los perfiles secretores normales de testosterona total en suero en hombres saludables (jóvenes y de edad).

[0022]La FIG. 2 muestra la estructura química del citrato de clomifeno.

[0023]La FIG.3. es una demostración gráfica de los niveles de testosterona en suero en el tiempo con Clomid (citrato de clomifeno), Enclomid (*trans*-clomifeno) y Zuclomid (*cis*-clomifeno).

[0024]La FIG. 4 es una demostración gráfica de los niveles de colesterol en el tiempo en mandriles machos tratados con Clomid (citrato de clomifeno), Enclomid (*trans*-clomifeno) y Zuclomid (*cis*-clomifeno).

[0025]La FIG. 5 demuestra el efecto de Androxal™ o Androgel® sobre los niveles de testosterona.

[0026]La FIG. 6 demuestra el efecto de Androxal™ o Androgel® sobre los niveles de LH.

[0027]La FIG. 7 demuestra el efecto de Androxal™ o Androgel® sobre los niveles de FSH

[0028]La FIG. 8 demuestra el nivel basal de glucosa en sangre en los grupos de tratamiento con Androxal™, Androgel® y placebo.

[0029]La FIG. 9 demuestra el efecto de Androxal™ sobre los niveles de glucosa en sangre.

[0030]La FIG. 10 demuestra el efecto de Androgel® sobre los niveles de glucosa en sangre.

22

DESCRIPCIÓN DETALLADA

[0031]La presente invención provee métodos para tratar el síndrome metabólico y las condiciones asociadas con el mismo. La presente invención se basa en el descubrimiento sorpresivo que la administración de una composición que comprende *trans*-clomifeno a sujetos con niveles bajos de testosterona total causa una disminución en los niveles de glucosa sérica en ayunas concomitante con un incremento en los niveles de testosterona y una disminución de los niveles de colesterol y triglicéridos en los sujetos. Por consiguiente, se encontró sorpresivamente que las composiciones que comprenden *trans*-clomifeno son de utilidad en el tratamiento del síndrome metabólico. El descubrimiento es inesperado en vista de lo que sugieren los estudios recientes: (1) que la resistencia a insulina asociada con niveles bajos de testosterona no es el resultado de un defecto en el hipotálamo o la pituitaria; (2) que falta correlación entre estrógenos y sensibilidad a la insulina; y (3) que los efectos de niveles bajos de testosterona sobre la sensibilidad a la insulina, si hubiera alguno, están mediados por cambios en el índice de masa corporal (BMI).

[0032]En una realización de la presente invención, se emplea la administración de una composición que comprende una cantidad eficaz de un antiestrógeno para tratar el síndrome metabólico en un sujeto que necesita dicho tratamiento. El sujeto puede ser de sexo masculino o femenino. El sujeto también pueden sufrir de hipogonadismo hipogonadotrófico idiopático o secundario.

[0033]En una realización preferida de la presente invención, se usa una composición que comprende una cantidad eficaz de *trans*-clomifeno o una

mezcla predefinida de los isómeros de clomifeno que se describirán más adelante que difieren de la mezcla producida normalmente, en el tratamiento del síndrome metabólico en un sujeto masculino o femenino.

[0034] Se debe tener en cuenta que cuando se utiliza el término "síndrome metabólico" en la presente, se relaciona con el síndrome metabólico definido por el Panel de Tratamiento de Adulto o cualquier otra definición reconocida de este síndrome. Los sinónimos de "síndrome metabólico" usados en el arte incluyen síndrome de Reaven, síndrome de resistencia a insulina y síndrome X. Se debe tener en cuenta entonces que cuando se utiliza el término "síndrome metabólico" en la presente, también hace referencia al síndrome de Reaven, síndrome de resistencia a insulina y síndrome X.

[0035] En otra realización de la presente invención, se emplea la administración de una composición que comprende una cantidad eficaz de un antiestrógeno, preferentemente *trans*-clomifeno, para tratar un síntoma del síndrome metabólico en un sujeto que necesita dicho tratamiento. El síntoma del síndrome metabólico puede incluir, en un sentido no limitativo, niveles de glucosa elevados, niveles de triglicéridos elevados, niveles de colesterol elevados, resistencia a insulina, presión sanguínea alta, obesidad abdominal, estado protrombótico, estado proinflamatorio o cualquier combinación de dos o más síntomas. El sujeto puede ser de sexo masculino o femenino. El sujeto también pueden sufrir de hipogonadismo hipogonadotrófico idiopático o secundario.

[0036] En otra realización de la presente invención, se puede combinar la administración de una composición que comprende una cantidad eficaz de un antiestrógeno, preferentemente *trans*-clomifeno, a un sujeto con el síndrome

metabólico con cualquier régimen de tratamiento conocido. Los regímenes de tratamiento del síndrome metabólico incluyen, en un sentido no limitativo, regímenes de ejercicio, regímenes de reducción de peso, medicaciones para la presión sanguínea tales como inhibidores de ACE, medicaciones reductores del colesterol y metformina. Las composiciones de la invención pueden ser administradas de manera simultánea, separada o sucesiva con cualquiera de los regímenes de tratamiento conocidos mencionados previamente.

[0037] En otra realización de la presente invención, la administración de una composición que comprende una cantidad eficaz de un antiestrógeno se usa para tratar la glucosa en ayunas deteriorada en un sujeto. El sujeto puede ser de sexo masculino o femenino. El sujeto pueden sufrir de hipogonadismo hipogonadotrófico idiopático o secundario.

[0038] Se debe tener en cuenta que la "glucosa en ayunas deteriorada" según se usa en la presente se define con respecto a la prueba de tolerancia de glucosa en sangre en ayunas. En esta prueba, se mide la glucosa en sangre de un sujeto después de un ayuno de 8 a 12 horas. Una persona con una glucosa en ayunas normal tiene un nivel de glucosa en sangre en ayunas por debajo de 110 mg/dl. Una persona con glucosa en ayunas deteriorada tiene un nivel de glucosa en sangre en ayunas entre 110 mg/dl y 125 mg/dl. Un nivel de glucosa en ayunas mayor que 125 mg/dl indica diabetes. Por lo tanto, las composiciones de la presente invención pueden administrarse a un sujeto con niveles de glucosa en sangre en ayunas entre 110 mg/dl y 125 mg/dl. Por ejemplo, el sujeto puede tener un nivel de glucosa en sangre en ayunas de 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124 ó 125 mg/dl.

25

[0039]La administración de las composiciones de la invención puede disminuir los niveles de glucosa en sangre en ayunas por debajo de 125, 124, 123, 122, 121, 120, 119, 118, 117, 116, 115, 114, 113, 112, 111 y preferentemente por debajo de 110 mg/dl.

[0040]Los pacientes con glucosa en ayunas deteriorada tienen un riesgo significativo de desarrollar diabetes. Por lo tanto, la presente invención provee un método para prevenir la transición de glucosa en ayunas deteriorada a diabetes mellitus en un sujeto que comprende la administración al sujeto de una composición que comprende una cantidad eficaz de un antiestrógeno, preferentemente *trans*-clomifeno. El sujeto puede ser de sexo masculino o femenino. El sujeto también pueden sufrir de hipogonadismo hipogonadal idiopático o secundario.

[0041]En otra realización de la presente invención, a un paciente con hipogonadismo hipogonadotrófico idiopático o secundario que tiene la necesidad o el deseo de disminuir los niveles de glucosa en sangre en ayunas se le administra una composición que comprende una cantidad eficaz de un antiestrógeno, preferentemente *trans*-clomifeno. El paciente hipogonadal puede tener cualquier nivel de glucosa en ayunas, pero preferentemente tiene un nivel de glucosa en ayunas por encima de aproximadamente 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 160, 165, 170, 175, 180, 185, 190, 195 ó 200 mg/dl. Por ejemplo, el paciente hipogonadal puede tener niveles de glucosa en ayunas entre 125 y 140 mg/dl. La composición puede comprender una

cantidad de un antiestrógeno, preferentemente *trans*-clomifeno, para disminuir el nivel de glucosa en ayunas del paciente hipogonadal por debajo de 200, 195, 190, 185, 180, 175, 170, 165, 160, 155, 154, 153, 152, 151, 150, 149, 148, 147, 148, 147, 146, 145, 144, 143, 142, 141, 140, 139, 138, 137, 136, 135, 134, 133, 132, 131, 130, 129, 128, 127, 126, 125, 124, 123, 122, 121, 120, 119, 118, 117, 116, 115, 114, 113, 112, 111 o preferentemente por debajo de 110 mg/dl.

[0042]Cuando el nivel de glucosa de un paciente hipogonadal se encuentra por encima de aproximadamente 125 mg/dl, el paciente también puede recibir un diagnóstico de diabetes mellitus tipo 2. Por consiguiente, la presente invención también provee un método de tratamiento de diabetes mellitus tipo 2 que comprende administrarle a un sujeto que lo necesita, una composición que comprende una cantidad eficaz de un antiestrógeno, preferentemente *trans*-clomifeno, o una sal aceptable para uso farmacéutico del mismo. En este sentido, las composiciones de la invención se pueden combiner con cualquier régimen de tratamiento conocido para la diabetes mellitus tipo 2. Los regímenes de tratamiento conocidos para la diabetes mellitus tipo 2 incluyen, en un sentido no limitativo: regímenes de ejercicio; regímenes de reducción de peso; medicaciones para la presión sanguínea tal como inhibidores de la enzima convertidora de angiotensina (ACE) (por ejemplo, ramipril); metformina; tiazolidindionas (TZDs); inhibidores de α-glucosidasa tal como acarbosa y miglitol; meglitinidas tal como nateglinida, repaglinida; inhibidores de análogos peptídicos tal como dipeptidil peptidasa-4 (DPP-4) y análogos de agonistas de amilina; e insulina. Las composiciones de la invención pueden ser administradas de manera simultánea, separada o sucesiva con cualquiera de los regímenes de tratamiento conocidos

27

mencionados previamente.

[0043]Los sujetos que necesitan del tratamiento con cualquiera de los métodos de la presente invención pueden tener niveles bajos o bajos normales de testosterona total. Por ejemplo, los sujetos de sexo masculino que necesitan del tratamiento pueden tener niveles total de testosterona por debajo de aproximadamente 320, 310, 300, 295, 290, 285, 280, 275, 270, 265, 260, 255, 250, 245, 240, 235, 230, 225, 220, 215, 210, 205, 200, 195, 190, 185, 180, 175, 170, 165, 160, 155, 150, 145, 140, 135, 130, 125, 120, 115, 105, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10 ó 5 ng/dl. Los sujetos de sexo masculino con la testosterona total por debajo de aproximadamente 300 ng/dl se definen como hipogonadales.

[0044]En un aspecto relacionado, la presente invención provee un método de tratamiento del hipogonadismo hipogonadotrófico idiopático de comienzo adulto (AIHH) o una condición asociada con el mismo, que comprende administrarle a un sujeto que lo necesita una cantidad eficaz de una composición que comprende un antiestrógeno, preferentemente *trans*-clomifeno o una sal del mismo. Los hombres con AIHH se caracterizan por tener baja la testosterona y la hormona luteinizante (LH) a menudo acompañado de, entre otros, obesidad y glucosa en sangre elevada. Las composiciones de la invención pueden ser de utilidad en el tratamiento de cualquiera de estas condiciones.

[0045]En una realización preferida de la presente invención, a un paciente con hipogonadismo hipogonadotrófico idiopático o secundario quien a desarrollado el síndrome metabólico se le administra una o más dosis de una cantidad eficaz de una composición que comprende *trans*-clomifeno a una

88

dosificación entre un mg y 200 mg aproximadamente (aunque la determinación de las dosificaciones óptimas se encuentra dentro del nivel del conocimiento propio en la técnica) con el fin de tratar el síndrome metabólico o una condición asociada con el mismo. El *cis*-clomifeno también puede estar presente en la composición siempre y cuando la relación de *trans*-clomifeno a *cis*-clomifeno sea mayor que 71/29. Los análogos de los isómeros *trans* y *cis* de clomifeno, tales como los que se describió en Ernst, *et al. supra*, también son de utilidad en la práctica de la presente invención.

[0046]Las dosificaciones se administran preferentemente (pero no necesariamente) como parte de un régimen de dosificación diseñado para dar lugar a niveles de testosterona en suero que imitan o corresponden al perfil de testosterona total normal secretora en suero descrito en la FIG. 1durante el período de administración y preferentemente también durante el período de discontinuación. Por ejemplo, de acuerdo con la FIG 1 se puede administrar una dosificación de la composición preferida en una formulación farmacéutica que daría lugar a niveles pico de testosterona en suero a las 8 a.m. aproximadamente. Dichas formulaciones farmacéuticas se pueden encontrar en la forma de formulaciones de liberación sostenida preparadas como se describe, por ejemplo, en la Patente de los EE.UU. Nº: 6.221.399, Patente de Japón 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. y Ind. Pharm.* 21 (20):2323-2337 (1995); Patentes de los EE.UU. Nº: 6.143.353, 6.190.591, 6.096.338, 6.129.933, 6.126.969, 6.248.363 y otras formulaciones de liberación sostenida bien conocidas en la técnica. La dosificación de *trans*-clomfeno puede comprender

entre 5 y 100 mg. La dosificación de *trans*-clomfeno también puede comprender entre 12,5 y 50 mg. La dosificación de *trans*-clomifeno también puede ser de 12,5 mg, 25 mg o 50 mg.

[0047] Los términos "tratar" o "tratamiento" según se usan en la presente solicitud, se refieren tanto a un tratamiento terapéutico y profiláctico como medidas preventivas, en donde el objetivo es prevenir o demorar (disminuir) un cambio o trastorno fisiológico o psicológico, tal como las condiciones asociadas con el síndrome metabólico. A los efectos de la presente invención, los resultados clínicos beneficiosos o deseados incluyen, pero en un sentido no limitativo, alivio de los síntomas, disminución del grado de enfermedad, estabilización del estado de la enfermedad (es decir, no hay empeoramiento), demora o disminución del avance de la enfermedad, alivio o mitigación del estado de enfermedad y remisión (ya sea parcial o total), ya sean detectables o no detectables. El término "tratamiento" también puede significar la prolongación de la sobrevida en comparación con la sobrevida esperada si no se recibiera tratamiento. Los individuos que necesitan del tratamiento incluyen a los que ya sufren de la afección o trastorno así como los que son propensos a desarrollar la afección o el trastorno o quienes necesitan prevenir la condición o trastorno.

[0048] Los términos "modular" o "modulación", según se usan en la presente solicitud, se refieren tanto a un tratamiento terapéutico y profiláctico o a medidas preventivas, en donde el objetivo comprende prevenir o demorar (disminuir) un parámetro clínico indeseado. A los efectos de la presente invención, los resultados clínicos beneficiosos o deseados incluyen, pero en un sentido no limitativo, la corrección de un parámetro clínico, la disminución de la

extensión de un parámetro clínico, la estabilización de un parámetro clínico (es decir, no empeora) y la demora o enlentecimiento de la extensión del parámetro clínico.

[0049]Un "antiestrógeno" se refiere a un compuesto que impide que los estrógenos expresen sus efectos sobre tejidos blanco dependientes de estrógenos y en consecuencia antagoniza una variedad de procesos dependientes de estrógenos. Sobre la base del hallazgo inesperado que el isómero antiestrogénico *trans*-clomifeno es de utilidad en el tratamiento del síndrome metabólico en sujetos hipogonadales, se espera que los compuestos con actividad antiestrogénica serán de utilidad en la presente invención. En todos los casos, los antiestrógenos de utilidad en la práctica de la presente invención son aquellos que tienen la capacidad de elevar los niveles de testosterona en un mamífero. Sin tener en cuenta una teoría, se cree que la administración de antiestrógenos dará como resultado niveles elevados de testosterona por bloqueo de la retroalimentación negativa ejercida por los estrógenos normales sobre la pituitaria lo que conduce a incrementos en LH y FSH. En hombres, estos mayores niveles de gonadotropinas estimulan las células de Leydig en testículos y dan como resultado la producción de mayores niveles de testosterona.

[0050]Los antiestrógenos de utilidad en la práctica de la presente invención pueden ser antiestrógenos puros o pueden tener una acción estrogénica parcial como en el caso de los moduladores selectivos del receptor de estrógenos (SERMs) que exhiben propiedades antiestrogénicas en algunos tejidos y estrogénicos en otros tejidos.

[0051]Los antiestrógenos puros de la invención incluyen, en un sentido

no limitativo: RU 58.688, descrito en Van de Velde *et al.*, *Ann. NY Acad. Sci.*, 761(3):164-175 (1995); 13-metil-7-[9-(4,4,5,5,5-pentafluoropentilsulfinil)nonil]-7,8,9,11,12,13,14,15,16,17-decahidro-6H-ciclopenta[a]-fenantren-3,17-diol (ICI 182,780/fulvestrant) y otros compuestos descritos en la EP 0138504; N-butil-11-[(7R,8S,9S,13S,14S,17S)-3,17-dihidroxi-13-metil-6,7,8,9,11,12,14,15,16,17-decahidrociclopena[a]fenantren-7-il]-N-metil-undecanamida (ICI 164.384), descrita en Wakeling y Bowler, *J. Endocrin.*, 112:R7-R110 (1987); (#)-7-pivaloiloxi-3-(4'pivaloiloxifenil)-4-metil-2-(4"-(2"piperidinetoxi)fenil)-2H-benzopiran (EM-800/SCH 57050) y otros compuestos descritos en WO 96/26201; (2S)-3-(4-hidroxifenil)-4-metil-2-[4-[2-(1-piperidil)etoxi]fenil]-2H-cromen-7-ol (EM-652/SCH 57068) y semejantes.

[0052] Los SERMs de la invención incluyen, en un sentido no limitativo, trifenilalquilenos tal como trifeniletilenos, que incluyen: 2-[4-(1,2-difenilbut-1-enil)fenoxi]-N,N-dimetil-etanamina (tamoxifeno) y otros compuestos descritos en la Patente de los EE.UU. Nº: 4.536.516, incorporada en la presente a modo de referencia; trans-4-(1-(4-(2-dimetilamino)etoxi)fenil)-2-fenil-1-butenil)fenol (4-hidroxitamoxifeno) y otros compuestos descritos en la Patente de los EE.UU. Nº: 4.623.660, incorporada en la presente a modo de referencia; 1-[4'-dimetilaminoetoxi)fenil]-1-(3'-hidroxifenil)-2-fenilbut-1-eno (droloxifeno) y otros compuestos descritos en la Patente de los EE.UU. Nº: 5.047.431, incorporada en la presente a modo de referencia; 2-[p-[(Z)-4-cloro-1,2-difenil-1-butenil]fenoxi]-N,N-dimetiletilamina (toremifeno) y otros compuestos descritos en las Patentes de los EE.UU. Nº: 4.696.949, 5.491.173 y 4.996.225, cada una de las cuales se incorpora en la presente a modo de referencia; (E)-1-(2-(4-(1-(4-iodo-fenil)-2-fenil-but-1-enil)-fenoxi)-etil)-pirrolidinona (idoxifeno) y otros

compuestos descritos en la pat 4.839.155, incorporada en la presente a modo de referencia; clomifeno y sus dos isómeros; y los compuestos descritos en las Patentes de los EE.UU. N°: 4.696.949 y 5.491.173 y 6.576.645, cada una de las cuales se incorpora en la presente a modo de referencia.

[0053] Los SERMS de la invención también incluyen, en un sentido no limitativo, derivados de benzotiofeno tales como: [6-hidroxi-2-(4-hidroxifenil)-benzotiofen-3-il]-[4-[2-(1-piperidinil)etoxi)fenil]-metanona (raloxifeno) y otros compuestos descritos en las Patentes de los EE.UU. N°: 4.418.068 y 5.393.763, ambas incorporadas en la presente a modo de referencia; LY353381; y LY335563 y otros compuestos descritos en WO 98/45286, WO 98/45287 y WO 98/45288; derivados de benzopirano tales como: (#)-7-pivaloiloxi-3-(4'pivaloiloxifenil)-4-metil-2-(4"-(2"piperidinetoxi)fenil)-2H-benzopirano (EM 800 /SCH 57050) y otros compuestos descritos en WO 96/26201; (2S)-3-(4-hidroxifenil)-4-metil-2-[4-[2-(1-piperidil)etoxi]fenil]-2H-cromen-7-ol (EM 652); derivados de naftaleno tales como: cis-6-fenil-5-[4-(2-pirrolidin-1-il-etoxi)-fenil]-5,6,7,8-tetrahidronaftalen-2-ol (lasofoxifeno/CP 336,156) y otros compuestos descritos en la Patente de los EE.UU. N°: 5.552.412; 3,4-dihidro-2-(p-metoxifenil)-1-naftil-p-[2-(1-pirrolidinil)etoxi]fenilcetona (trioxifeno/LY133314) y otros compuestos descritos en la Patente de los EE.UU. N°: 4.230.862, incorporada en la presente a modo de referencia; y compuestos 1-(4-alcoxi sustituidos)benzil)naftaleno tal como los que se describen en la Patente de los EE.UU. N°: 6.509.356, incorporada en la presente a modo de referencia; cromanos tal como 3,4-trans-2,2-dimetil-3-fenil-4-[4-(2-(2-(pirrolidin-1-il)etoxi)fenil]-7-metoxicromano (levormeloxifeno) y otros compuestos descritos en WO 97/25034, WO 97/25035, WO 97/25037 y

33

WO 97/25038; y 1-(2-((4-(-metoxi-2,2,-dimetil-3-fenil-croman-4-il)-fenoxi)-etil)-pirrolidina (centcromano) y otros compuestos descritos en la Patente de los EE.UU. N°: 3.822.287, incorporada en la presente a modo de referencia.

[0054] Otros SERMs de la invención incluyen, en un sentido no limitativo, los compuestos descritos en las Patentes de los EE.UU. Nº: 6.387.920, 6.743.815, 6.750.213, 6.869.969, 6.927.224, 7.045.540, 7.138.426, 7.151.196 y 7.157.604, cada una de las cuales se incorpora en la presente a modo de referencia.

[0055] Otros antiestrógenos no limitativos de la invención incluyen: 6α-cloro-16α-metil-pregn-4-en-3,20-diona (clometerona); 6-cloro-17-hidroxipregna-1,4,6-trien-3,20-diona (delmadinona); 1-[2-[4-[1-(4-metoxifenil)-2-nitro-2-feniletenil]fenoxi]etil]-pirrolidina (nitromifeno/CN-55,945-27); y 1-[2-[p-(3,4-dihidro-6-metoxi-2-fenil-1-naftil)fenoxi]etil]pirrolidina (nafoxideno).

[0056] Otros antiestrógenos no limitativos de la invención incluyen indoles tales como los que se divulgan en *J. Med. Chem.*, 33:2635-2640 (1990), *J. Med. Chem.*, 30:131-136 (1987), WO 93/10741, WO 95/17383, WO 93/23374 y las Patente de los EE.UU. Nº: 6.503.938 y 6.069.153, ambas incorporadas en la presente a modo de referencia.

[0057] Otros antiestrógenos no limitativos de la invención incluyen 2-[3-(1-ciano-1-metil-etil)-5-(1H-1,2,4-triazol-1-ilmetil)fenil]-2-metil-propannitrilo (anastrozol) y otros compuestos descritos en EP 0296749; 6-metilenandrosta-1,4-dien-3,17-diona (exemestano) y otros compuestos descritos en la Patente de los EE.UU. N°: 4.808.616, incorporada en la presente a modo de referencia; 4-[(4-cianofenil)-(1,2,4-triazol-1-il)metil]benzonitrilo (letrozol) y otros compuestos descritos en la Patente de los EE.UU. N°: 5.473.078, incorporada

en la presente a modo de referencia; 1-[4'-dimetilaminoetoxi)fenil]-1-(3'-hidroxifenil)-2-fenilbut-1-eno (droloxifeno) y otros compuestos descritos en la Patente de los EE.UU. Nº: 5.047.431, incorporada en la presente a modo de referencia; 2α,3α-epitio-5α-androstan-17β-ol (epitiostanol); 2α,3α-epitio-5α-androstan-17β-il-1-metoxiciclopentiloxi (mepitiostano); 4-[(2Z,4Z)-4-(4-hidroxifenil)hexa-2,4-dien-3-il]fenol (cicladieno) y otros compuestos descritos en las Patentes de los EE.UU. Nº: 2.464.203 y 2.465.505, ambas incorporadas en la presente a modo de referencia; CI-680 descrito en *Unlisted Drugs*, 28(10): 169(O) (1976); CI-628 descrito en *Unlisted Drugs*, 26(7): 106(1) (1974); 13-etil-17α-etinil-17β-hidroxigona-4,9,1-trien-3-ona (R2323); difenolhidrocriseno y eritiro-MEA ambos descritos en Geynet, *et al.*, *Gynecol. Invest.* 3(1):2-29 (1972); 1-[1-cloro-2,2-bis(4-metoxifenil)etenil]-4-metoxi-benceno (clorotrianiseno) descrito en Merck Index, 10ª ed., N°: 2149; 1-[4-(2-dietilaminoetoxi)fenil]-1-fenil-2-(p-anisil)etanol (etamoxitrifetol) descrito en Merck Index, 10ª ed., N°: 3668; y 2-p-clorofenil-1-[p-(2-dietilaminoetoxi)fenil]-1-p-toliletanol (triparanol) y otros compuestos descritos en la Patente de los EE.UU. N°: 2.914.562, incorporada en la presente a modo de referencia.

[0058]Aún otros antiestrógenos de la invención incluyen, en un sentido no limitativo: ácido (2e)-3-(4-((1e)-1,2-difenilbut-1-enil)fenil)acrílico (GW5638), GW7604 y otros compuestos descritos en Wilson *et al.*, *Endocrinology*, 138(9):3901-3911 (1997) y WO 95/10513; 1-[4-(2-dietilaminoetoxi)fenil]-2-(4-metoxifenil)-1-fenil-etanol (MER-25), clorhidrato de N,N-dietil-2-[4-(5-metoxi-2-fenil-3H-inden-1-il)fenoxi]etanamina (U-11,555A), clorhidrato 1-[2-[4-(6-metoxi-2-fenil-3,4-dihidronaftalen-1-il)fenoxi]etil]pirrolidina (U-11,100A), ICI-46,669, 2-[4-[(Z)-1,2-difenilbut-1-enil]fenoxi]-N,N-dimetil-etanamina; ácido 2-

hidroxipropan-1,2,3-tricarboxílico (ICI-46,474) y otros compuestos descritos en Terenius *et al.*, *Gynec. Invest.*, 3:96-107 (1972); ácido 2-hidroxi-6-naftalenpropiónico (ácido alenólico); [4-[(4-acetiloxifenil)-ciclohexiliden-metil]fenil]acetato (ciclofenil/ICI-48213); [6-hidroxi-2-(4-hidroxifenil)benzotiofen-3-il]-[4-[2-(1-piperidil)etoxi]fenil]metanona (keoxifeno); 4-[(Z)-1-[4-(2-dimetilaminoetoxi)fenil]-2-(4-propan-2-ilfenil)but-1-enil]fenol (DP-TAT-59/miproxifeno); (1RS,2RS)-4,4'-diacetoxi-5,5'-difluoro-(1-etil-2-metilen)di-m-fenilendiacetato (acefluranol); 6-hidroxi-2-(p-hidroxifenil)-benzo(b)tien-3-il[2-(1-pirrolidinil)-etoxifenil]cetona (LY-117018); y [6-hidroxi-2-(4-hidroxi-fenil)benzo(b)tien-3-il]-[4-(2-(1-piperdinil)-etoxi)fenil]metanona (LY-156758).

[0059]Aún otros antiestrógenos de la invención incluyen, en un sentido no limitativo: ligandos de receptores de estrógenos no esteroides tales como los que se describen en las Patentes de los EE.UU. Nº: 5.681.835, 5.877.219, 6.207.716, 6.340.774 y 6.599.921, cada una de las cuales se incorpora en la presente a modo de referencia; derivados de esteroides tales como los que se describen en la Patente de los EE.UU. N°: 4.659.516, incorporada en la presente a modo de referencia; 7α-11-aminoalquil-estratrienos tales como los que se describen en WO 98/07740; estratrienos sustituidos en 11-β-halógeno-7α tales como los que se describen en WO 99/33855; 17α-alquil-17β-oxi-estratrienos tales como los que se describen en la Solicitud de Patente de los EE.UU. Nº: 10/305.418, incorporada en la presente a modo de referencia; 2-fenil-1-[4-(2-aminoetoxi)-benzil]-indoles tales como los que se describen en la Patente de los EE.UU. N°: 7.132.417, incorporada en la presente a modo de referencia; 4-fluoroalquil-2h-benzopiranos tales como los que se describen en la Patente de los EE.UU. N°: 6.844.336, incorporada en la presente a modo de

referencia; (4-(2-(2-aza-biciclo[2.2-1]hept-2-il)-etoxi)-fenil)-(6-hidroxi-2-(4-hidroxi-fenil)-benzo[b]tiofen-3-il)-metanona y otros benzotiofenos descritos en WO 95/10513 y en la Patente de los EE.UU. N°: 4.133.814, incorporada en la presente a modo de referencia; 2-fenil-1-[4-(2-aminoetoxi)-bencil]-indoles tales como los que se describen en la Patente de los EE.UU. N°: 5.998.402, incorporada en la presente a modo de referencia; 3-[4-(2-fenil-indol-1-ilmetil)fenil]-acrilamidas y otros compuestos descritos en la Patente de los EE.UU. N°: 5.985.910, incorporada en la presente a modo de referencia; 2-fenil-1-[4-(amino-1-il-alqu-1-inil)-bencil]-1H-indol-5-oles y otros compuestos descritos en las Patentes de los EE.UU. Nº: 5.780.497 y 5.880.137, ambas incorporadas en la presente a modo de referencia; esteroides tales como los que se describen en las Patentes de los EE.UU. Nº: 6.455.517, 6.548.491, 6.747.018 y 7.041.839, cada una de las cuales se incorpora en la presente a modo de referencia; compuestos de di-(3'-hidroxifenil)-alcano tal como los que se describen en la Patente de los EE.UU. N°: 4.094.994, incorporada en la presente a modo de referencia; derivados de fenol tales como los que se describen en la Patente de los EE.UU. N°: 4.751.240, incorporada en la presente a modo de referencia; análogos de 2,3-diaril-2H-1-benzopirano tales como los que se describen en Saeed *et al.*, *J. Med. Chem.*, 33:3210-3216 (1990) y Sharma *et al.*, *J. Med. Chem.* 33:3216-3229 (1990); y análogos de benzofurano y triarilfurano tales como los que se describen en Durani *et al.*, *J. Med. Chem.*, 32:1700-1707 (1989).

[0060]En una realización, las composiciones de la invención comprenden uno o más antiestrógenos o sales aceptables para uso farmacéutico de los mismos. Dependiendo de las condiciones de proceso el

37

compuesto de sal obtenido puede ser una forma neutra o salina. Las formas salinas incluyen hidratos y otros solvatos y también polimorfos cristalinos. Tanto la base libre como las sales de estos productos finales se pueden usar de acuerdo con la invención.

[0061] Las sales de adición ácida se pueden transformar de la manera conocida *per se* en la base libre usando agentes básicos tales como álcalis o por intercambio iónico. La base libre obtenida también puede formar sales con ácidos orgánicos o inorgánicos.

[0062] En la preparación de las sales de adición ácida, preferentemente se usan aquellos ácidos que forman sales aceptables para uso farmacéutico adecuados. Los ejemplos de dichos ácidos son ácido clorhídrico, ácido sulfúrico, ácido fosfórico, ácido nítrico, ácido alifático, los ácidos alicíclicos carboxílico o sulfónico, tales como ácido fórmico, ácido acético, ácido propiónico, ácido succínico, ácido glicólico, ácido láctico, ácido málico, ácido tartárico, ácido cítrico, ácido ascórbico, ácido glucurónico, ácido fumárico, ácido maleico, ácido hidroximaleico, ácido pirúvico, ácido aspártico, ácido glutámico, ácido p-hidroxibenzoico, ácido embónico, ácido etansulfónico, ácido hidroxietansulfónico, ácido fenilacético, ácido mandélico, ácido alogenbencenesulfónico, ácido toluensulfónico, ácido galactárico, ácido galacturónico, ácido naftalensulfónico. Todos los polimorfos de las formas cristalinas se pueden usar de acuerdo con la invención.

[0063] También se pueden usar sales de adición básica de acuerdo con la invención y se pueden preparar por reacción de la forma del ácido libre con una cantidad suficiente de la base deseada para producir la sal de manera convencional. La forma del ácido libre se puede regenerar por contacto de la

forma salina con un ácido y aislamiento del ácido libre de manera convencional. Las sales de adición básica aceptables para uso farmacéutico se forman con metales o aminas, tales como metales alcalinos y alcalino-térreos o aminas orgánicas. Los ejemplos de metales usados como cationes son sodio, potasio, calcio, magnesio y semejantes. Los ejemplos de aminas adecuadas son aminoácidos tales como lisina, colina, dietanolamina, etilendiamina, N-metilglucamina y semejantes.

[0064] Las composiciones de la presente invención se pueden preparar en la forma de una dosis unitaria o de dosis unitarias adecuadas para una administración oral, parenteral, transdérmica, rectal, transmucosa o tópica. La administración parenteral incluye, pero en un sentido no limitativo, intravenosa, intraarterial, intraperitoneal, subcutánea, intramuscular, intratecal e intraarticular.

[0065] Los términos "administración oral" o "administrable por vía oral" en la presente incluyen cualquier forma de administración de un agente terapéutico o una composición del mismo a un sujeto, en donde el agente o composición se coloca en la boca del sujeto, ya sea si el agente o la composición se traga, o no. Por consiguiente, una "administración oral" incluye una administración bucal y sublingual así como esofágica (por ejemplo inhalación).

[0066] En aún otra realización, las composiciones de la presente invención se formulan como supositorios rectales, que pueden contener bases de supositorios incluyendo, pero en un sentido no limitativo, manteca de cacao o glicéridos.

[0067] Las composiciones de la presente invención también se pueden

formular para inhalación, que pueden ser en una forma que incluye, pero en un sentido no limitativo, una solución, suspensión o emulsión que puede ser administrada como un polvo seco o en la forma de un aerosol usando un propelente, tal como diclorofuorometano o triclorofluorometano.

[0068] Las composiciones de la presente invención también se pueden formular para una administración transdérmica, por ejemplo como una crema, unguento, loción, pasta, gel, yeso impregnado con compuestos activos, parche o membrana. Dichas composiciones pueden comprender cualquier excipiente adecuado, por ejemplo mejoradores de la penetración y semejantes.

[0069] Las composiciones de la presente invención también se pueden formular para una administración parenteral incluyendo, pero en un sentido no limitativo, por inyección o infusión continua. Las formulaciones para inyecciones se pueden encontrar en la forma de suspensiones, soluciones o emulsiones en vehículos oleosos o acuosos. Dichas composiciones también se pueden proveer en la forma de un polvo para su reconstitución con un vehículo adecuado incluyendo, pero en un sentido no limitativo, agua estéril, libre de pirógenos, WFI y semejantes.

[0070] Las composiciones de la presente invención también se pueden formular como una preparación depot, que puede ser administrada por implantes o por inyección intramuscular. Dichas composiciones se pueden formular con materiales poliméricos o hidrofóbicos adecuados (como una emulsión, por ejemplo, en un aceite aceptable), resinas de intercambio iónico o como derivados escasamente solubles (por ejemplo, como una sal escasamente soluble).

[0071] Las composiciones de la presente invención también se pueden

40

formular como una preparación de liposomas. Las preparaciones de liposomas pueden comprender liposomas que penetran las células de interés o el estrato córneo y fusionar con la membrana celular lo que da como resultado la administración del contenido del liposoma en la célula. Por ejemplo, se pueden usar liposomas tales como los que se describen en la Patente de los EE.UU. N°: 5.077.211 de Yarosh, la Patente de los EE.UU. N°: 4.621.023 de Redziniak *et al.*, o la Patente de los EE.UU. N°: 4.508.703 de Redziniak *et al.*

[0072] Una composición de la invención se puede encontrar en la forma de unidades de dosificación sólidas tales como tabletas, (por ejemplo tabletas en suspensión, tabletas de suspensión, tabletas de dispersión rápida, tabletas masticables, tabletas efervescentes, tabletas en bicapas, *etc.*), cápsulas ovaladas, cápsulas (por ejemplo, una cápsula de gelatina blanda o dura), polvos (por ejemplo un polvo envasado, un polvo dispensable o un polvo efervescente), pastillas, sachéts, píldoras, comprimidos, pelets, gránulos, microgránulos, microgránulos encapsulados, formulaciones de polvo en aerosol o cualquier otra forma de dosificación sólida adaptada razonablemente para una administración.

[0073] Las tabletas se pueden preparar de acuerdo con cualquiera de las muchas técnicas relevantes de farmacia bien conocidas. En una realización, las tabletas u otras formas de dosificación sólidas se pueden preparar mediante procesos que emplean uno o una combinación de métodos incluyendo, en un sentido no limitativo, (1) mezclado en seco, (2) compresión directa, (3) molienda, (4) granulación seca o no acuosa, (5) granulación húmeda o (6) fusión.

[0074] Los pasos individuales en el proceso de granulación húmeda de

la preparación de tabletas típicamente incluyen molienda y tamizado de los ingredientes, mezclado en polvo seco, formación de una masa húmeda, granulación y trituración final. La granulación seca comprende comprimir una mezcla de polvos en una tableta gruesa o "cápsula o lingote blando" sobre una prensa para tabletas rotatoria de servicio pesado. Los lingotes blandos se rompen luego en partículas de gránulos mediante una operación de molienda, habitualmente por pasaje a través de un granulador oscilatorio. Los pasos individuales incluyen mezclado de los polvos, compresión (compresión doble) y trituración (reducción o granulación del lingote blando). Típicamente, no hay aglutinantes húmedos o humedad en ninguno de los pasos.

[0075] En otra realización, las formas de dosificación sólidas se pueden preparar mezclando un antiestrógeno con uno o más excipientes farmacéuticos para formar una mezcla de preformulación sustancialmente homogénea. Luego se puede subdividir la mezcla de preformulación y opcionalmente se puede procesar adicionalmente (por ejemplo, comprimir, encapsular, empaquetar, dispersar, *etc.*) en cualquier forma de dosificación deseada.

[0076] Las tabletas comprimidas se pueden preparar compactando un polvo o una composición granulada de la invención. El término "tableta comprimida" se refiere en general a una tableta común, no recubierta, adecuada para su ingestión por vía oral, preparada por compresión simple o por precompactación con vibración seguido por una compresión final. Las tabletas de la presente invención se pueden recubrir o componer de otra manera para proveer una forma de dosificación que ofrezca la ventaja de características manejo o almacenamiento mejoradas. En una realización, cualquiera de dichos recubrimientos se seleccionará de modo que no demore

sustancialmente el inicio del efecto terapéutico de una composición de la invención con la administración a un sujeto. El término "tableta en suspensión" según se usa en la presente se refiere a una tableta comprimida que rápidamente se desintegra luego introducirla en agua.

[0077]Las formas de dosificación líquidas adecuadas de una composición de la invención incluyen soluciones, suspensiones acuosa u oleosas, elixires, jarabes, emulsiones, formulaciones líquidas en aerosol, geles, cremas, ungüentos, *etc.* Dichas composiciones también se pueden formular como un producto seco para su reconstitución con agua u otros vehículos adecuados antes de su uso.

[0078]En una realización, las composiciones líquidas o semisólidas, luego de su almacenamiento en un recipiente cerrado mantenido ya sea a temperatura ambiente, a temperature de refrigerador (por ejemplo, a 5 -10 °C aproximadamente) o a temperatura de congelamiento por un período de aproximadamente 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 ó 12 meses, exhiben al menos un 90% aproximadamente, al menos un 92,5% aproximadamente, al menos un 95% aproximadamente o al menos un 97,5% aproximadamente del compuesto antiestrógeno original presente en las mismas.

[0079]Las composiciones de la invención pueden, si se deseara, incluir uno o más excipientes aceptables para uso farmacéutico. El término "excipiente" en la presente significa cualquier sustancia, que no sea ella misma un agente terapéutico, usada como un transportador o vehículo para la administración de un agente terapéutico a un sujeto o que se agrega a una composición farmacéutica para mejorar sus propiedades de manejo o almacenamiento o para permitir o facilitar la formación de una dosis unitaria de

la composición. Los excipientes incluyen, a modo ilustrativo y no en un sentido limitativo, diluyentes, desintegrantes, agentes de unión, adhesivos, agentes humectantes, lubricantes, deslizantes, agentes modificadores de la superficie o agentes tensioactivos, fragancias, agentes de suspensión, agentes emulsionantes, vehículos no acuosos, conservantes, antioxidantes, adhesivos, agentes para ajustar el pH y la osmolaridad (por ejemplo, agentes amortiguadores), conservantes, agentes espesantes, agentes edulcorantes, agentes saborizantes, agentes enmascaradores del sabor, colorantes o tinturas, mejoradores de la penetración y sustancias que se agregan para mejorar el aspecto de la composición.

[0080] Los excipientes empleados opcionalmente en las composiciones de la invención pueden ser sólidos, semisólidos, líquidos o combinaciones de los mismos. Las composiciones de la invención que contienen excipientes se pueden preparar mediante cualquier técnica conocida de farmacia que comprenda mezclar un excipiente con una droga o agente terapéutico.

[0081] Las composiciones de la invención opcionalmente comprenden uno o más diluyentes aceptables para uso farmacéutico como excipientes. Los diluyentes adecuados incluyen a modo ilustrativo, ya sea individualmente o en combinación, lactosa, incluyendo lactosa anhidra y lactosa monohidrato; almidones, incluyendo almidón directamente compresible y almidones hidrolizados (por ejemplo, Celutab™ y Emdex™); manitol; sorbitol; xilitol; dextrosa (por ejemplo, Cerelose™ 2000) y dextrosa monohidrato; fosfato de calcio dibásico dihidrato; diluyentes basados en sacarosa; azúcar de repostería; sulfato de calcio monobásico monohidrato; sulfato de calcio dihidrato; lactato de calcio granulado trihidrato; dextratos; inositol; sólidos de

cereales hidrolizados; amilosa; celulosas incluyendo celulosa microcristalina, fuentes de celulosa α y amorfa de grado alimentario (por ejemplo, Rexcel™) y celulosa en polvo; carbonato de calcio; glicina; bentonita; polivinilpirrolidona; y semejantes. Dichos diluyentes constituyen, si están presentes, en total entre aproximadamente 5% y aproximadamente 99%, entre aproximadamente 10% y aproximadamente 85% o entre aproximadamente 20% y aproximadamente 80%, del peso total de la composición. Cualquier diluyente o diluyentes seleccionados exhiben preferentemente las propiedades de flujo adecuadas y, cuando se desearan tabletas, compresibilidad.

[0082]El uso de celulosa microcristalina extragranulada (es decir, celulosa microcristalina que se agrega a una composición granulada en húmedo después de un paso de secado) permite mejorar la dureza (para tabletas) y/o el tiempo de desintegración.

[0083]Las composiciones de la invención comprenden opcionalmente uno o más desintegrantes aceptables para uso farmacéutico como excipientes, en particular para tabletas, cápsulas u otras formulaciones sólidas. Los desintegrantes adecuados incluyen, ya sea individualmente o en combinación, almidones, incluyendo almidón glicolado de sodio (por ejemplo, Explotab™ de PenWest) y almidones de maíz pregelatinizados (por ejemplo, National™ 1551, National™ 1550 y Colocorn™ 1500), arcillas (por ejemplo, Veegum™ HV), celulosas tales como celulosa purificada, celulosa microcristalina, metilcelulosa, carboximetilcelulosa y carboximetilcelulosa sódica, croscarmellosa de sodio (por ejemplo, Ac-Di-Sol™ de FMC), alginatos, crospovidona y gomas tales como agar, guar, xantán, de algarroba, karaya, pectina y tragacanto.

[0084]Los desintegrantes se pueden agregar en cualquier paso

45

adecuado durante la preparación de la composición, en particular antes de un paso de granulación o durante un paso de lubricación antes de la compresión. Dichos desintegrantes constituyen, si están presentes, en total entre aproximadamente 0,2% y aproximadamente 30%, entre aproximadamente 0,2% y aproximadamente 10% o entre aproximadamente 0,2% y aproximadamente 5%, del peso total de la composición.

[0085] Las composiciones de la invención comprenden opcionalmente uno o más agentes de unión o adhesivos aceptables para uso farmacéutico como excipientes, en particular para formulaciones de tabletas. Dichos agentes de unión y adhesivos preferentemente imparten suficiente cohesión al polvo que está siendo conformado como tabletas como para permitir operaciones de procesamiento normales tales como determinación del tamaño, lubricación, compresión y envasado, pero aún permitir que la tableta se desintegre y que la composición sea absorbida con la ingestión. Los agentes de unión y adhesivos adecuados incluyen, ya sea de manera individual o en combinación, acacia; tragacanto; sacarosa; gelatina; glucosa; almidones tal como, pero en un sentido no limitativo, almidones pregelatinizados (por ejemplo, National™ 1511 y National™ 1500); celulosas tales como, pero en un sentido no limitativo, metilcelulosa y carmellosa de sodio (por ejemplo, Tylose™); ácido algínico y sales de ácido algínico; silicato de magnesio y aluminio; PEG; goma guar; ácidos de polisacáridos; bentonitas; povidona, por ejemplo povidona K-15, K-30 y K-29/32; polimetacrilatos; HPMC; hidroxipropilcelulosa (por ejemplo, Klucel™); y etilcelulosa (por ejemplo, Ethocel™). Dichos agentes de unión y/o adhesivos constituyen, si están presentes, en total entre aproximadamente 0,5% y aproximadamente 25%,

entre aproximadamente 0,75% y aproximadamente 15% o entre aproximadamente 1% y aproximadamente 10%, del peso total de la composición.

[0086]Las composiciones de la invención opcionalmente comprenden uno o más agentes humectantes aceptables para uso farmacéutico como excipientes. Los ejemplos no limitativos de agentes tensioactivos que se pueden usar como agentes humectantes en las composiciones de la invención incluyen compuestos de amonio cuaternario, por ejemplo cloruro de benzalconio, cloruro de benzetonio y cloruro de cetilpiridinio, dioctilsulfosuccinato de sodio, polioxietilenalquilfenil éteres, por ejemplo nonoxinol 9, nonoxinol 10 y octoxinol 9, poloxámeros (copolímeros de bloques de polioxietileno y polioxipropileno), glicéridos de ácidos grasos polioxietilenizados y aceites, por ejemplo polioxietileno (8) mono- y diglicéridos caprílicos/cápricos (por ejemplo, Labrasol™ de Gattefossé), aceite de castor de polioxietileno (35) y aceite de castor de polioxietileno (40) hidrogenado; alquiléteres de polioxietileno, por ejemplo cetoestearil éter de polioxietileno (20), ésteres de ácidos grasos de polioxietileno, por ejemplo estearato de polioxietileno (40), sorbitán ésteres de polioxietileno, por ejemplo polisorbato 20 y polisorbato 80 (por ejemplo, Tween™ 80 de ICI), ésteres de ácidos grasos de propilenglicol, por ejemplo laurato de propilenglicol (por ejemplo, Lauroglycol™ de Gattefossé), laurilsulfato de sodio, ácidos grasos y sales de los mismos, por ejemplo ácido oleico, oleato de sodio y oleato de trietanolamina, glicerilésteres de ácidos grasos, por ejemplo monoestearato de glicerilo, sorbitán ésteres, por ejemplo sorbitán monolaurato, sorbitán monooleato, sorbitán monopalmitato y sorbitán monoestearato, tiloxapol y mezclas de los mismos. Dichos agentes

47

humectantes constituyen, si están presentes, en total entre aproximadamente 0,25% y aproximadamente 15%, entre aproximadamente 0,4% y aproximadamente 10% o entre aproximadamente 0,5% y aproximadamente 5%, del peso total de la composición.

[0087]Las composiciones de la invención comprenden opcionalmente uno o más lubricantes aceptables para uso farmacéutico (incluyendo antiadherentes y/o deslizantes) como excipientes. Los lubricantes adecuados incluyen, ya sea de manera individual o en combinación, behapato de glicerilo (por ejemplo, Compritol™ 888); ácido esteárico y sales del mismo, incluyendo estearatos de magnesio (estearato de magnesio), calcio y sodio; aceites vegetales hidrogenados (por ejemplo, Sterotex™); sílica coloidal; talco; ceras; ácido bórico; benzoato de sodio; acetato de sodio; fumarato de sodio; cloruro de sodio; DL-leucina; PEG (por ejemplo, Carbowax™ 4000 y Carbowax™ 6000); oleato de sodio; laurilsulfato de sodio; y laurilsulfato de magnesio. Dichos lubricantes constituyen, si están presentes, en total entre aproximadamente 0,1% y aproximadamente 10%, entre aproximadamente 0,2% y aproximadamente 8% o entre aproximadamente 0,25% y aproximadamente 5%, del peso total de la composición.

[0088]Los antiadherentes adecuados incluyen talco, almidón de maíz, DL-leucina, laurilsulfato de sodio y estearatos de metales. El talco es un antiadherente o deslizante usado, por ejemplo, para reducir la adherencia de la formulación a las superficies de los equipos y también para reducir la estática en la mezcla. Dichos uno o más antiadherentes constituyen, si están presentes, entre aproximadamente 0,1% y aproximadamente 10%, entre aproximadamente 0,25% y aproximadamente 5% o entre aproximadamente

0,5% y aproximadamente 2%, del peso de la composición.

[0089]Los deslizantes se pueden usar para promover el flujo de polvo de una formulación sólida. Los deslizantes adecuados incluyen dióxido siliconado coloidal, almidón, talco, fosfato de calcio tribásico, polvo de celulosa y trisilicato de magnesio. Se prefiere particularmente dióxido de silicona coloidal.

[0090]Las composiciones de la presente invención pueden comprender uno o más agentes anti-espumantes. La simeticona es un agente anti-espumante ilustrativo. Los agentes anti-espumantes constituyen, si están presentes, entre aproximadamente 0,001% y aproximadamente 5%, entre aproximadamente 0,001% y aproximadamente 2% o entre aproximadamente 0,001% y aproximadamente 1%, del peso total de la composición.

[0091]Los antioxidantes ilustrativos para su uso en la presente invención incluyen, pero en un sentido no limitativo, hidroxitolueno butilado, hidroxianisol butilado, metabisulfito de potasio y semejantes. Si se deseara, típicamente hay uno o más antioxidantes en una composición de la invención en una cantidad entre aproximadamente 0,01% y aproximadamente 2,5%, por ejemplo aproximadamente 0,01%, aproximadamente 0,05%, aproximadamente 0,1%, aproximadamente 0,5%, aproximadamente 1%, aproximadamente 1,5%, aproximadamente 1,75%, aproximadamente 2%, aproximadamente 2,25% o aproximadamente 2,5% en peso.

[0092]En diversas realizaciones, las composiciones de la invención pueden comprender un conservante. Los conservantes adecuados incluyen, pero en un sentido no limitativo, cloruro de benzalconio, metil, etil, propil o butilparabeno, alcohol bencílico, alcohol feniletílico, benzetonio, p-

hidroxibenzoato de metilo o propilo y ácido sórbico o combinaciones de los mismos. Típicamente, el conservante opcional está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 0,5% o entre aproximadamente 0,01% y aproximadamente 2,5%, en peso.

[0093]En una realización, las composiciones de la invención comprenden opcionalmente un agente amortiguador. Los agentes amortiguadores incluyen agentes que reducen los cambios de pH. Las clases ilustrativas de agentes amortiguadores para su uso en diversas realizaciones de la presente invención comprenden una sal de un Grupo de metal IA incluyendo, por ejemplo, una sal de bicarbonato de un Grupo de metal IA, una sal de carbonato de un Grupo de metal IA, un agente amortiguador de un metal alcalino o de un metal alcalino-térreo, un agente amortiguador de aluminio, un agente amortiguador de calcio, un agente amortiguador de sodio o un agente amortiguador de magnesio. Los agentes amortiguadores adecuados incluyen carbonatos, fosfatos, bicarbonatos, citratos, boratos, acetatos, ftalatos, tartratos, succinatos de cualquiera de los anteriores, por ejemplo fosfato, citrato, borato, acetato, bicarbonato y carbonato de sodio o potasio.

[0094]Los ejemplos no limitativos de agentes amortiguadores adecuados incluyen aluminio, hidróxido de magnesio, glicinato de aluminio, acetato de calcio, bicarbonato de calcio, borato de calcio, carbonato de calcio, citrato de calcio, gluconato de calcio, glicerofosfato de calcio, hidróxido de calcio, lactato de calcio, ftalato de calcio, fosfato de calcio, succinato de calcio, tartrato de calcio, fosfato de sodio dibásico, fosfato ácido de dipotasio, fosfato de dipotasio, fosfato ácido disódico, succinato disódico, gel de hidróxido de aluminio seco, acetato de magnesio, aluminato de magnesio, borato de

magnesio, bicarbonato de magnesio, carbonato de magnesio, citrato de magnesio, gluconato de magnesio, hidróxido de magnesio, lactato de magnesio, metasilicato aluminato de magnesio, óxido de magnesio, ftalato de magnesio, fosfato de magnesio, silicato de magnesio, succinato de magnesio, tartrato de magnesio, acetato de magnesio, carbonato de magnesio, bicarbonato de magnesio, borato de potasio, citrato de potasio, metafosfato de potasio, ftalato de potasio, fosfato de potasio, polifosfato de potasio, pirofosfato de potasio, succinato de potasio, tartrato de potasio, acetato de sodio, bicarbonato de sodio, borato de sodio, carbonato de sodio, citrato de sodio, gluconato de sodio, fosfato ácido de sodio, hidróxido de sodio, lactato de sodio, ftalato de sodio, fosfato de sodio, polifosfato de sodio, pirofosfato de sodio, sesquicarbonato de sodio, succinato de sodio, tartrato de sodio, tripolifosfato de sodio, hidrotalcita sintética, pirofosfato tetrapotásico, pirofosfato tetrasódico, fosfato de tripotasio, fosfato de trisodio y trometamol. (Basado en parte en el listado provisto en *The Merck Index*, Merck & Co. Rahway, N.J. (2001)). Aún más, se pueden usar combinaciones o mezclas de cualesquiera dos o más de los agentes amortiguadores mencionados previamente en las composiciones farmacéuticas descritas en la presente. Hay uno o más agentes amortiguadores, si se deseara, en las composiciones de la invención en una cantidad entre aproximadamente 0,01% y aproximadamente 5% o entre aproximadamente 0,01% y aproximadamente 3%, en peso.

[0095]En diversas realizaciones, las composiciones de la invención pueden incluir uno o más agentes que incrementan la viscosidad. Los agentes ilustrativos que incrementan la viscosidad incluyen, pero en un sentido no limitativo, metilcelulosa, carboximetilcelulosa de sodio, etilcelulosa,

57

carragenina, carbopol y/o combinaciones de las mismas. Típicamente, hay uno o más agentes para incrementar la viscosidad, si se deseara, presentes en las composiciones de la invención en una cantidad que comprende entre aproximadamente 0,1% y aproximadamente 10% o entre aproximadamente 0,1% y aproximadamente 5%, en peso.

[0096]En diversas realizaciones, las composiciones de la invención comprenden un "agente organoléptico" para mejorar las propiedades organolépticas de la composición. El término "agente organoléptico" en la presente se refiere a cualquier excipiente que pueda mejorar el sabor u olor o ayudar a enmascarar un sabor u olor desagradable de una composición de la invención. Dichos agentes incluyen edulcorantes, agentes saborizantes y/o agentes enmascaradores del sabor. Los edulcorantes y/o agentes saborizantes adecuadas incluyen cualquier agente que pueda endulzar o saborizar una composición farmacéutica. Los agentes organolépticos opcionales típicamente están presentes en una composición de la invención en una cantidad entre aproximadamente 0,1 mg/ml y aproximadamente 10 mg/ml, entre aproximadamente 0,5 mg/ml y 5 mg/ml o de aproximadamente 1 mg/ml.

[0097]Los edulcorantes o agentes saborizantes ilustrativos incluyen, en un sentido no limitativo, jarabe de acacia, anetol, aceite de anís, elixir aromático, benzaldehído, elixir de benzaldehído, ciclodextrinas, alcaravea, aceite de alcaravea, aceite de cardamomo, semilla de cardamomo, licor de cardamomo, tintura de cardamomo, jugo de cereza, jarabe de cereza, canela, aceite de canela, agua de canela, ácido cítrico, jarabe de ácido cítrico, aceite de trébol, cacao, jarabe de cacao, aceite de coriandro, dextrosa, eriodictiona, extracto líquido de eriodictiona, jarabe de eriodictiona, aromáticos, etilacetato,

52

vainillina de etilo, aceite hinojo, gengibre, extracto líquido de gengibre, oleorresina de gengibre, dextrosa, glucosa, azúcar, maltodextrina, glicerina, glicirriza, elixir de glicirriza, extracto de glicirriza, extracto puro de glicirriza, extracto líquido de glicirriza, jarabe de glicirriza, miel, elixir iso-alcohólico, aceite de lavanda, aceite de limón, tintura de limón, manitol, salicilato de metilo, aceite de nuez moscada, naranja amarga, elixir, naranja amarga, aceite, aceite de flores de naranja, agua de flores de naranja, aceite de naranja, cáscara de naranja, amarga, cáscara de naranja dulce, tintura, licor de naranja, jarabe de naranja, menta peperina, aceite de menta peperina, licor de menta peperina, agua de menta peperina, alcohol feniletílico, jugo de frambuesa, jarabe de frambuesa, aceite de romero, aceite de rosas, agua de rosas, más fuerte, sacarina, sacarina de calcio, sacarina de sodio, jarabe de sarsaparilla, sarsaparilla, solución de sorbitol, hierba buena, aceite de hierba buena, sacarosa, sucralosa, jarabe, aceite de tomillo, bálsamo de tolu, jarabe de bálsamo de tolu, vanilla, tintura de vainilla, vanillina, jarabe de cereza salvaje o combinaciones de los mismos.

[0098] Los agentes enmascaradores del sabor ilustrativos incluyen, pero en un sentido no limitativo, ciclodextrinas, emulsiones de ciclodextrinas, partículas de ciclodextrinas, complejos dde ciclodextrinas o combinaciones de los mismos.

[0099] Los agentes de suspensión ilustrativos incluyen, pero en un sentido no limitativo, jarabe de sorbitol, metilcelulosa, glucosa/jarabe de azúcar, gelatina, hidroxietilcelulosa, carboxímetilcelulosa, gel de estearato de aluminio y grasas comestibles hidrogenadas.

[00100] Los agentes emulsionantes ilustrativos incluyen, pero en

53

un sentido no limitativo, lecitina, sorbitán monooleato y acacia. Los vehículos no acuosos incluyen, pero en un sentido no limitativo, aceites comestibles, aceite de almendra, aceite de coco fraccionado, ésteres oleosos, propilenglicol y alcohol etílico.

[00101] Los excipientes anteriores pueden cumplir múltiples roles como es sabido en la técnica. Por ejemplo, el almidón puede servir como relleno así como también como un desintegrante. La clasificación de excipientes anterior no debe considerarse limitativo en modo alguno.

[00102] Las composiciones de la presente invención se pueden administrar de cualquier manera incluyendo, pero en un sentido no limitativo, la administración por vía oral, parenteral, sublingual, transdérmica, rectal, transmucosa, tópica, vía inhalación, vía bucal o combinaciones de los mismos. La administración parenteral incluye, pero en un sentido no limitativo, intravenosa, intraarterial, intraperitoneal, subcutánea, intramuscular, intratecal, intraarticular, intracisternal e intraventricular.

[00103] Una cantidad eficaz para uso terapéutico de la composición requerida para su uso en terapias varía con el tiempo que se desea la actividad y con la edad y la condición del paciente a tratar, entre otros factores, y en última instancia está determinada por el médico a cargo. Sin embargo, en general las dosis empleadas para tratamiento en humanos se encuentran típicamente en el rango entre aproximadamente 0,001 mg/kg y aproximadamente 500 mg/kg por día, por ejemplo entre aproximadamente 1 μg/kg y aproximadamente 1 mg/kg por día o entre aproximadamente 1 μg/kg y aproximadamente 100 μg/kg por día. Para la mayoría de los grandes mamíferos, la dosificación diaria total comprende entre aproximadamente 1 y

54

100 mg, preferentemente entre aproximadamente 2 y 80 mg. El régimen de dosificación se puede ajustar para proporcionar una respuesta terapéutica óptima. La dosis deseada puede administrarse convenientemente en una sola dosis, o como múltiples dosis administradas a intervalos apropiados, por ejemplo como dos, tres, cuatro o más subdosis por día.

[00104] A modo ilustrativo, una composición de la invención puede administrarse a un sujeto para suministrarle a dicho sujeto un antiestrógeno en una cantidad entre aproximadamente 1 μg/kg y aproximadamente 1 mg/kg de peso corporal, por ejemplo aproximadamente 1 μg/kg, aproximadamente 25 μg/kg, aproximadamente 50 μg/kg, aproximadamente 75 μg/kg, aproximadamente 100 μg/kg, aproximadamente 125 μg/kg, aproximadamente 150 μg/kg, aproximadamente 175 μg/kg, aproximadamente 200 μg/kg, aproximadamente 225 μg/kg, aproximadamente 250 μg/kg, aproximadamente 275 μg/kg, aproximadamente 300 μg/kg, aproximadamente 325 μg/kg, aproximadamente 350 μg/kg, aproximadamente 375 μg/kg, aproximadamente 400 μg/kg, aproximadamente 425 μg/kg, aproximadamente 450 μg/kg, aproximadamente 475 μg/kg, aproximadamente 500 μg/kg, aproximadamente 525 μg/kg, aproximadamente 550 μg/kg, aproximadamente 575 μg/kg, aproximadamente 600 μg/kg, aproximadamente 625 μg/kg, aproximadamente 650 μg/kg, aproximadamente 675 μg/kg, aproximadamente 700 μg/kg, aproximadamente 725 μg/kg, aproximadamente 750 μg/kg, aproximadamente 775 μg/kg, aproximadamente 800 μg/kg, aproximadamente 825 μg/kg, aproximadamente 850 μg/kg, aproximadamente 875 μg/kg, aproximadamente 900 μg/kg, aproximadamente 925 μg/kg, aproximadamente 950 μg/kg, aproximadamente 975 μg/kg o aproximadamente 1 mg/kg de peso corporal..

55

[00105] En una realización preferida, las composiciones de acuerdo con la presente invención comprenden *trans*-clomifeno a una dosificación entre un mg y aproximadamente 200 mg (aunque la determinación de las dosificaciones óptimas es propia del nivel del especialista en la técnica). La composición puede comprender *trans*-clomifeno a una dosificación de aproximadamente 1 mg, 2 mg, 3, mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg o valores comprendidos entre ellos. La composición también puede comprender *trans*-clomifeno y *cis*-clomifeno a una relación de aproximadamente 71/29, 72/28, 73/27, 74/26, 75/25, 76/24, 77/23, 78/22, 79/21, 80/20, 81/19, 82/18, 83/17, 84/16, 85/15, 86/14, 87/13, 88/12, 89/11, 90/10, 91/9, 92/8, 93/7, 94/6, 95/5, 96/4, 97/3, 98/2, 99/1, 99,5/0,5 o valores comprendidos entre ellos. Los análogos de los isómeros de clomifeno *trans* y *cis,* tal como los que se describen en Ernst, *et al. supra*, también son de utilidad en la práctica de la presente invención.

[00106] Las composiciones de la presente invención también se pueden administrar a largo plazo. En este sentido, las composiciones se pueden administrar por un período de al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 o más días. Las composiciones también se pueden administrar por un período de administración de al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más meses. Las composiciones también se pueden administrar por un período de administración de al menos 1, 2, 3, 4, 5, 6, 7 8, 9, 10 o más años. Durante el período de administración, la composición se puede administrar diariamente o

56

periódicamente, tal como día por medio y semejantes.

[00107] Las composiciones de la presente invención también se pueden administrar de forma intermitente. Por ejemplo, las composiciones se pueden administrar por un período de administración de 1, 2, 3, 4, 5 o más semanas, seguido por un período de discontinuación, seguido por un período de administración de 1, 2, 3, 4, 5 o más semanas y así sucesivamente.

[00108] Todas las referencias a las cuales se hace referencia en la presente se incorporan por completo a modo de referencia.

[00109] Los siguientes Ejemplos se ofrecen a efectos ilustrativos de la invención y no pretenden limitar el alcance de la invención tal como se la define en las reivindicaciones adjuntas.

EJEMPLO 1

Efectos de clomifeno y sus isómeros sobre testosterona en suero y colesterol en mandriles macho

[00110] Se administraron 1,5 mg/kg de Clomid (citrato de clomifeno), Enclomid (*trans*-clomifeno) o Zuclomid (*cis*-clomifeno) a mandriles macho adultos, durante 12 días consecutivos. Las muestras analizadas eran sueros tomados el día del primer tratamiento antes de la administración del artículo 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 en suero

[00111] Se observaron incrementos significativos en la testosterona total en suero en el grupo que recibió Enclomid. Véase la Tabla 1. No se observaron diferencias entre grupos en el período basal o el día 0. Tampoco

57

hubo diferencias entre los tres grupos 7 días después del tratamiento (el período de lavado). Sin embargo, Enclomid produjo niveles más altos de testosterona en comparación con Clomid y Zuclomid el día 6 (p = 0,03 y p = 0,00002 respectivamente) y en comparación con Zuclomid el día 12 (p = 0,047). Resultó claro que Zuclomid no elevaba la testosterona total en suero en grado alguno. En comparación con los animales que recibieron Enclomid, los animales que recibieron Clomid exhibieron niveles de testosterona total más variables el día 6 y luego fueron evaluados por sus coeficientes de variación. Al observar los efectos en el tiempo (FIG. 3), los autores determinaron que solamente Enclomid elevaba de manera significativa y estadística la testosterona total en suero los días 6 y 12 en comparación con el valor basal o los valores del día 0. Más aún, el cese del tratamiento con Enclomid dio como resultado una caída significativa en el nivel de testosterona total en suero entre el día 12 y el día 18 (lavado). Esto indica que Enclomid es depurado rápidamente de la circulación lo que era consistente con la depuración metabólica observada para Enclomid en humanos. Enclomid era claramente mejor y más consistente que el propio Clomid y Zuclomid no era eficaz.

Tabla 1 - Niveles de testosterona en suero (ng/dl)

Grupo	ID	Nivel basal 12/3/01	día 0 12/7/01	6 días 12/13/01	12 días 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
	media	**111,5**	**161,4**	**559,3**	**588,7**	**203,6**

58

	DE	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
	media	**134,0**	**105,0**	**1144,4**	**1088,5**	**325,8**
	DE	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
	media	**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**

[00112] No se observaron cambios en los valores de LH o FSH en suero. La relación de testosterona total a LH en suero seguía el mismo patrón que la testosterona total en suero, lo cual sugiere una falta de dependencia (no se muestran los datos). Tampoco se observaron cambios en el peso corporal durante los 12 días de estudio. Había una disminución en la prolactina (PRL) en suero durante el estudio en el grupo que recibía Enclomid, lo que sugiere un efecto del antiestrógeno que ha sido descrito en parte (Ben-Jonathan y Hnasko, 2001) y que era esperado sobre la base del hecho que a medida que los hombres envejecen, disminuye la testosterona y aumenta la prolactina (Feldman *et al.*, 2002).

2. Efectos sobre los niveles de colesterol

59

[00113] El tratamiento con Enclomid tendía a disminuir el valor de colesterol en suero y Zuclomid tendía a incrementar el mismo parámetro. El análisis preliminar indicó que los cambios en los niveles de colesterol no eran estadísticamente significativos y que los cambios se encontraban dentro del rango normal. Se abordaron análisis adicionales debido a la tendencia observada para los dos isómeros para demostrar efectos opuestos sobre los niveles de colesterol sobre un período de tiempo corto.

[00114] Un análisis detallado indicó que Enclomid dio como resultado una disminución del 8% en los niveles de colesterol en suero. Por el contrario, el tratamiento con Zuclomid dio como resultado un incremento del 22% en los niveles de colesterol en suero. El tratamiento con Clomid dio como resultado un incremento ligero en los niveles de colesterol en suero. El efecto opuesto de Enclomid y Zuclomid sobre los niveles de colesterol en suero no resulta inesperado dado que los isómeros tienen, de manera alternativa, actividad agonista o antagonista de estrógenos. Estos resultados indican que se puede usar Enclomid para el tratamiento de pacientes con niveles altos de colesterol. Estos resultados también indican que Enclomid puede ser más benigno que Zuclomid con respecto al colesterol sérico si se usa crónicamente para elevar los niveles de testosterona.

3. Efectos sobre los parámetros de química clínica

[00115] Los valores de las medias para cada parámetro no diferían entre los tres grupos para ninguno de los parámetros de prueba al comienzo del estudio según se determinó con ANOVA o con la prueba de Kruskal-Wallis. Todos los grupos exhibieron valores normales para cada parámetro excepto para (1) sodio sérico; un parámetro calculado relacionado, la brecha aniónica o

equilibrio de electrolitos [*anionic gap*], que era bajo en los nueve mandriles durante todo el estudio; (2) glucosa sérica; y (3) BUN que era alto el día 0 para el grupo que sería tratado con Enclomid. El día 12 de tratamiento y 7 días después del tratamiento (lavado), no había diferencias entre grupos para ninguno de los parámetros excepto para la brecha aniónica que mostró que los grupos con Clomid y Zuclomid presentaban valores más bajos que el grupo con Enclomid. Los valores de sodio sérico y de la brecha aniónica parecen ser anomalías asociadas con este grupo de mandriles.

[00116] Había efectos mayores sobre la población de glóbulos rojos con Enclomid y Zuclomid y sobre el hematocrito con Zuclomid. Todos los compuestos disminuyen la concentración de hemoglobina corpuscular media (MCHC) ya sea el día 0 o en el punto final. Cuando no hay cambio en la hemoglobina corpuscular media (MCH) y hay un incremento en el volumen corpuscular medio (MCV), la disminución de la MCHC es predecible. Aunque se podría esperar que la testosterona elevara el hematocrito, solamente el tratamiento con Zuclomid, que no incrementa la testosterona total en suero, demostró una diferencia estadística. Claramente, en un estudio clínico que emplea Zuclomid los hombres deberían ser monitoreados por las características de su población de glóbulos rojos. Se podría prever que Enclomid tuviera menos efecto.

[00117] Parece haber un claro efecto del tratamiento de 12 días con Enclomid sobre las plaquetas aunque los valores hallados permanecieron dentro del rango normal. Un tema que se debe considerar en este caso es el dimorfismo sexual en los recuentos de plaquetas entre mandriles macho y hembra (279 para machos vs. 348 para hembras). Es probable que esto se

deba a hormonas. Dado que el grupo con Enclomid demostró un incremento de testosterona, la disminución del recuento de plaquetas sería secundario al cambio en la testosterona en este grupo. Más aún, el tratamiento con Enclomid empujó el recuento de plaquetas hasta su nivel normal en machos desde un nivel el día 0 que estaba en el extremo alto del rango normal para este grupo. No sería necesariamente previsible que el tratamiento con Enclomid produjera un efecto nocivo sobre las plaquetas.

[00118] Todos los compuestos citrato de clomifeno, Enclomid y Zuclomid tenían efectos sobre la población de glóbulos blancos (WBC), siendo lo más notable el efecto de Enclomid sobre la elevación de los recuentos de linfocitos y eosinófilos. Los efectos no son tan directos como parecieran ser. Parece que existe un fuerte efecto de Enclomid sobre la disminución del porcentaje de granulocitos en la sangre. Los efectos son muy fuertes después del período de 7 días de lavado cuando los valores han disminuido por debajo del rango normal. (Este transcurso en el tiempo reflejaría el tiempo relativamente prolongado requerido para afectar un cambio en la población de WBC.) Hay algo de dimorfismo sexual en mandriles con respecto a las poblaciones de glóbulos blancos, de modo que es más probable que los efectos se deban al compuesto por sí mismo que a cambios en la testosterona. Sin embargo, cuando se observa el recuento calculado de granulocitos usando el recuento de WBC, no se hallan diferencias en el recuento de granulocitos debidas a ninguno de los compuestos. Al mismo tiempo, lo más interesante es lo que sucede con los linfocitos. Tanto el recuento como el porcentaje de linfocitos en la población incrementan con el tratamiento con Enclomid. En tanto los valores de la media del porcentaje de linfocitos permanecen en el

rango normal, dada la tendencia de un incremento en el recuento de WBC, el efecto neto es un incremento en el recuento de linfocitos con Enclomid. Este resultado es análogo para eosinófilos. Existe una clara consecuencia en el caso del tratamiento de hombres con valores bajos de linfocitos, tal como hombres que son VIH positivos. Dado que es poco probable que Enclomid disminuya los linfocitos basado en este resultado, se podría aprovechar para su uso en la población de hombres con SIDA. Estos individuos a menudo son tratados con agentes destinados a elevar la testosterona debido a los efectos desgastantes de la enfermedad. Una menor toxicidad en hígado y riñón y los efectos favorables sobre colesterol y lípidos también constituyen atributos muy favorables para cualquier medicación que se pretenda utilizar en hombres VIH positivos quienes ya están comprometidos debido a su enfermedad.

[00119] El incremento en la glucosa sérica con Clomid o Zuclomid se encontraba dentro del rango normal. En el caso de Enclomid donde los valores promedio de glucosa sérica eran altos el día 0, no hubo incrementos con el tratamiento. No hubo evidencia que Enclomid tuviera un efecto nocivo sobre la glucosa en sangre.

[00120] No hay efectos claramente adversos sobre la función hepática a juzgar por las enzimas AST y ALT. La tendencia en estos valores era una disminución con el tratamiento. Un incremento en el nivel de enzimas en suero sería indicativo de daño hepático. Los valores de ALT/SGPT estaban fuera de rango al final del estudio para el grupo Clomid aunque las diferencias sobre el período de tratamiento no eran estadísticamente significativas. Los cambios con Enclomid y Zuclomid se encontraban dentro del rango normal. El valor de AST está deprimido durante el embarazo; por consiguiente se podría

racionalizar la acción de un agonista de estrógenos, tal como Zuclomid, en la disminución del nivel marginal de AST. En el hígado también hay fosfatasa alcalina (ALP) y está elevado en diversos estados de enfermedad. La disminución de ALP actúa contra en el daño hepático. No hubo cambios en la albúmina sérica, que también es un producto del hígado. Una fuerte supresión de la albúmina sérica sobre un período de tiempo prolongado podría contribuir en los niveles de hormonas esteroides libres en suero en humanos aunque un rol más importante lo cumple la globulina de unión a hormonas sexuales. Como nivel basal, ninguno de los compuestos se podría ligar con el daño hepático sobre la base de los parámetros evaluados.

[00121] La actividad osteoblástica y las enfermedades de los huesos están acompañadas por valores altos de ALP en suero. El valor de ALP no era elevado después del tratamiento con Zuclomid y su valor había disminuido luego del tratamiento con Enclomid. Las tendencias indicarían un resultado más benigno para el uso de Enclomid en comparación con Zuclomid.

[00122] Aunque los valores de BUN y BUN/creatinina estaban alterados durante el estudio en los grupos con Clomid y Enclomid, la falta de un cambio definitivo en la creatinina no produciría una disfunción renal. Una pérdida de la capacidad de filtración glomerular daría como resultado un incremento en el valor de BUN. Un disminución en BUN tiene lugar en humanos debido a una pobre nutrición (poco probable en un entorno controlado) o a una gran ingesta de líquidos (presumiblemente acompañado de edema). Además, a pesar de un incremento en la testosterona total en suero entre el día 0 y el día 12 con Enclomid, no había diferencias entre los valores de creatinina en suero, lo que se opone a un incremento en la masa muscular

sobre este corto intervalo de tiempo.

[00123] Los niveles de sodio sérico eran menores que los valores de referencia para los animales durante todo el estudio. El valor de dióxido de carbono en suero era más alto que los valores de referencia el día 12 para los grupos con Clomid y Zuclomid. La brecha aniónica en suero era menor para todos los animales durante todo el estudio, de manera similar a los resultados para sodio. Enclomid elevó este parámetro hasta valores normales. Los desequilibrios de electrolitos detectados en los animales de prueba durante todos los períodos de tratamiento siguen siendo inciertos pero podrían formar parte del mismo fenómeno de perturbación de líquidos sugerido por los resultados de BUN.

[00124] Los resultados anteriores indican que Enclomid es más eficaz que Clomid o Zuclomid para aumentar la testosterona total en suero. Claramente Zuclomid no es eficaz y esa deficiencia limita cualquier uso de Clomid para hipogonadismo, en particular dado que el componente Zuclomid de Clomid predominaría en la circulación en el tiempo dada su mayor vida media.

[00125] Enclomid parecía ser relativamente benigno en todos los aspectos en comparación con Zuclomid y, a menudo, aún con Clomid. Esto se cumple particularmente cuando se tiene en cuenta la tendencia de Enclomid para disminuir el colesterol, y las enzimas hepáticas a diferencia de la tendencia de Zuclomid para elevar los mismos parámetros. La tendencia sorpresiva de Enclomid para elevar el recuento de linfocitos puede ser de utilidad para hombres con SIDA si se puede demostrar que la subpoblación de linfocitos CD4+ está disminuida o aumentada.

65

EJEMPLO 2

Método de tratamiento de glucosa en ayunas deteriorada en hombres mediante administración de *trans*-clomifeno y mezclas de *trans*-clomifeno y *cis*-clomifeno a relaciones mayores que 71/29

[00126] Los sujetos de prueba de sexo masculino son sometidos a un período de ayuno durante la noche de 8-12 horas después de lo cual se tomaron muestras de sangre de los sujetos y se midieron los niveles de glucosa en sangre en ayunas.

[00127] Los hombres con niveles de glucosa en sangre en ayunas entre 110 y 125 mg/dl recibieron dosificaciones diarias de clomifeno 1,5 mg/kg, en donde la relación de *trans*-clomifeno a *cis*-clomifeno es mayor que 71/29. Se monitorean los niveles de glucosa en sangre en ayunas a intervalos regulares de modo que sea posible ajustar la cantidad de dosificación y la frecuencia de dosificación para alcanzar niveles terapéuticos de glucosa en sangre en ayunas en el sujeto.

EJEMPLO 3

Método de tratamiento de resistencia a insulina en hombres mediante administración de *trans*-clomifeno y mezclas de *trans*-clomifeno y *cis*-clomifeno a relaciones mayores que 71/29

[00128] Se evalúa la sensibilidad a la insulina en hombres usando, por ejemplo, el *clamp* hiperinsulinémico-euglucémico como se describe en Defronzo *et al.*, *Am. J. Physiol.* 237:E214-E223 (1979) y/o la evaluación del modelo homeostático por resistencia a insulina (HOMA-IR) como se describe en Matthews *et al.*, *Diabetologia*. 28:412-419 (1985).

[00129] Los sujetos con resistencia a insulina reciben

dosificaciones diarias de clomifeno 1,5 mg/kg, en donde la relación de *trans*-clomifeno a *cis*-clomifeno es mayor que 71/29. La sensibilidad a la insulina se monitorea a intervalos regulares de modo que se puede ajustar la cantidad de dosificación y la frecuencia de dosificación para lograr incrementos terapéuticos en la sensibilidad a la insulina en el sujeto.

EJEMPLO 4

Comparación de Androxal™ con Androgel®

[00130] Se condujo un estudio de evaluación controlado por placebo en *Advanced Biological Research*, Inc. (ABR) Clinical Research Center en Hackensack, Nueva Jersey para comparar la administración de Androxal™ (*trans*-clomifeno) con Androgel® por vía oral en hombres hipogonadales. Androgel® (Solvay Pharmaceuticals, Inc.) consiste de una crema que administra testosterona exógena en una matriz transdérmica.

[00131] En el estudio se enrolaron 62 hombres hipogonadales con niveles de testosterona menores que 300 ng/dl (normal 298-1034 ng/dl) asignados aleatoriamente en 6 brazos diferentes, tres dosis de Androxal™ (12,5 mg, 25 mg y 50 mg), placebo y dosis altas y bajas de Androgel®. La mitad de los hombres en cada uno de los brazos con Androxal™ y placebo fue asignada aleatoriamente en cohortes que fueron sometidos a sesiones en la clínica los días 1 y 14 para determinar los parámetros farmacocinéticos para Androxal™, así como los cambios cíclicos en la testosterona. Las dosis de placebo y Androxal™ fueron administradas de manera doble ciego. La crema Androgel® fue administrada de una manera de etiqueta abierta. La mitad de los pacientes con Androgel® fueron sometidos a sesiones en la clínica similares a las de los otros pacientes en el estudio. Después de dos semanas de

exposición a la droga, se efectuó un seguimiento de los pacientes por siete a diez días para determinar el estado de sus niveles de testosterona. No se notaron efectos secundarios en ninguno de los brazos con Androxal™ o Androgel® del estudio que fueran diferentes del placebo.

1. Efectos sobre los niveles de testosterona

[00132] Todas las dosis de Androxal™ o Androgel® produjeron cambios estadísticamente significativos en testosterona con respecto a los niveles basales de de testosterona (FIG. 5). Las dosis baja, media y alta de Androxal™ permitió alcanzar incrementos promedio de 169, 247 y 294 ng/dl, respectivamente, en tanto las dosis de Androgel® 5G, la menor dosis aprobada, y de Androgel® 10G, la dosis más alta aprobada, produjo cambios con respecto al nivel basal que eran 212 y 363 ng/dl. Estos valores no eran estadísticamente diferenciables de los cambios logrados con Androxal™. Esta incapacidad para mostrar diferencias entre Androxal™ y Androgel® parece deberse a los resultados altamente variables observados cuando se usa Androgel®. Por ejemplo, la dosis de 50 mg de Androxal™ elevó la testosterona total promedio a 589±172 ng/dl después de 15 días, con un coeficiente de variación (CV) del 29% y similar al grupo placebo (36%). Por otro lado, con Androgel® 5G y 10G se obtuvieron los siguientes valores promedio de testosterona total de 473±289 ng/dl y 608±323 ng/dl, con CV del 61% y 53%, respectivamente.

[00133] Después de 14 días de terapia con Androxal™ todas las dosis fueron asociadas con un patrón diurno de testosterona total similar al del grupo placebo, es decir un pico por la mañana, un disminución al mediodía y un aumento durante la noche. Sin tener en cuenta la teoría, este patrón puede

deberse al modo de acción de Androxal™, que parece estar mediada por efectos sobre el eje hipotalámico-pituitario como se mostrará más adelante. El patrón diurno para hombres con Androgel® era prácticamente plano. Sin embargo, los picos en testosterona total para Androgel® se asociaron con la dosificación y a menudo excedía el nivel normal alto de 1,034 ng/dl. Algunos individuos con Androgel® 10G pudieron alcanzar niveles pico de testosterona total de más de 2500 ng/dl.

[00134] Vale destacar que nivel de testosterona total en suero en el período de seguimiento (es decir, 7-10 días después de terminar el tratamiento diario oral) permanecía inesperadamente alto después del tratamiento con Androxal™. Además, los niveles de testosterona total en suero eran significativamente más altos a las dosis más altas de Androxal™ en comparación con la dosis alta de AndroGel® 1% ($p = 0,017$, prueba t).

2. Efectos sobre los niveles de LH y FSH

[00135] El tratamiento con Androxal™ produjo un incremento estadísticamente significativo en los niveles de LH en suero en sujetos hipogonadales de sexo masculino (FIG. 6). Al igual que en el caso de testosterona total en suero había una continuación inesperada en el nivel de LH en suero en el período de seguimiento (es decir, 7-10 días después de terminar el tratamiento oral diario) donde dichos niveles permanecían altos con las tres dosis de Androxal™. En comparación, el tratamiento con AndroGel® disminuyó inicialmente el valor de LH y después de terminar había un rebote evidente hacia los niveles de pretratamiento.

[00136] El tratamiento con Androxal™ también produjo un incremento estadísticamente significativo en los niveles de FSH en suero en

sujetos hipogonadales de sexo masculino (FIG. 7). El patrón de incremento de FSH es similar al observado en el caso de LH, es decir, todas las dosis de Androxal™ elevan la FSH en suero que permanecía alta durante el período de seguimiento, en tanto el AndroGel® suprime el nivel de FSH en suero y el cese de tratamiento permite una recuperación de la FSH en suero hacia concentraciones más similares a los niveles de pre-tratamiento.

3. Efectos sobre otros parámetros de química clínica

[00137] También se midió el efecto sobre los niveles de dihidroxitestosterona (DHT) en suero. Los hombres con Androxal™ experimentaron un cambio favorable en su DHT a testosterona total. Por ejemplo, los hombres que recibieron la dosis de 50 mg de Androxal™ experimentaron una relación de DHT/TT de 0,83 en comparación con la relación para el grupo placebo de 1,07. Por el contrario, la relación de DHT/TT para cualquiera de los grupos con Androgel® era de >1,5. Los resultados indican que los hombres con Androgel® experimentaban una ganancia de DHT más rápidamente que de testosterona total. Por consiguiente, se inerrumpían los niveles normales de DHT con relación a testosterona en hombres que recibían la terapia con Androgel®.

[00138] Los resultados de los parámetros de química clínica también indicaron, inesperadamente, que los hombres con Androxal™ experimentaban una reducción de triglicéridos no dependiente de la dosis. La reducción en los triglicéridos mostró una disminución promedio del 19,1% después de dos semanas de terapia. Esto se compara con la reducción del 5,9% en el grupo placebo y con incrementos del 0,3% y 22% para Androgel® 5G y 10G, respectivamente.

70

4. Discusión

[00139] Sobre la base de este estudio los autores infieren un número de potenciales ventajas para Androxal™ como una terapia potencial. El Androxal™ parece elevar la testosterona total en el rango normal de una manera altamente consistente sin picos anormalmente altos de testosterona en suero. Además, el uso de *trans*-clomifeno para el tratamiento de hombres que sufren de hipogonadismo secundario ofrece un nuevo enfoque que potencialmente podría contrarrestar uno de los principales efectos secundarios de las terapias exógenas, tal como Androgel®. Las terapias exógenas proveen una retroalimentación negativa disminuyendo de esa manera la producción de FSH y LH. La FSH es una hormona reproductora esencial y en los hombres estimula la espermatogénesis. La exposición a largo plazo a testosterona exógena, como resultado de sus efectos sobre la producción de FSH, causa una reducción en la síntesis de esperma, lo que conduce a una potencial esterilidad transitoria debido al recuento bajo de esperma y por ello un encogimiento resultante de los testículos, dado que el volumen de los testículos se relaciona con el nivel de espermatogénesis dentro de los túbulos seminíferos. El incremento en los niveles de FSH también indica que se puede usar Androxal™ para tratar la esterilidad en hombres, incluyendo hombres hipogonadales. Más aún, los efectos extendidos de Androxal™ sobre los niveles de testosterona en suero, de FSH y de LH indican que se puede administrar Androxal™ con dosificaciones o programas alterados, quizás hasta tratamientos no diarios o episódicos.

EJEMPLO 5

Efecto de *trans*-clomifeno sobre los niveles de glucosa en ayunas

71

[00140] Se condujo un estudio controlado por placebo para determinar los efectos de Androxal™ (*trans*-clomifeno) y Androgel® administrados por vía oral sobre los niveles de glucosa en sangre. Androgel® (Solvay Pharmaceuticals, Inc.) consiste de una crema que administra testosterona exógena en una matriz transdérmica.

[00141] En el estudio se enrolaron hombres hipogonadales (testosterona menor que 300 ng/dl) con un amplio rango de indices de masa corporal (BMI). Los pacientes fueron asignados aleatoriamente en 3 brazos diferentes, con dosis de 50 mg de Androxal™, placebo y dosis altas de Androgel®. Las dosis de placebo y Androxal™ fueron administradas de manera doble ciego. La crema Androgel® fue administrada de una manera de etiqueta abierta. Se monitorearon los niveles de glucosa en ayunas en los pacientes inmediatamente antes del tratamiento (nivel basal) y a intervalos regulares durante el estudio. No se notaron efectos secundarios en ninguno de los brazos con Androxal™ o Androgel® del estudio que fueran diferentes del placebo.

[00142] En la Figura 8 se muestran los niveles basales de glucosa en sangre de cada grupo de tratamiento. Los pacientes de cada grupo de tratamiento están separados en el gráfico de acuerdo con el BMI. Las barras de sombreado oscuro representan el nivel basal de glucosa en sangre en los pacientes de cada grupo de tratamiento con un BMI > 26 (EP300). Las barras con sombreado claro representan el valor basal de glucosa en sangre en los pacientes de cada grupo de tratamiento con un BMI <27. Como se puede observar en la Figura 8, el valor basal de glucosa en sangre en pacientes con un BMI > 26 era significativamente elevado en todos los grupos de tratamiento

con relación a los pacientes con un BMI < 27.

[00143] La Figura 9 muestra los cambios en la glucosa sérica con respecto al valor basal en el grupo de tratamiento con Androxal. Los pacientes están separados sobre el gráfico de acuerdo con el BMI. Las barras con sombreado oscuro representan los cambios en la glucosa sérica con respecto al valor basal en pacientes con un BMI > 26 (EP300). Las barras con sombreado claro representan cambios en la glucosa sérica con respecto al valor basal en pacientes con un BMI < 27. Como se puede observar en la Figura 9, el tratamiento con Androxal era eficaz para disminuir los niveles de glucosa sérica en pacientes con un BMI > 26 durante todo el período de tratamiento, con una reducción cercana a 24 mg/dl observada para los períodos de 3 y 4,5 meses.

[00144] La Figura 10 representa los cambios en la glucosa sérica con respecto al valor basal en los grupos de tratamiento con Androgel® y placebo en pacientes con un BMI > 26 (EP300). Las barras con sombreado oscuro representan los cambios en la glucosa sérica con respecto al valor basal en pacientes del grupo placebo. Las barras con sombreado claro representan los cambios en la glucosa sérica con respecto al valor basal en pacientes del grupo de tratamiento con Androgel®. Como se puede observar en la Figura 10, no se observaron diferencias significativas en la glucosa sérica con respecto al valor basal en los pacientes con un BMI > 26 en ninguno de los grupos de tratamiento con Androgel® o placebo.

[00145] Estos datos sugieren que Androxal™ es sorpresivamente eficaz para reducir los niveles de glucosa en ayunas (y la resistencia simultánea a insulina) en pacientes con testosterona normal baja o debajo de

normal quienes han desarrollado el síndrome metabólico y demuestra la eficacia de Androxal™ en el tratamiento del síndrome metabólico y las condiciones asociadas con el mismo, tal como niveles de glucosa elevados, niveles de triglicéridos elevados, niveles de colesterol elevados, resistencia a insulina, presión sanguínea alta y obesidad. Por el contrario, la administración de testosterona exógena resulta ineficaz para reducir los niveles de glucosa en los pacientes con testosterona normal baja o debajo de normal quienes han desarrollado el síndrome metabólico.

REIVINDICACIONES:

1. Un método de tratamiento de un síntoma del síndrome metabólico, CARACTERIZADO PORQUE comprende administrarle a un sujeto que lo necesita una cantidad eficaz de una composición que comprende un antiestrógeno.

2. El método de la reivindicación 1, CARACTERIZADO PORQUE la composición comprende entre 0% y 29% p/p aproximadamente de *cis*-clomifeno y entre aproximadamente 100% y aproximadamente 71% de *trans*-clomifeno o análogos de los mismos.

3. El método de la reivindicación 2, CARACTERIZADO PORQUE la composición consiste esencialmente de *trans*-clomifeno o un análogo del mismo.

4. El método de la reivindicación 3, CARACTERIZADO PORQUE el síntoma se selecciona del grupo formado por niveles de glucosa elevados, niveles de triglicéridos elevados, niveles de colesterol elevados, resistencia a insulina, presión sanguínea alta, obesidad abdominal, estado protrombótico o estado proinflamatorio.

5. El método de la reivindicación 4, CARACTERIZADO PORQUE la dosificación de *trans*-clomifeno comprende entre aproximadamente 12,5 y aproximadamente 50 mg.

6. El método de la reivindicación 5, CARACTERIZADO PORQUE la dosificación es de 12,5, 25 ó 50 mg.

7. El método de la reivindicación 1, CARACTERIZADO PORQUE el nivel de testosterona de dicho sujeto se encuentra por debajo de 300 ng/dl.

8. Un método de tratamiento de una glucosa en ayunas deteriorada

en un sujeto, CARACTERIZADO PORQUE comprende administrarle al sujeto que lo necesita, una cantidad eficaz de una composición que comprende un antiestrógeno.

9- El método de la reivindicación 8, CARACTERIZADO PORQUE la composición comprende entre 0% y 29% p/p aproximadamente de *cis*-clomifeno y entre aproximadamente 100% y aproximadamente 71% de *trans*-clomifeno o análogos de los mismos.

10. El método de la reivindicación 9, CARACTERIZADO PORQUE la composición consiste esencialmente de *trans*-clomifeno o un análogo del mismo.

11. El método de la reivindicación 8, CARACTERIZADO PORQUE dicho paciente tiene un nivel de glucosa en sangre en ayunas de entre 110 mg/dl y 125 mg/dl antes de dicha administración.

12. El método de la reivindicación 8, CARACTERIZADO PORQUE dicha administración reduce el nivel de glucosa en sangre en ayunas en dicho paciente por debajo de 110 mg/dl.

13. El método de la reivindicación 12, CARACTERIZADO PORQUE la dosificación de *trans*-clomifeno comprende entre aproximadamente 12,5 y aproximadamente 50 mg.

14. El método de la reivindicación 13, CARACTERIZADO PORQUE la dosificación es de 12,5, 25 ó 50 mg.

15. El método de la reivindicación 8, CARACTERIZADO PORQUE el nivel de testosterona de dicho sujeto se encuentra por debajo de 300 ng/dl.

16. Un método de tratamiento del síndrome metabólico, CARACTERIZADO PORQUE comprende administrarle a un sujeto que lo

necesita una cantidad eficaz de una composición que comprende un antiestrógeno.

17. El método de la reivindicación 16, CARACTERIZADO PORQUE la composición comprende entre 0% y 29% p/p aproximadamente de *cis*-clomifeno y entre aproximadamente 100% y aproximadamente 71% de *trans*-clomifeno o análogos de los mismos.

18. El método de la reivindicación 17, CARACTERIZADO PORQUE la composición consiste esencialmente de *trans*-clomifeno o un análogo del mismo.

19. El método de la reivindicación 18, CARACTERIZADO PORQUE la dosificación de *trans*-clomifeno comprende entre aproximadamente 12,5 y aproximadamente 50 mg.

20. El método de la reivindicación 19, CARACTERIZADO PORQUE la dosificación es de 12,5, 25 ó 50 mg.

21. El método de la reivindicación 20, CARACTERIZADO PORQUE el tratamiento disminuye la concentración de glucosa en suero en el sujeto.

22. El método de la reivindicación 18, CARACTERIZADO PORQUE el tratamiento incrementa la sensibilidad a la insulina en el sujeto.

23. El método de la reivindicación 18, CARACTERIZADO PORQUE el tratamiento disminuye la concentración de triglicéridos en suero en el sujeto.

24. Un método para reducir los niveles de glucosa en ayunas en un sujeto con hipogonadismo hipogonadotrófico secundario o idiopático, CARACTERIZADO PORQUE comprende administrarle al sujeto una cantidad eficaz de una composición que comprende un antiestrógeno.

25. El método de la reivindicación 24, CARACTERIZADO PORQUE

77

la composición comprende entre 0% y 29% p/p aproximadamente de *cis*-clomifeno y entre aproximadamente 100% y aproximadamente 71% de *trans*-clomifeno o análogos de los mismos.

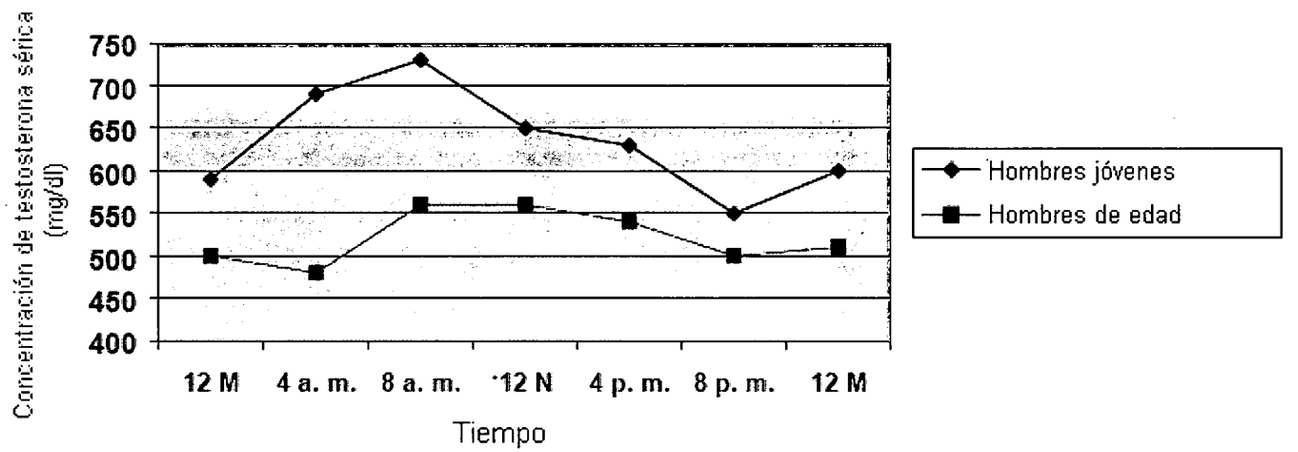
26. El método de la reivindicación 25, CARACTERIZADO PORQUE la composición consiste esencialmente de *trans*-clomifeno o un análogo del mismo.

27. El método de la reivindicación 25, CARACTERIZADO PORQUE el sujeto tiene un nivel de glucosa en ayunas de entre 125 y 140 mg/dl antes de dicha administración.

28. El método de la reivindicación 25, CARACTERIZADO PORQUE dicho tratamiento reduce los niveles de glucosa en ayunas por debajo de aproximadamente 110 mg/dl en dicho sujeto.

FIG. 1

Perfiles de secreción normal de testosterona sérica total en hombres jóvenes y de edad saludables



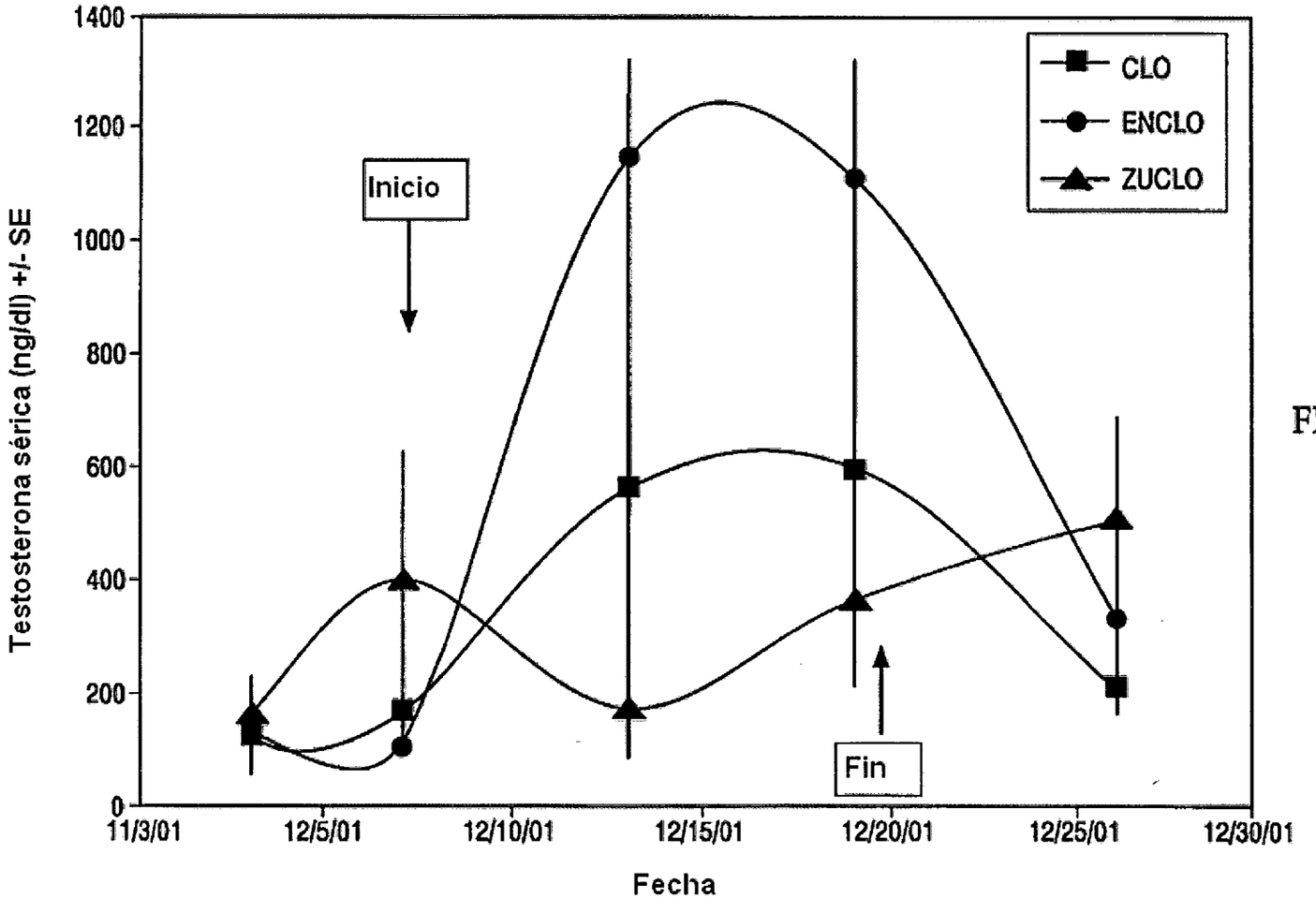

1400
1200
1000
800
600
400
200
0
Testosterona sérica (ng/dl) +/- SE
Inicio
Fin
CLO
ENCLO
ZUCLO
11/3/01
12/5/01
12/10/01
12/15/01
12/20/01
12/25/01
12/30/01
Fecha

FIG. 3

FIG. 4

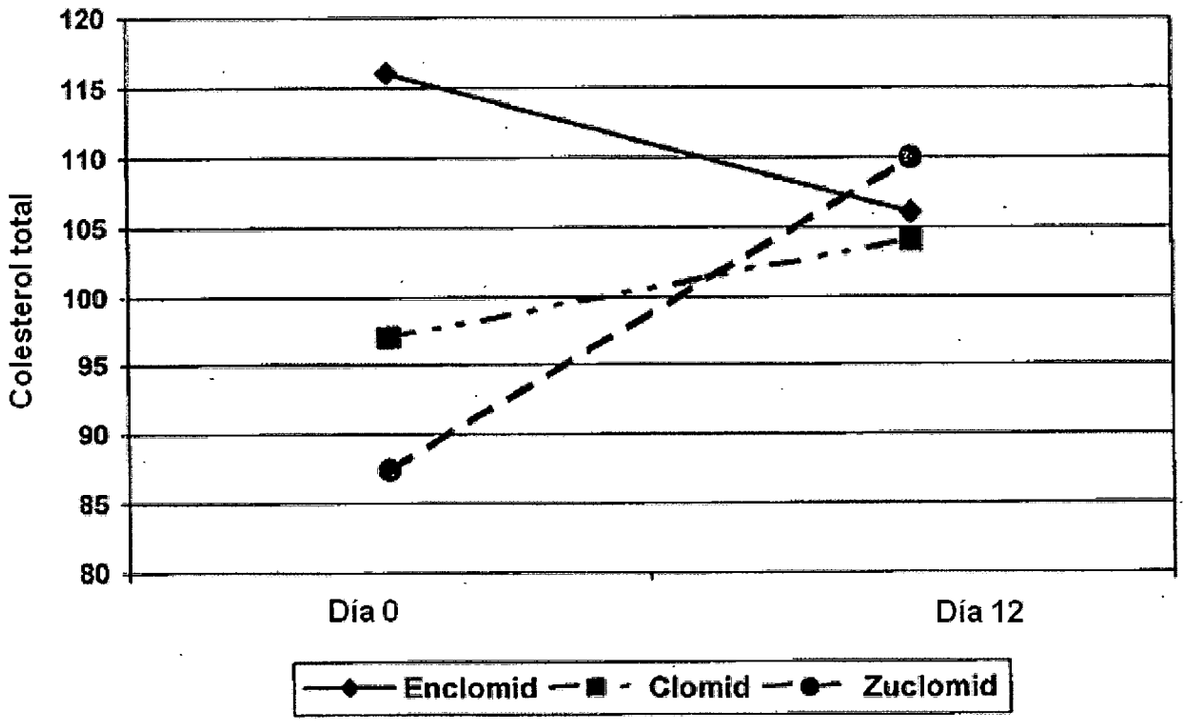

120
115
110
105
100
95
90
85
80
Colesterol total
Día 0
Día 12
Enclomid
Clomid
Zuclomid

FIG. 5

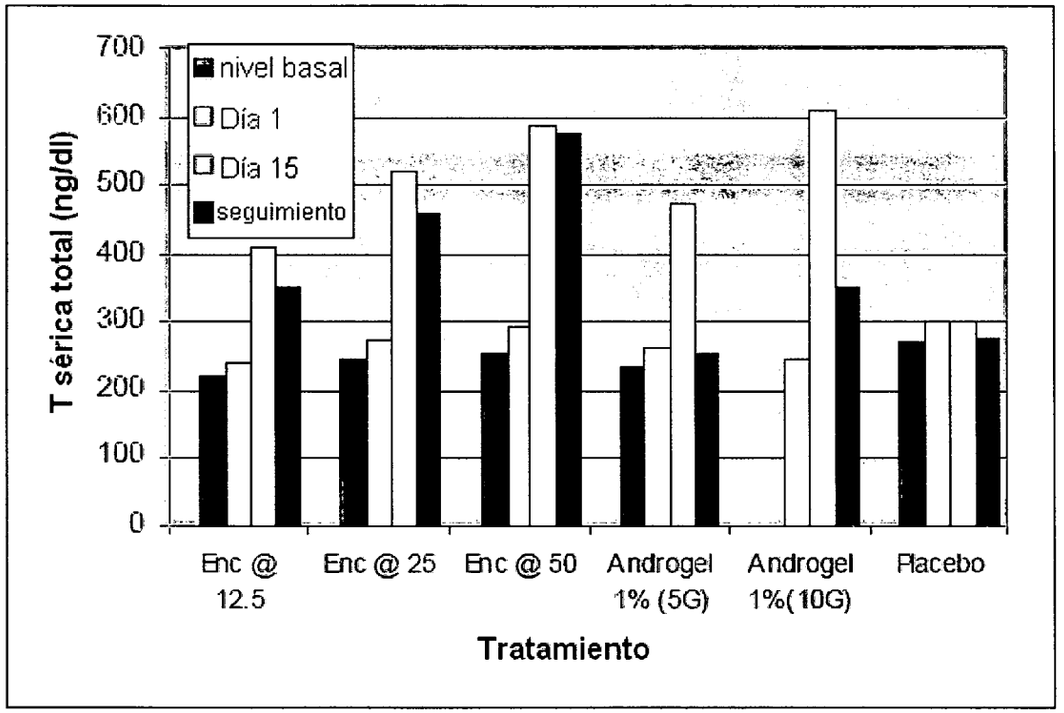

700
600
500
400
300
200
100
0
nivel basal
Día 1
Día 15
seguimiento
T sérica total (ng/dl)
Enc @ 12.5
Enc @ 25
Enc @ 50
Androgel 1% (5G)
Androgel 1%(10G)
Placebo
Tratamiento

FIG. 6

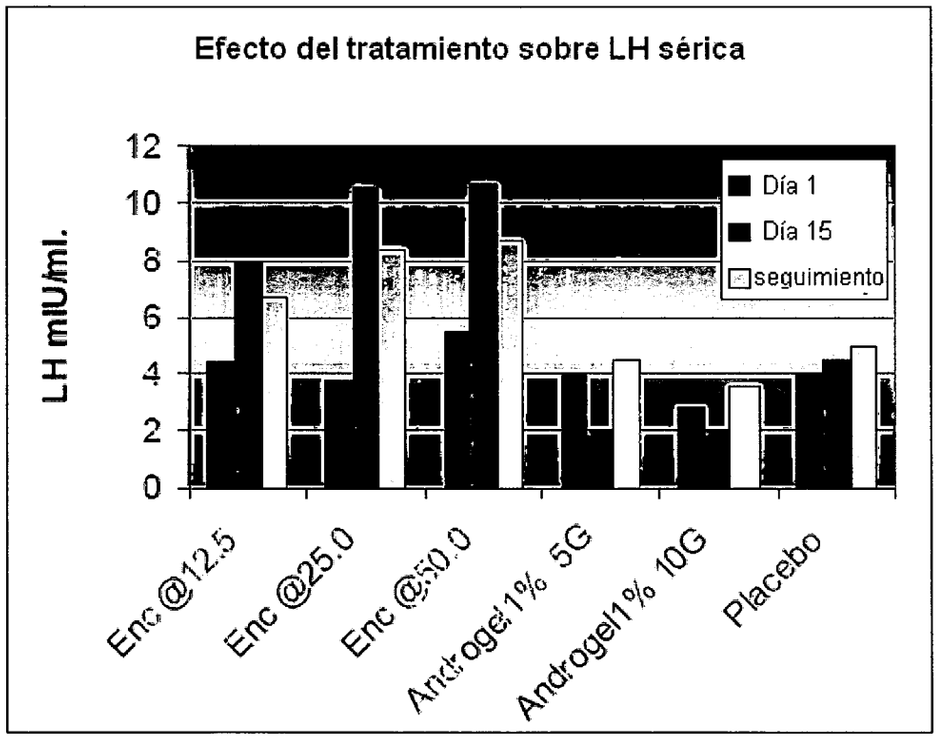

Efecto del tratamiento sobre LH sérica
LH mIU/ml.
12
10
8
6
4
2
0
Día 1
Día 15
seguimiento
Enc @12.5
Enc @25.0
Enc @50.0
Androgel1% 5G
Androgel1% 10G
Placebo

FIG. 7

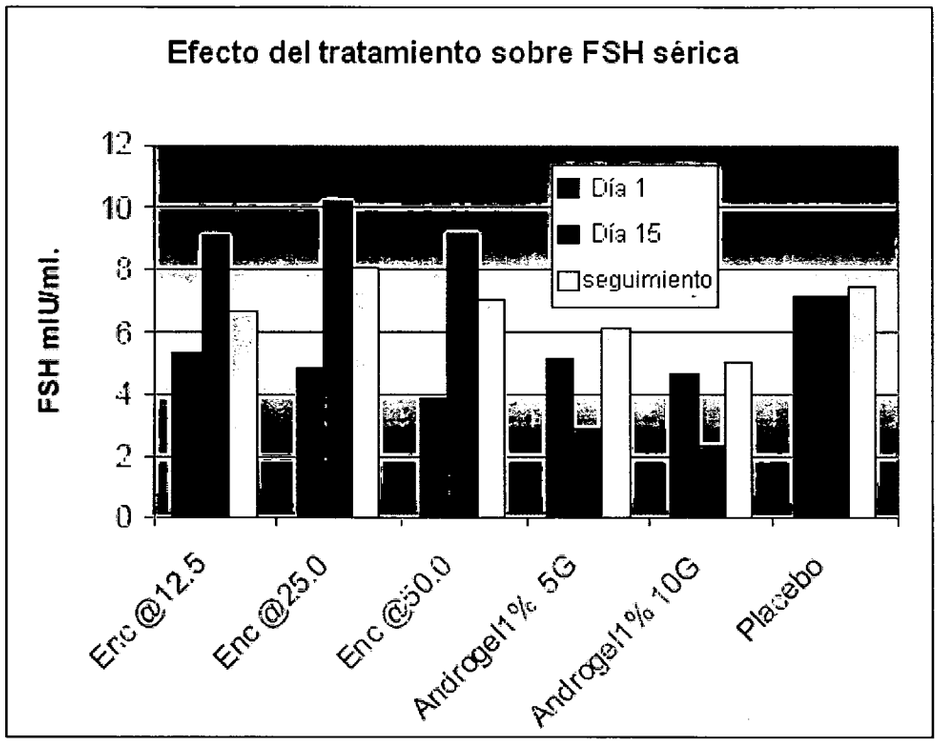
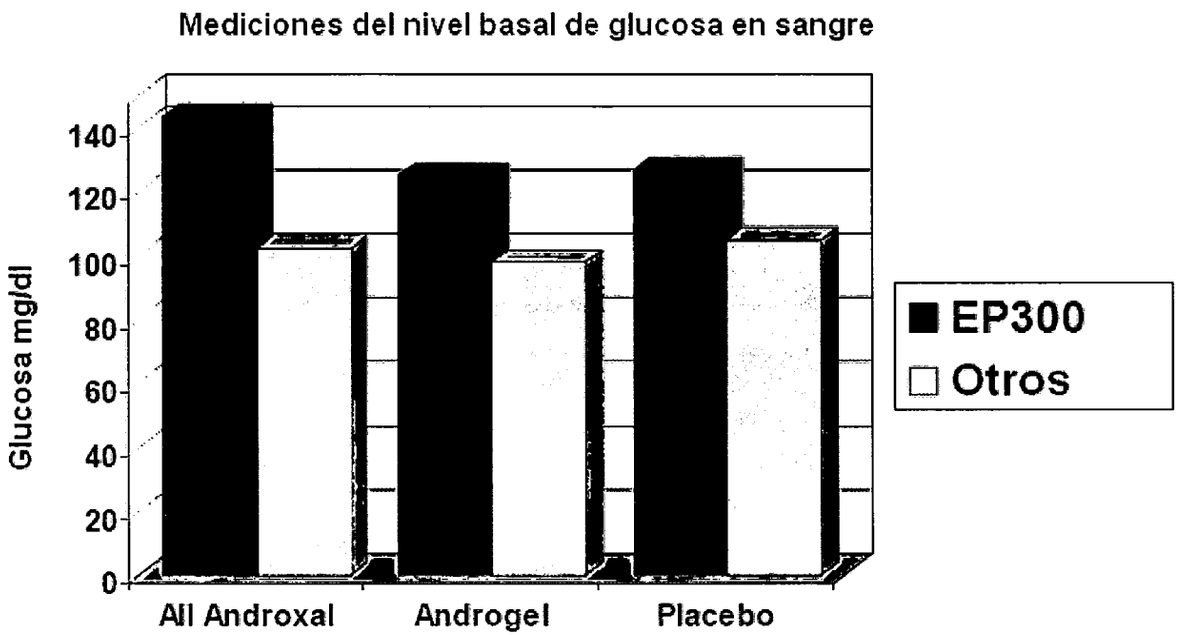

Efecto del tratamiento sobre FSH sérica
FSH mIU/ml.
12
10
8
6
4
2
0
Día 1
Día 15
seguimiento
Enc @12.5
Enc @25.0
Enc @50.0
Androgel1% 5G
Androgel1% 10G
Placebo

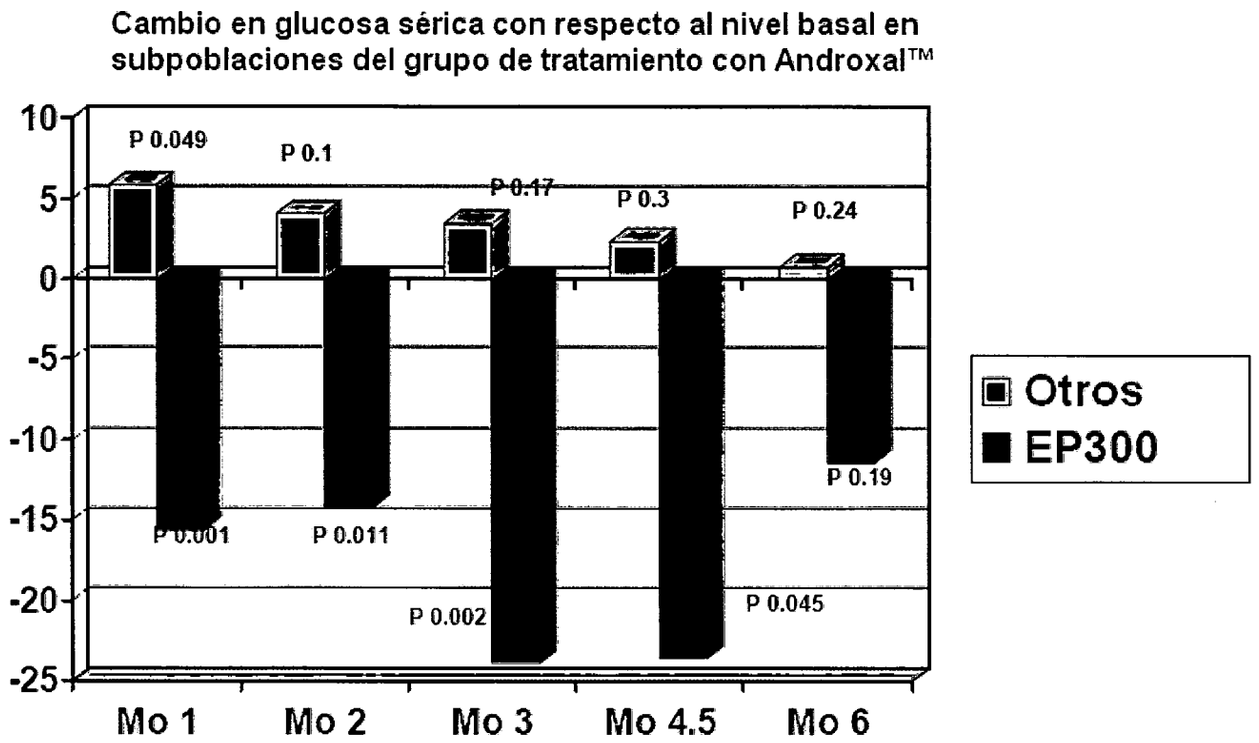
FIG. 8



EP300 = BMI>26, Glu >99, T<300
Otros = BMI<27, Glu <100, T<300
EP300 vs. Otherwise p<0.0001 para todos los tratamientos

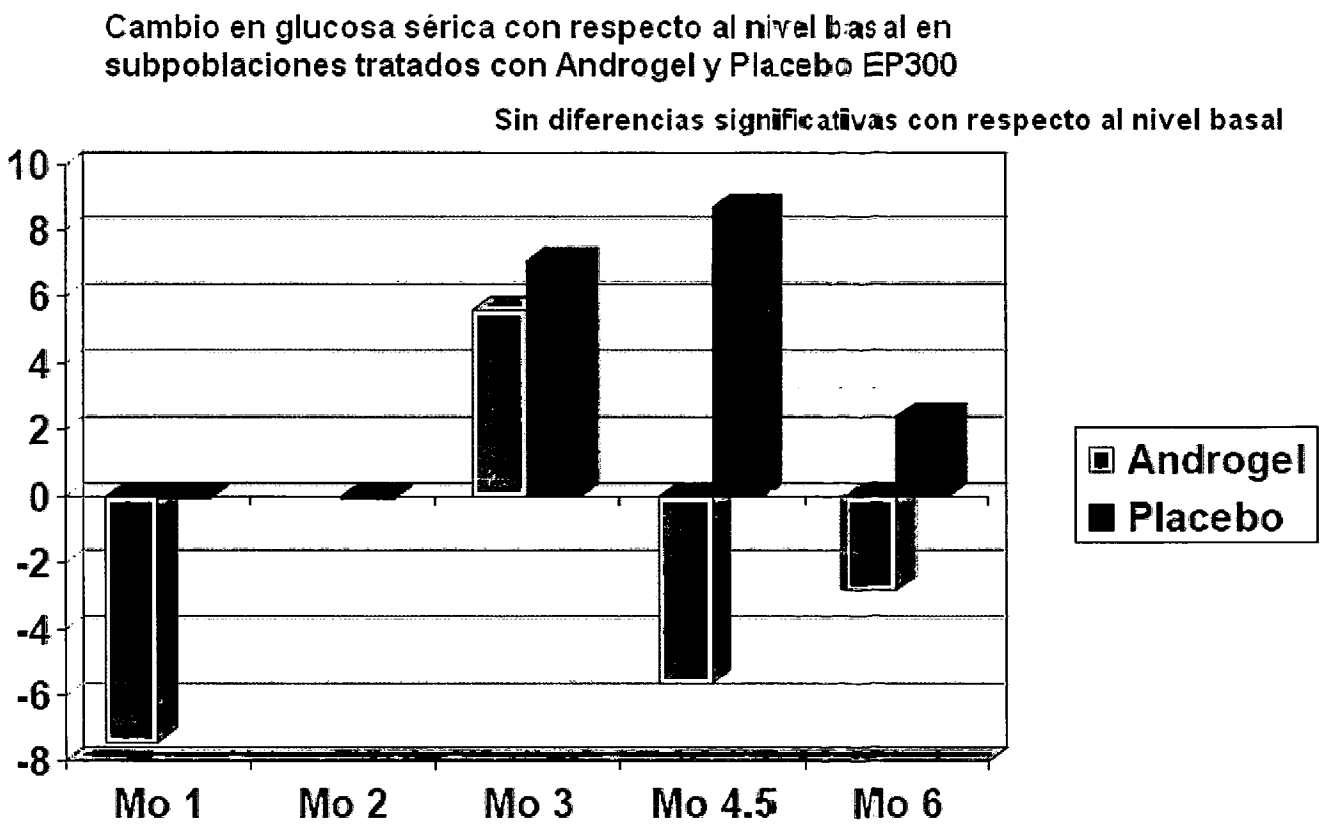
98

FIG. 9


Cambio en glucosa sérica con respecto al nivel basal en subpoblaciones del grupo de tratamiento con Androxal™
10
5
0
-5
-10
-15
-20
-25
P 0.049
P 0.1
P 0.17
P 0.3
P 0.24
P 0.19
P 0.001
P 0.011
P 0.002
P 0.045
Mo 1
Mo 2
Mo 3
Mo 4.5
Mo 6
Otros
EP300
EP300 = BMI>26, Glu >99, T<300
Otros = BMI<27, Glu <100, T<300

84

FIG. 10


Cambio en glucosa sérica con respecto al nivel basal en subpoblaciones tratados con Androgel y Placebo EP300
Sin diferencias significativas con respecto al nivel basal
10
8
6
4
2
0
-2
-4
-6
-8
Mo 1
Mo 2
Mo 3
Mo 4.5
Mo 6
Androgel
Placebo
EP300 = BMI>26, Glu >99, T<300

88

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)* 07189.0003.00PC09

Box No. I TITLE OF INVENTION

TRANS-CLOMIPHENE FOR METABOLIC SYNDROME

Box No. II APPLICANT ☐ This person is also inventor

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. 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.)*

REPROS THERAPEUTICS INC.
2408 Timberloch Place, Suite B-7
The Woodlands, Texas 77380

Telephone No.

Facsimile No.

Applicant's registration No. with the Office

☐ **E-mail authorization**: Marking this check-box authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, if the Office or Authority so wishes, advance copies of notifications in respect of this international application. (*See also the Notes to Boxes Nos. II and III.*)

E-mail address

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)

☒ 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 name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CLOUGH, David W., Ph.D.
Howrey LLP
Docketing Department
2941 Fairview Park Drive, Suite 200
Falls Church, VA 22042-9922

Telephone No.
(312) 595-1408

Facsimile No.
(703) 336-6950

Agent's registration No. with the Office
36,107

☒ **E-mail authorization**: Marking this check-box authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, if the Office or Authority so wishes, advance copies of notifications in respect of this international application. (*See also the Notes to Boxes Nos. II and III.*)

E-mail address
kozlowskid@howrey.com

☐ **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.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

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. 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.)*

vAN AS, Andre
1273 Robynwood Lane
West Chester, PA 19380
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

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. 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.)*

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:

State *(that is, country)* of residence:

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

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. 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.)*

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:

State *(that is, country)* of residence:

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

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. 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.)*

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:

State *(that is, country)* of residence:

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 another continuation sheet.

90

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, **the space is insufficient** to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

   (i) ***if more than one person is to be indicated as applicant and/or inventor** and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. 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;*

   (ii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the indication **"the States indicated in the Supplemental Box"** is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

   (iii) *if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America**: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

   (iv) *if, in addition to the agent(s) indicated in Box No. IV, there are **further agents**: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

   (v) *if, in Box No. VI, there are **more than four earlier applications whose priority is claimed**: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*

2. *If the applicant intends to make an indication of the wish that the international application be treated, in certain designated States, as an application for a patent of addition, certificate of addition, inventor's certificate of addition or utility certificate of addition: in such a case, write the name or two-letter code of each designated State concerned and the indication **"patent of addition," "certificate of addition," "inventor's certificate of addition"** or **"utility certificate of addition,"** the number of the parent application or parent patent or other parent grant and the date of grant of the parent patent or other parent grant or the date of filing of the parent application (Rules 4.11(a)(i) and 49bis.1(a) or (b)).*

3. *If the applicant intends to make an indication of the wish that the international application be treated, in the United States of America, as a continuation or continuation-in-part of an earlier application: in such a case, write "United States of America" or "US" and the indication **"continuation"** or **"continuation-in-part"** and the number and the filing date of the parent application (Rules 4.11(a)(ii) and 49bis.1(d)).*

John F. Lynch, Reg. No. 22,504;
Stephen H. Cagle, Reg. No. 26,445;
Floyd R. Nation, Reg. No. 27,580;
John D. Norris, Reg. No. 28,246;
J. Paul Williamson, Reg. No. 29,600;
Patricia A. Kammerer, Reg. No. 29,775;
Craig M. Lundell, Reg. No. 30,284;
Melinda L. Patterson, Reg. No. 33,062;
Susan K. Knoll, Reg. No. 33,254;
Michael S. Dowler, Reg. No. 34,582;
J. Dean Lechtenberger, Reg. No. 34,859;
David W. Clough, Reg. No. 36,107;
Janelle D. Waack, Reg. No. 36,300;
Robert J. McAughan, Reg. No. 36,599;
Nicolas G. Barzoukas, Reg. No. 38,823;
Peter J. Chassman, Reg. No. 38,841;
Stephen E. Edwards, Reg. No. 38,865;
Connie Flores-Jones, Reg. No. 41,755;
Brian L. Jackson, Reg. No. 41,868;
Gregory A. Duffey, Reg. No. 42,501;
John R. Keville, Reg. No. 42,723;
Darrell G. Dotson, Reg. No. 44,661;
Suzy Harbison, Reg. No. 45,139;
Matthew Madsen, Reg. No. 45,594;
Robert P. Auerbach, Reg. No. 46,525;
Raymond Reese, Reg. No. 47,891;
Amy G. Klann, Reg. No. 48,155;
Sean McDermott, Reg. No. 49,000;
Kate G. Berezutskaya, Reg. No. 53,984;

91

Box No. V DESIGNATIONS

The filing of this request **constitutes under Rule 4.9(a) the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany **is not designated** for any kind of national protection

☐ JP Japan **is not designated** for any kind of national protection

☐ KR Republic of Korea **is not designated** for any kind of national protection

☐ RU Russian Federation **is not designated** for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing or subsequently under Rule 26bis.1, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application.)

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) (16/10/2007) 16 October 2007	60/980,334	US		
item (2)				
item (3)				
item (4)				

☐ Further priority claims are indicated in the Supplemental Box.

Transmit certified copy: 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) ☐ other, see Supplemental Box

Restore the right of priority: the receiving Office is requested to restore the right of priority for the earlier application(s) identified above or in the Supplemental Box as item(s) (_____). *(See also the Notes to Box No. VI; further information **must** be provided to support a request to restore the right of priority.)*

Incorporation by reference: where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

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

ISA/ EP

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 April 2009 (23.04.2009)

PCT

(10) International Publication Number
WO 2009/051908 A1

(51) International Patent Classification:
A61K 31/135 (2006.01) *A61P 3/06* (2006.01)
A61P 3/00 (2006.01) *A61P 3/10* (2006.01)
A61P 3/04 (2006.01)

(21) International Application Number:
PCT/US2008/075433

(22) International Filing Date:
5 September 2008 (05.09.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/980,334 16 October 2007 (16.10.2007) US

(71) Applicant *(for all designated States except US)*: **REPROS THERAPEUTICS INC.** [US/US]; 2408 Timberloch Place, Suite B-7, The Woodlands, TX 77380 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **VAN AS, Andre** [US/US]; 1273 Robynwood Lane, West Chester, PA 19380 (US).

(74) Agent: **CLOUGH, David, W.**; Howrey Llp, Docketing Department, 2941 Fairview Park Drive, Suite 200, Falls Church, VA 22042-9922 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(54) Title: TRANS-CLOMIPHENE FOR METABOLIC SYNDROME

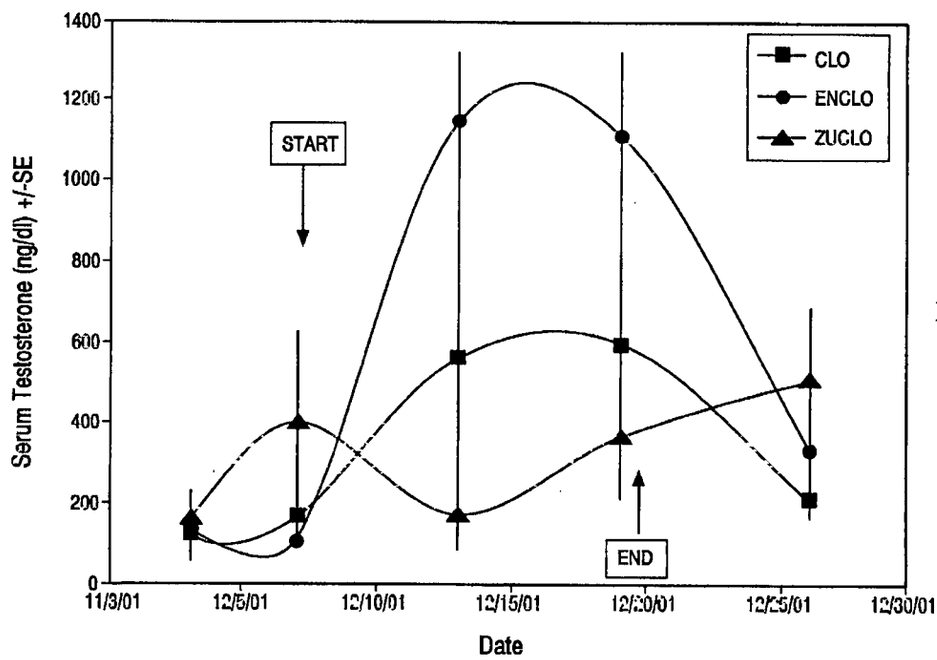


FIG. 3

(57) Abstract: The present invention relates to the administration of compositions comprising an antiestrogen, preferably *trans*-clomiphene, for treating metabolic syndrome in a subject. The invention is also directed to methods for reducing fasting glucose levels in a subject by administering a composition comprising an antiestrogen, preferably *trans*-clomiphene.

WO 2009/051908 A1

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
HOWREY, LLP
Attn. Clough, David W.
Docketing Department
2941 Fairview Park Drive, Suite 200
Falls Church, VA 22042-9922
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 19/12/2008
Applicant's or agent's file reference 07199.0003.00PC09	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2008/075433	International filing date *(day/month/year)* 05/09/2008
Applicant REPROS THERAPEUTICS INC.	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

RECD HOWREY LLP 12/30/08

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Iris Hodzic

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
07189.0003.00PC09		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2008/075433	05/09/2008	16/10/2007
Applicant		
REPROS THERAPEUTICS INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 3
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERN TIONAL SEARCH REPORT

International application No
PCT/US2008/075433

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/138 A61P3/00 A61P3/04 A61P3/06 A61P3/10

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 829 534 A (ESTEVE LABOR DR [ES]) 5 September 2007 (2007-09-05) page 3, paragraph 12 claim 13	1,16
Y	-----	1-23
Y	WO 2006/019916 A (ZONAGEN INC [US]; PODOLSKI JOSEPH [US]; WIEHLE RONALD [US]) 23 February 2006 (2006-02-23) page 2, paragraph 8 page 4, paragraph 17 page 8, paragraphs 28,31 page 9, paragraph 36 page 10 - page 17	1-23

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 December 2008	19/12/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Terenzi, Carla

2

Form PCT/ISA/210 (second sheet) (April 2005)

96

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JONES ET AL: "Testosterone Associations with Erectile Dysfunction, Diabetes, and the Metabolic Syndrome" EUROPEAN UROLOGY SUPPLEMENTS, XX, XX, vol. 6, no. 16, 24 August 2007 (2007-08-24), pages 847-857, XP022211152 ISSN: 1569-9056 the whole document	1-28

2

97

INTERN TIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/075433

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1829534 A	05-09-2007	NONE	
WO 2006019916 A	23-02-2006	BR PI0513129 A	29-04-2008
		EP 1776098 A1	25-04-2007
		US 2008242726 A1	02-10-2008

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 February 2006 (23.02.2006)

PCT

(10) International Publication Number
WO 2006/019916 A1

(51) International Patent Classification[7]: A61K 31/138, A61P 3/06, 15/08, 35/00

(21) International Application Number: PCT/US2005/025000

(22) International Filing Date: 14 July 2005 (14.07.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/588,130	14 July 2004 (14.07.2004)	US
60/588,223	14 July 2004 (14.07.2004)	US
60/588,123	14 July 2004 (14.07.2004)	US

(71) Applicant *(for all designated States except US)*: **ZONAGEN, INC.** [US/US]; 2408 Timberloch Drive, B-1, The Woodlands, TX 77380 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PODOLSKI, Joseph** [US/US]; 3 Pebble Hollow Court, The Woodlands, TX 77381 (US). **WIEHLE, Ronald** [US/US]; 13903 Viewfield Court, Houston, TX 77059 (US).

(74) Agents: **SCOTT, Teddy, C., Jr.** et al.; Howrey LLP, 2941 Fairview Park Drive, Box No. 7, Falls Church, VA 22042 (US).

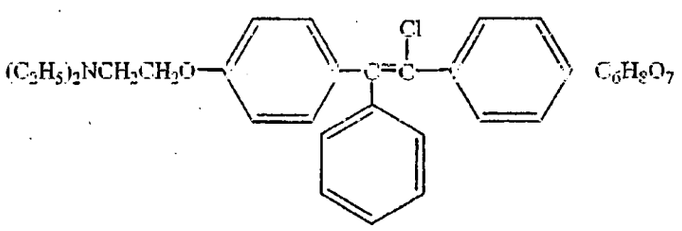
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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

(54) Title: TRANS-CLOMIPHENE FOR THE TREATMENT OF BENIGN PROSTATE HYPERTROPHY, PROSTATE CANCER, HYPOGONADISM, ELEVATED TRIGLYCERIDES AND HIGH CHOLESTEROL



(57) Abstract: Compositions comprising trans-clomiphene may be used in treating benign prostate hypertrophy, prostate cancer, elevated triglyceride levels and hypogonadism.

WO 2006/019916 A1

TRANS-CLOMIPHENE FOR THE TREATMENT OF BENIGN PROSTATE HYPERTROPHY, PROSTATE CANCER, HYPOGONADISM, ELEVATED TRIGLYCERIDES AND HIGH CHOLESTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Application No. 60/588,123 filed July 14, 2004, U.S. Provisional Application No. 60/588,223 filed July 14, 2004, and U.S. Provisional Application No. 60/588,130 filed July 14, 2004, each of which is incorporated herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to the use of a composition comprising clomiphene.

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. 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%).

[0005] 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. 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 (±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). 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.

[0006] 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 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. Many of these disorders are generically referred to as male menopause.

[0007] Several forms of testosterone therapy exist in the United States today. Recently, transdermal preparations have gained favor in the market. However, a scrotal testosterone patch results in supraphysiologic levels of 5α-dihydrotestosterone (DHT) due to the high concentration of 5α-reductase in scrotal skin. 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

[0008] The present invention is related to methods and compositions comprising *trans*-clomiphene. The composition may also comprise *cis*-clomiphene. The composition may comprise greater than 1/1 w/w of *trans*-clomiphene. The composition may comprise 0% to 29% weight/weight of (*cis*, -Z-, *trans*-clomiphene) ("*cis*-clomiphene" or "Zuclomid") and 100% to 71% w/w (*trans*-, E-, *cis*-clomiphene) ("*trans*-clomiphene" or "Enclomid") or pharmaceutically acceptable salts or solvates thereof. The composition may contain both *cis*-clomiphene and *trans*-clomiphene, and the ratio of *trans*-clomiphene and *cis*-clomiphene may

be greater than 71/29. The composition may further comprise suitable pharmaceutical excipients, diluents, carriers, and the like. The composition may also comprise analogs of *cis*-clomiphene and *trans*-clomiphene isomers.

[0009] The composition may be formulated for a variety of methods of administration including oral, intravenous, subcutaneous, buccal, transmucosal, intrathecal, intradermal, and intracisternal administration. The composition may also be formulated for extended release. In some methods, the compositions may be administered so as to give rise to serum testosterone levels generally similar to the serum testosterone levels of a normal patient. Dosages of the composition may be administered in a pharmaceutical formulation that would give rise to peak serum testosterone levels between about 4 a.m. and noon. The composition may also be administered to give rise to peak serum testosterone levels at around 8 a.m. Alternatively, the composition may be administered to give rise to peak serum testosterone levels at any time of day deemed suitable by the patient and/or the prescribing physician.

[0010] The composition may be used for treating conditions such as prostate cancer and benign prostate hypertrophy. In treating prostate cancer, the composition may be administered in a treatment regimen also including a chemotherapeutic. Exemplary chemotherapeutics include Taxotere® (docetaxel), Novantrone® (mitoxantrone hydrochloride), Emcyt® (estramustine sodium phosphate) doxorubicin, ketoconazole and vinblastine although other chemotherapeutics may also be used. In some cases, the chemotherapeutic may be administered closely in time to the dosage of the composition. In other cases the chemotherapeutic may be administered to the patient during the same period of time in which the patient is undergoing treatment with the composition. Treatment with the composition may precede or follow treatment with the chemotherapeutic.

[0011] The composition may also be used for increasing serum testosterone levels in hypogonadal male mammals, and for ameliorating or preventing the sequelae of low testosterone levels. Some symptoms, or sequelae, of low testosterone levels, which the present invention may be used to treat, include reduction of muscle mass, limitation of body performance capacity, reduction of bone density, reduction of libido, and/or reduction of potency.

[0012] The composition may also be used for decreasing triglyceride levels in mammals, and more specifically in male mammals, and for ameliorating or preventing the sequelae of high cholesterol levels. The composition may also be used in treating high cholesterol levels in mammals, and more specifically in male mammals. Although methods of decreasing

triglyceride levels and ameliorating or preventing the sequelae of high cholesterol levels are preferably used to treat males, they may also be used to treat females.

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.

[0016] FIG. 4 is a graphic demonstration of the time course of cholesterol levels in baboon males treated with Clomid, Enclomid and Zuclomid.

DETAILED DESCRIPTION

[0017] Administration of clomiphene may result in an increase in testosterone levels. As shown in Example 3, administration of a composition comprising *trans*-clomiphene may increase testosterone levels and may provide an effective therapy for ameliorating or preventing one or more symptoms of low testosterone levels. Surprisingly, the administration of a composition comprising *trans*-clomiphene to males favorably affects the ratio of DHT to testosterone. As a result, compositions comprising *trans*-clomiphene may be used to treat benign prostate hypertrophy and prostate cancer in males by lowering the relative ratio of DHT to testosterone. Additionally, administration of a composition comprising *trans*-clomiphene may be used to lower triglyceride levels.

1. Clomiphene Compositions

[0018] The present invention is related to a composition comprising clomiphene. 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, which may lead to increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH). Clomiphene has 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. In men, these increased levels of

103

gonadotropins stimulate the Leydig cells of the testes and result in the production of higher testosterone levels.

[0019] Clomiphene is a mixture of two geometric isomers. *cis*, -Z-, clomiphene (*cis*-clomiphene or zuclomiphene) and *trans* -,E-, clomiphene, (*trans*-clomiphene or enclomiphene). *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. The isomers are also reported to have different *in vivo* half-life. 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. When administered to 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.

[0020] The *trans*-isomer of clomiphene 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 effect of clomiphene on ovulatory activity is attributed to both forms because 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.

[0021] 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 was 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.

104

[0022] The clomiphene composition may comprise *trans*-clomiphene or a pharmaceutically acceptable salt thereof. *Cis*-clomiphene or a pharmaceutically acceptable salt thereof may also be present in the composition. The ratio of *trans*-clomiphene to *cis*-clomiphene may be greater than 1/1 w/w. The ratio of *trans*-clomiphene to *cis*-clomiphene may also be greater than 71/29. The composition may comprise about 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% w/w of active ingredients of *trans*-clomiphene. Analogs of the *trans*- and *cis*- isomers of clomiphene such as those described in Ernst *et al.*, J. Pharmaceut. Sci. *65*:148 (1976) may also be used.

a. Formulations

[0023] The clomiphene composition may be formulated for oral, intravenous, subcutaneous, buccal, transmucosal, intrathecal, intradermal, intracisternal, or other routes of administration. 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 composition may also be in the form of sterile injectable solutions or emulsions for parenteral (including subcutaneous) use. The composition may also be in the form of patches, ointments, suppositories, inhalants, or lozenges. Other formulations for administration may also be appropriate and will be understood by one of skill in the art. Such pharmaceutical composition and unit dosage forms thereof may comprise additional pharmaceutically acceptable ingredients such as adjuvants, diluents, carriers, or excipients in conventional proportions.

[0024] 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.

2. Methods of Treatment

[0025] As used herein, "treatment" or "to treat" or "treating" when referring to protection of a mammal from a condition, means preventing, suppressing, repressing, or eliminating the condition. Preventing the condition involves administering the composition to a mammal

105

prior to onset of the condition. Suppressing the condition involves administering the composition to a mammal after induction of the condition but before its clinical appearance. Repressing the condition involves administering the composition to a mammal after clinical appearance of the condition such that the condition is reduced or maintained. Eliminating the condition involves administering the composition to a mammal after clinical appearance of the condition such that the mammal no longer suffers the condition.

[0026] Several studies have been conducted on the effects of clomiphene treatment for conditions other than anovulation described above. For example, studies have been 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. Shamis, *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.

[0027] 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)).

106

a. Hypogonadism

[0028] Hypogonadism may be treated by administering to a patient in need thereof an effective amount of a clomiphene composition. The condition associated with hypogonadism may include, but is not limited to, reduction of muscle mass, limitation of body performance capacity, reduction of bone density, reduction of libido, reduction of potency, benign prostatic hyperplasia, oligospermia or azoospermia, absence or regression of secondary sexual characteristics, reduction of muscle mass, fatigue, and depression.

b. Benign Prostate Hypertrophy (BPH)

[0029] BPH may be treated by administering to a patient in need thereof an effective amount of a clomiphene composition. Testosterone levels may be increased by administering the clomiphene composition while positively affecting the ratio of testosterone to DHT compared to testosterone supplements.

c. Prostate Cancer

[0030] Prostate cancer may be treated by administering an effective amount of a clomiphene composition. Administration of the compositions may decrease the ratio of testosterone to DHT compared to testosterone supplements. Preferably, in treating prostate cancer, the composition may be administered in a treatment regimen also including a chemotherapeutic. Exemplary chemotherapeutics include Taxotere® (docetaxel), Novantrone® (mitoxantrone hydrochloride), Emcyt® (estramustine sodium phosphate) doxorubicin, ketoconazole and vinblastine although other chemotherapeutics may also be used. In some cases, the chemotherapeutic may be administered closely in time to the dosage of the composition. In other cases the chemotherapeutic may be administered to the patient during the same period of time in which the patient is undergoing treatment with the clomiphene composition. In still other cases, treatment with the clomiphene composition may precede or follow treatment with the chemotherapeutic.

d. Elevated Triglycerides

[0031] Elevated triglycerides may be treated by administering an effective amount of a clomiphene composition. The patient may be a male or a female.

e. Methods of Administration

[0032] The clomiphene compositions may be administered orally. They may also be administered by the intravenous, subcutaneous, buccal, transmucosal, intrathecal,

intradermal, intracisternal or other routes of administration. Depending on the needs of the patient, and the judgment of the prescribing physician, DHT and serum testosterone levels may be measured and dosages may be altered to achieve beneficial levels of DHT and testosterone. Testosterone levels may also be measured for a sufficient increase in the serum testosterone levels to achieve the desired physiological results associated with normal testosterone described above. Likewise, triglyceride levels may be measured before and/or after administration to determine the appropriate dosage.

f. Dosages

[0033] In general, the clomiphene composition may be administered as part of a dosage regimen designed to give rise to serum testosterone levels that mimic or correspond to the normal secretary 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 between about 4 a.m. and noon. More specifically, the composition could be administered to give rise to peak serum testosterone levels at around 8 a.m.. Alternatively, the compositions may be administered to give rise to peak serum testosterone levels at any time of day deemed suitable by the patient and/or the prescribing physician. In another alternative, such as in some of the cases where the patient has elevated triglycerides, but also in other cases depending on the patient's condition and symptoms, the prescribing physician may wish to administer the compositions without regard to serum testosterone levels.

[0034] The clomiphene composition may be administered in one or more dosages from about one mg to about 200 mg (although the determination of optimal dosages is with the level of ordinary skill in the art).

[0035] The following Examples are meant to be illustrative of the invention and are not intended to limit the scope of the invention as set out in the appended claims.

EXAMPLE 1

Effects of Clomids on Serum Testosterone and Cholesterol in Male Baboons

[0036] Adult, male, Baboons were given 1.5 mg/kg of Clomid, Enclomid (*trans*-Clomid) or Zuclomid (*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).

108

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

[0037] 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 Zuclomid on day 6 ($p = 0.03$ and $p = 0.00002$ respectively) and compared to Zuclomid on day 12 ($p = 0.047$). Zuclomid 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 Zuclomid 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**

[0038] 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 Cholesterol levels

[0039] Treatment with Enclomid tended to decrease serum cholesterol and Zuclomid tended to increase the same parameter. Preliminary analysis indicated that the changes in cholesterol levels were not statistically significant and that the changes were within the normal range. Due to the observed trend for the two isomers to demonstrate opposite effects on cholesterol levels over a short period of time, further analysis was conducted.

[0040] Detailed analysis indicated that Enclomid resulted in an 8% decrease in serum cholesterol levels. Conversely, treatment with Zuclomid resulted in a 22% increase in serum

110

cholesterol levels. Treatment with Clomid resulted in a slight increase in serum cholesterol levels. The opposite effect of Enclomid and Zuclomid on serum cholesterol levels is not unexpected given that the isomers have, alternatively, estrogen agonist or antagonist activity. These results indicate that Enclomid may be used for treating patients with high cholesterol levels. These results also indicate that Enclomid may be more benign than Zuclomid with respect to serum cholesterol if used chronically for increasing testosterone levels.

3. Effects on Clinical Chemistry Parameters

[0041] 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 Zuclomid 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.

[0042] There were substantive effects on the red blood cell population with Enclomid and Zuclomid and on hematocrit with Zuclomid. 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 Zuclomid treatment, which did not increase total serum testosterone, demonstrated a statistical difference. Clearly, men in a clinical trial that uses Zuclomid should be monitored for the characteristics of their red blood cell population. Enclomid would be predicted to have less of an effect.

[0043] 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. 345 for 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

111

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.

[0044] 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 percent 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.

[0045] The increase in serum glucose with Clomid or Zuclomid 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.

[0046] 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 Zuclomid were within the normal range. AST is depressed in pregnancy; thus the action of an estrogen agonist such as Zuclomid in lowering the marginal AST level could be rationalized. Alkaline

112

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.

[0047] Osteoblastic activity and diseases of the bone are accompanied by high serum ALP values. ALP was not elevated following Zuclomid treatment and was decreased in value following Enclomid treatment. The trends would predict a more benign result for the use of Enclomid compared to Zuclomid.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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

113

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

[0052] 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 [^{3}H] 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.

[0053] 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.

EXAMPLE 3

Method for Decreasing Triglyceride Levels in Men Using *Trans*-clomiphene and Mixtures of *Trans*-clomiphene and *Cis*-clomiphene at Ratios Greater Than 1

[0054] Prior to administration of *trans*-clomiphene, blood samples are taken from subject males and triglyceride levels are measured using methodologies described for example in Cooper, *et al.* (Selected methods for the small clinical chemistry laboratory. W.R. Faulkner and S. Meites, eds. Am. Assoc. for Clin. Chem., Washington, D.C. Pages 165-174), which is incorporated herein by reference.

[0055] Patients are given daily dosages of 1.5 mg/kg clomiphene, wherein the ratio of *trans*-clomiphene to *cis*-clomiphene is greater than 1. The dosage amount and dosage frequency of clomiphene may be adjusted to achieve therapeutic levels of triglycerides in the patient by monitoring for triglyceride levels on different days of the treatment.

114

EXAMPLE 4

Method for Decreasing Triglyceride Levels in Women Using *Trans*-clomiphene and Mixtures of *Trans*-clomiphene and *Cis*-clomiphene at Ratios Greater Than 1

[0056] Prior to administration of *trans*-clomiphene, blood samples are taken from subject females and triglyceride levels are measured as in Example 3.

[0057] Patients are given daily dosages of 1.5 mg/kg clomiphene, wherein the ratio of *trans*-clomiphene to *cis*-clomiphene is greater than 1. The dosage amount and dosage frequency of clomiphene may be adjusted to achieve therapeutic levels of triglycerides in the patient by monitoring for triglyceride levels on different days of the treatment.

EXAMPLE 5

Comparison of Androxal™ to Androgel®

[0058] A placebo controlled challenge study was conducted at the Advanced Biological Research, Inc. (ABR) Clinical Research Center in Hackensack, New Jersey to compare orally administered Androxal™ (*trans*-clomiphene) to Androgel® (testosterone) in hypogonadal men. Androgel® (Solvay Pharmaceuticals, Inc.) consists of a cream that administers exogenous testosterone in a transdermal matrix.

[0059] The study enrolled 62 hypogonadal men with testosterone levels less than 300 ng/dl (normal 298-1034 ng/dl) that were randomized into 6 different arms, three doses of Androxal™ (12.5 mg, 25 mg, and 50 mg), placebo, and both high and low doses of Androgel®. Half of the men in each of the Androxal™ and placebo arms were randomized into cohorts that underwent in-clinic sessions on days 1 and 14 to determine pharmacokinetic parameters for Androxal™ as well as cyclical changes in testosterone. The placebo and Androxal™ doses were administered in a double blind fashion. The Androgel® cream was administered in an open label fashion. Half of the Androgel® patients underwent in-clinic sessions similar to the other patients in the study. Following the two week drug exposure patients were followed for an additional seven to ten days to determine the status of their testosterone levels.

[0060] There were no side effects noted in either the Androxal™ or Androgel® arms of the study that were different than placebo. Furthermore, all doses produced statistically significant changes in testosterone from baseline testosterone levels. The low, mid and high doses of Androxal™ achieved mean increases of 169, 247, and 294 ng/dl respectively, while those of Androgel® 5G, the lowest approved dose, and Androgel® 10G, the highest approved dose, produced changes from baseline that were 212 and 363 ng/dl. These values

115

were statistically indistinguishable from those changes achieved with Androxal™. This inability to show differences between Androxal™ and Androgel© appears to result from the highly variable results found when Androgel® is used. For example the 50 mg dose of Androxal™ raised mean total testosterone to 589±172 ng/dl after 15 days, a coefficient of variation (CV) of 29% and similar to the placebo group (36%). On the other hand Androgel® 5G and 10G yielded mean total testosterone values 473±289 ng/dl and 608±323 ng/dl, CV's of 61% and 53% respectively.

[0061] After 14 days of Androxal™ therapy all doses were associated with a total testosterone diurnal pattern similar to the placebo group, i.e. a morning peak, a mid-day trough and a rise overnight. Without being bound by theory, this pattern may be due to the mode of action of Androxal™, which appears to be mediated through effects on the hypothalamic-pituitary axis. The diurnal pattern for men on Androgel® was nearly flat. However, spikes in total testosterone for Androgel® were associated with dosing and often exceeded the normal high level of 1,034 ng/dl. Certain individuals on Androgel® 10G were able to achieve peak levels of total testosterone of over 2500 ng/dl.

[0062] The effect on serum dihydroxytestosterone (DHT) levels were also measured. Men on Androxal™ experienced a favorable shift in their DHT to total testosterone. For example men on the 50 mg dose of Androxal™ experienced a DHT/TT ratio of 0.83 as compared to the placebo group ratio of 1.07. By contrast the DHT/TT ratio for either of the Androgel® groups was >1.5. The results indicate that men on Androgel® were gaining DHT faster than total testosterone. Thus the normal levels of DHT was disrupted relative to testosterone in men on Androgel® therapy.

[0063] Results of clinical chemistry parameters also indicated, unexpectedly, that men on Androxal™ experienced a non-dose dependent reduction in triglycerides. The reduction in triglycerides averaged a decrease of 19.1% after two weeks of therapy. This compared to a 5.9% reduction for the placebo group and increases of 0.3% and 22% for the Androgel© 5G and 10G respectively.

[0064] Based on this study we infer a number of potential advantages for Androxal™ as a potential therapy. First, Androxal™ appears to raise total testosterone into the normal range in a highly consistent manner without abnormally high spikes in serum testosterone. Secondly, Androxal™ appears to improve the DHT/TT ratio, a potentially important consideration from the standpoint of prostate cancer. Thirdly, the maintenance of a normal diurnal pattern improves testosterone levels in a more natural fashion. Finally, the tendency to lower triglycerides may be an advantage to many men.

116

CLAIMS

1. A method for treating a condition selected from the group consisting of benign prostate hypertrophy, prostate cancer, elevated triglycerides, high cholesterol and hypogonadism comprising administering to a patient in need thereof a composition comprising *trans*-clomiphene or an analog thereof or pharmaceutically acceptable salt or solvate thereof and optionally one or more pharmaceutically acceptable diluents, adjuvants, carriers or excipients.
2. The method of claim 1, wherein the composition further comprises *cis*-clomiphene or an analog thereof or pharmaceutically acceptable salt or solvate thereof and wherein the ratio of *trans*-clomiphene to *cis*-clomiphene is greater than 71/29.
3. 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.
4. The method of claim 1, wherein the condition is selected from the group consisting of benign prostate hypertrophy, prostate cancer, and hypogonadism.
5. The method of claim 4, wherein the composition is formulated for oral administration.
6. The method of claim 4, wherein the composition is formulated for extended release.
7. The method of claim 4, wherein the composition is administered to give rise to peak serum testosterone levels at around 8 a.m.
8. The method of claim 4, wherein the condition is benign prostate hypertrophy.
9. The method of claim 4, wherein the condition is prostate cancer.
10. The method of claim 4, wherein the composition is administered in a dosage regimen further comprising a chemotherapeutic.
11. The method of claim 7 wherein the condition is hypogonadism and the patient suffers from a symptom selected from the group consisting of reduction of muscle mass, limitation of body performance capacity, reduction of bone density, reduction of libido, reduction of potency.
12. The method of claim 4 wherein the patient is a mammal.
13. The method of claim 4 wherein the patient is a human.
14. The method of claim 1 wherein the condition is selected from the group consisting of elevated triglycerides and high cholesterol.
15. The method of claim 12, wherein the patient is male.

117

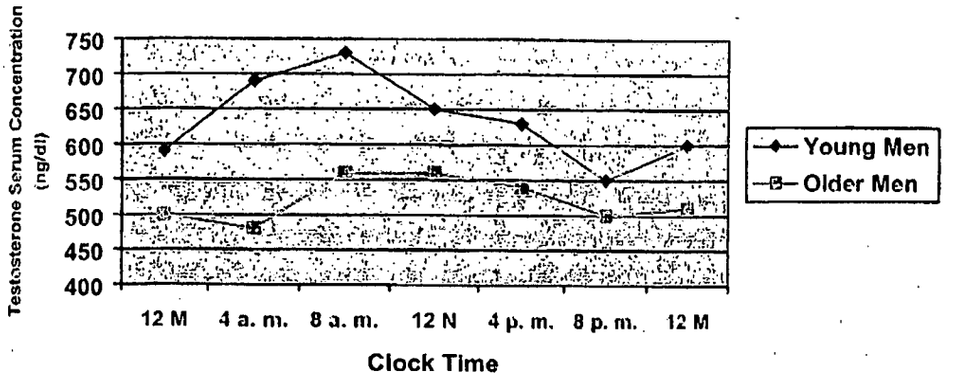
16. The method of claim 12, wherein the patient is female.

17. The method of claim 1, wherein the composition is formulated for oral administration.

18. The method of claim 1, wherein the composition is formulated for extended release.

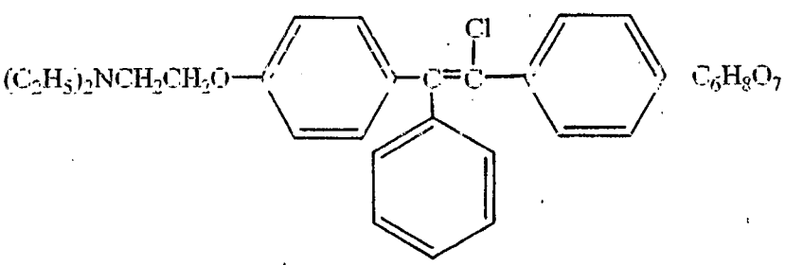
FIG. 1

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



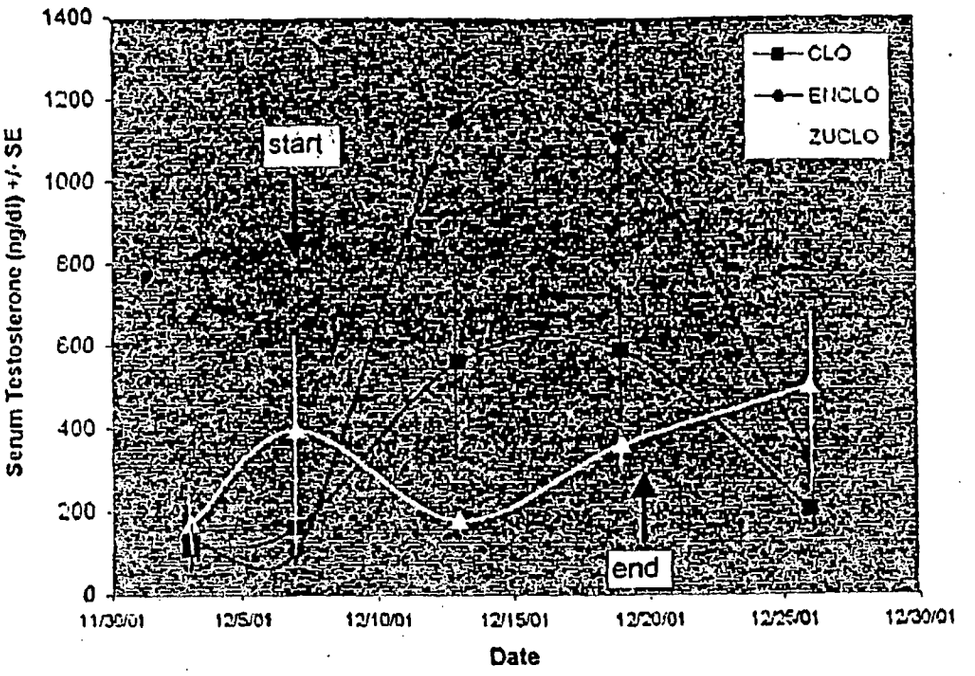
119

FIG. 2



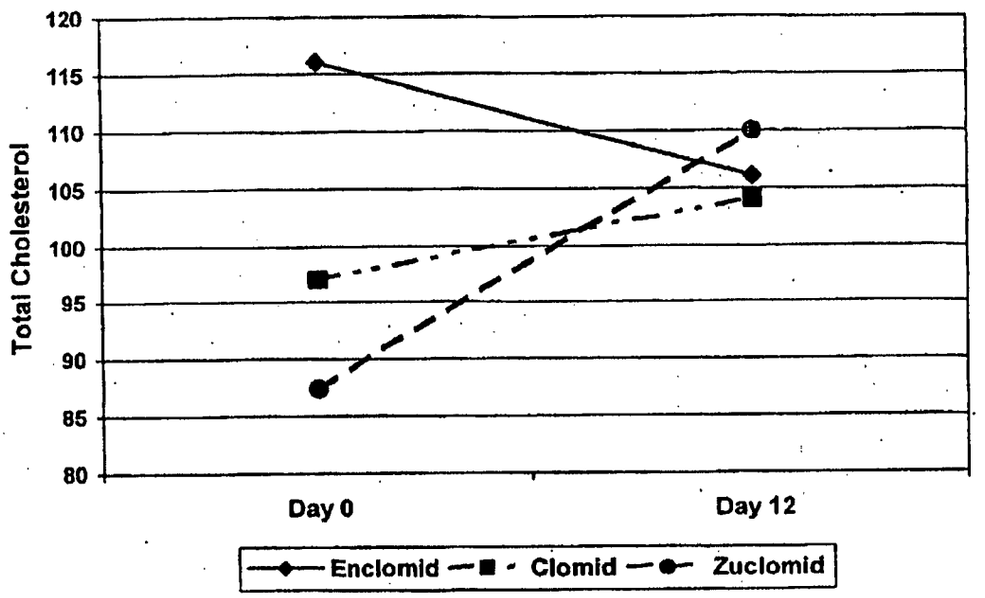
120

FIG. 3



121

FIG. 4



122

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/025000

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/138 A61P3/06 A61P15/08 A61P35/00

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WIEHLE R D ET AL: "Androxal(TM) (oral enclomiphene citrate) raises free and total serum testosterone in hypogonadal men: Comparison with Androgel 1%<(>R)" FERTILITY AND STERILITY, ELSEVIER SCIENCE INC, NEW YORK, NY, US, vol. 82, September 2004 (2004-09), page S87, XP004589295 ISSN: 0015-0282 the whole document ----- -/--	1,3-5,7, 12,13, 15,17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 2005	24/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Albrecht, S

Form PCT/ISA/210 (second sheet) (January 2004)

123

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/025000

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ANONYMOUS: "Zonagen Presents Data for Androxal in the Treatment of Hypogonadal Men and Data for Progenta as a Potential New Approach in the Treatment of Breast Cancer" INTERNET ARTICLE, 'Online! 1 November 2004 (2004-11-01), XP002352050 Retrieved from the Internet: URL:http://66.102.9.104/search?q=cache:hdwDDfR2kJwJ:www.salesandmarketingnetwork.com/news_release.php%3FID%3D2000275+androxal+triglycerides&hl=en> 'retrieved on 2005-10-28! paragraph '0002!	1,3-5,7, 12-15,17
X	US 2004/097597 A1 (PODOLSKI JOSEPH S ET AL) 20 May 2004 (2004-05-20) page 1, paragraph 9 page 1, paragraph 11 - page 2, paragraph 13 page 3, paragraph 27 - paragraph 31 examples 1-4	1-7, 11-15, 17,18
X	US 2002/120012 A1 (FISCH HARRY) 29 August 2002 (2002-08-29)	1,4-8, 12,13, 15,17,18
Y	page 1, paragraphs 6,10 page 1, paragraph 13 - page 2, paragraph 15 page 2, paragraphs 19,23	2,3
X	WO 01/34117 A (THE UNIVERSITY OF TENNESSEE RESEARCH CORPORATION; STEINER, MITCHELL, S) 17 May 2001 (2001-05-17) page 3, line 14 - page 4, line 29 page 5, line 27 - page 6, line 7 page 9, line 15 - page 10, line 18 page 11, line 15 - page 12, line 17 page 15, line 19 - page 16, line 12	1-10,12, 13,15, 17,18
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 12 May 1984 (1984-05-12), SHIDA, KEIZO ET AL: "Medical treatment of neoplasm with steroids and antisteroids" XP002352053 retrieved from STN Database accession no. 1981:115038	1,4-10, 12,13, 15,17,18
Y	abstract & IGAKU NO AYUMI , 115(9), 662-70 CODEN: IGAYAY; ISSN: 0367-7826, 1980,	2,3

-/--

124

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/025000

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JIANN BANG-PING ET AL: "Effect of clomiphene on Ca2+ movement in human prostate cancer cells" LIFE SCIENCES, vol. 70, no. 26, 17 May 2002 (2002-05-17), pages 3167-3178, XP002352051 ISSN: 0024-3205 page 3176, paragraph 4 - page 3177, paragraph 1	1-7,9, 10,12, 13,15, 17,18
Y	SINGH S P ET AL: "Changes in fructose & citric acid in accessory glands of reproduction of rats following long-term treatment with isomers of clomiphene citrate." INDIAN JOURNAL OF EXPERIMENTAL BIOLOGY. JAN 1973, vol. 11, no. 1, January 1973 (1973-01), pages 23-26, XP009056321 ISSN: 0019-5189 page 24, column 2, paragraph 2 page 24; table 1 page 25, column 1, paragraph 8 page 25, column 2, paragraph 1	2,3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/025000

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-18
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

126

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/025000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004097597 A1	20-05-2004	US 2004171697 A1	02-09-2004
US 2002120012 A1	29-08-2002	US 6391920 B1	21-05-2002
WO 0134117 A	17-05-2001	AU 782444 B2	28-07-2005
		AU 1588401 A	06-06-2001
		BG 106738 A	28-02-2003
		CA 2390295 A1	17-05-2001
		CN 1420765 A	28-05-2003
		CZ 20021763 A3	12-02-2003
		EP 1229903 A1	14-08-2002
		HR 20020422 A2	30-04-2004
		HU 0203304 A2	28-02-2003
		JP 2003513903 T	15-04-2003
		NO 20022221 A	28-06-2002
		PL 354726 A1	09-02-2004
		SK 8162002 A3	04-03-2003

Continuation of Box No. VII USE OF RESULTS OF EARLIER SEARCH, REFERENCE TO THAT SEARCH

☐ The ISA indicated in Box No. VII is requested to take into account the results of the earlier search(es) indicated below (*see also Notes to Box VII: use of results of more than two earlier searches*).

Filing date *(day/month/year)*	Application Number	Country *(or regional Office)*

☐ **Statement (Rule 4.12(ii))**: this international application is the same, or substantially the same, as the application in respect of which the earlier search was carried out except, where applicable, that it is filed in a different language.

☐ **Availability of documents**: the following documents are available to the ISA in a form and manner acceptable to it and therefore do not need to be submitted by the applicant to the ISA (Rule 12*bis*.1(f)):

- ☐ a copy of the results of the earlier search,*
- ☐ a copy of the earlier application,
- ☐ a translation of the earlier application into a language which is accepted by the ISA,
- ☐ a translation of the results of the earlier search into a language which is accepted by the ISA,
- ☐ a copy of any document cited in the results of the earlier search. *(If known, please indicate below the document(s) available to the ISA):*

☐ **Transmit copy of results of earlier search and other documents** *(where the earlier search **was not** carried out by the ISA indicated above but by the same Office as that which is acting as the receiving Office)*: the **receiving Office** is requested to prepare and transmit to the ISA (Rule 12*bis*.1(c)):

- ☐ a copy of the results of the earlier search,*
- ☐ a copy of the earlier application,
- ☐ a copy of any document cited in the results of the earlier search.

* Where the results of the earlier search are neither available from a digital library nor transmitted by the receiving Office, the applicant is required to submit them to the receiving Office (Rule 12*bis*.1(a)) (*See item 11. in the check-list and also Notes to Box No. VII*).

Filing date *(day/month/year)*	Application Number	Country *(or regional Office)*

☐ **Statement (Rule 4.12(ii))**: this international application is the same, or substantially the same, as the application in respect of which the earlier search was carried out except, where applicable, that it is filed in a different language.

☐ **Availability of documents**: the following documents are available to the ISA in a form and manner acceptable to it and therefore do not need to be submitted by the applicant to the ISA (Rule 12*bis*.1(f)):

- ☐ a copy of the results of the earlier search,*
- ☐ a copy of the earlier application,
- ☐ a translation of the earlier application into a language which is accepted by the ISA,
- ☐ a translation of the results of the earlier search into a language which is accepted by the ISA,
- ☐ a copy of any document cited in the results of the earlier search. *(If known, please indicate below the document(s) available to the ISA):*

☐ **Transmit copy of results of earlier search and other documents** *(where the earlier search **was not** carried out by the ISA indicated above but by the same Office as that which is acting as the receiving Office)*: the **receiving Office** is requested to prepare and transmit to the ISA (Rule 12*bis*.1(c)):

- ☐ a copy of the results of the earlier search,*
- ☐ a copy of the earlier application,
- ☐ a copy of any document cited in the results of the earlier search.

* Where the results of the earlier search are neither available from a digital library nor transmitted by the receiving Office, the applicant is required to submit them to the receiving Office (Rule 12*bis*.1(a)) (*See item 11. in the check-list and also Notes to Box No. VII*).

☐ Further earlier searches are indicated on a continuation sheet.

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 :	1
☒	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 :	1
☐	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 :	

Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to this international application:

REPROS THERAPEUTICS INC. is entitled to apply for and be granted a patent by virtue of the following:

an assignment from:

van AS, Andre, 1273 Robynwood Lane, West Chester, Pennsylvania 19380, United States of America

to REPROS THERAPEUTICS INC., dated 24 October 2007 (24.10.2007)

This declaration is made for the purposes of all designations, except for the designation of the United States of America.

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

Box No. VIII (iii) DECLARATION: ENTITLEMENT TO CLAIM PRIORITY

The declaration must conform to the standardized wording provided for in Section 213; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (iii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51*bis*.1(a)(iii)):

REPROS THERAPEUTICS INC. is entitled to claim priority of earlier application number, U.S. Provisional Application No. 60/980,334, filed October 16, 2007 by virtue of the following:

an assignment from:

van AS, Andre, 1273 Robynwood Lane, West Chester, Pennsylvania 19380, United States of America

to REPROS THERAPEUTICS INC., dated 24 October 2007 (24.10.2007)

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (iii)".

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application **contains**:

(a) **on paper**, the following number of sheets:

request (including declaration and supplemental sheets)	:	8
description (excluding sequence listing and/or tables related thereto)	:	35
claims	:	2
abstract	:	1
drawings	:	10
Sub-total number of sheets	:	56
sequence listing	:	
tables related thereto	:	
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)		
Total number of sheets	:	56

(b) ☐ **only in electronic form** (Section 801(a)(i))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

(c) ☐ **also in electronic form** (Section 801(a)(ii))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listing: . . . . . .
- ☐ tables related thereto: . . . . . .

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

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)*:

		Number of items
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 electronic form *(indicate type and number of carriers)*	
(i) ☐	copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:
(ii) ☐	*(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:
(iii) ☐	together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column	:
10. ☐	tables in electronic form related to sequence listing *(indicate type and number of carriers)*	
(i) ☐	copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	:
(ii) ☐	*(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	:
(iii) ☐	together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:
11. ☐	copy of results of earlier search(es) (Rule 12*bis*.1(a))	:
12. ☒	other *(specify)*: Transmittal Letter	:

Figure of the drawings which should accompany the abstract: 3

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).

David W. Clough, Ph.D. , Registration No. 36,107
Attorney for Applicant

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ 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):	☐ not received:
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:

131

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's file reference 07189.0003.00PC09

Applicant
REPROS THERAPEUTICS INC.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . US 300 [T]

2. SEARCH FEE . . . . . US 2665 [S]

International search to be carried out by EP

(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 FILING FEE

Where items (b) and/or (c) of Box No. IX apply, enter **Sub-total number of sheets** } 56
Where items (b) and (c) of Box No. IX do not apply, enter **Total number of sheets** }

[i1] first 30 sheets . . . . . US 1237 [i1]

[i2] 26 (number of sheets in excess of 30) x 15 (fee per sheet) = US 390 [i2]

[i3] additional component (only if a sequence listing and/or tables related thereto are filed in electronic form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):

400 x _____ (fee per sheet) = _____ [i3]

Add amounts entered at i1, i2 and i3 and enter total at I . . . . US 1627 [I]

(Applicants from certain States are entitled to a reduction of 90% of the international filing fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 10% of the international filing fee.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . [P]

5. FEE FOR RESTORATION OF THE RIGHT OF PRIORITY *(if applicable)* . [RP]

6. FEE FOR EARLIER SEARCH DOCUMENTS *(if applicable)* . . . . . [ES]

7. TOTAL FEES PAYABLE . . . . . US 4592
Add amounts entered at T, S, I, P, RP and ES, and enter total in the TOTAL box — TOTAL

MODE OF PAYMENT *(Not all modes of payment may be available at all receiving Offices)*

- [X] 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)

Receiving Office: RO/ US

Deposit Account No.: 08-3038

Date: September 5, 2008

Name: David W. Clough, Ph.D.-36,107

Signature: [signature]

- [X] Authorization to charge the total fees indicated above.
- [X] *(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.
- [X] Authorization to charge the fee for priority document.

PATENT COOPERATION TREATY PCT/US2008/075433

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

CLOUGH, David, W.
Howrey Llp
Docketing Department
2941 Fairview Park Drive, Suite 200
Falls Church, VA 22042-9922
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 15 October 2008 (15.10.2008)	
Applicant's or agent's file reference 07189.0003.00PC09	**IMPORTANT NOTIFICATION**
International application No. PCT/US2008/075433	International filing date *(day/month/year)* 05 September 2008 (05.09.2008)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 16 October 2007 (16.10.2007)
Applicant REPROS THERAPEUTICS INC. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "IB", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)* **An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
16 October 2007 (16.10.2007)	60/980,334	US	27 September 2008 (27.09.2008)

RECEIVED 11 NOV 2008

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Agnes Wittmann-Regis e-mail PT06.PCT@WIPO.INT Telephone No. +41 22 338 74 06

Form PCT/IB/304 (October 2005) 1/DTPFI39K0

133

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 829 534 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
05.09.2007 Bulletin 2007/36

(51) Int Cl.:
A61K 31/00 *(2006.01)* ***A61P 3/00*** *(2006.01)*
A61P 3/06 *(2006.01)* ***A61P 3/04*** *(2006.01)*

(21) Application number: **06384003.7**

(22) Date of filing: **02.03.2006**

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR
Designated Extension States:
AL BA HR MK YU

(71) Applicant: **LABORATORIOS DEL DR. ESTEVE, S.A.**
08041 Barcelona (ES)

(72) Inventors:
- **Buschmann, Helmut H.**
  08960 Sant Just Desvern (ES)
- **Vela Hernandez, Jose Miguel**
  08041 Barcelona (ES)

(74) Representative: **Peters, Hajo**
Bosch Graf von Stosch Jehle
Patentanwaltsgesellschaft mbH
Flüggenstrasse 13
80639 München (DE)

(54) Use of compounds binding to the sigma receptor for the treatment of metabolic syndrome

(57) The present invention refers to the use of compounds binding to the sigma receptor for the treatment of metabolic syndrome.

EP 1 829 534 A1

Description

Field of the invention

[0001] The present invention refers to the use of compounds binding to the sigma receptor for the treatment of metabolic syndrome, especially hyperlipidemias, in particular hypertriglyceridemias and the prevention or the prophylaxis of the symptoms of metabolic syndrome, especially hyperlipidemias, in particular hypertriglyceridemias.

Background of the invention

[0002] The treatment of metabolic syndrome is of great importance in medicine. The metabolic syndrome is a widespread disease, particularly in the United States and Europe. Based on survey data from 1988 to 1994 and 2000 census data, the American Center for Disease Control and Prevention estimates that 47 million people in the US have metabolic syndrom. There is currenily a world-wide need for treatment of this syndrome as it is identified as heightening the risk of cardiovascular mortality.

[0003] Consequently, it was an object of the present invention to provide medicaments, which are suitable for the treatment of metabolic syndrome.

[0004] Therefore, it was the underlying problem solved by this invention to find new ways of treating metabolic syndrome.

[0005] So, the main object of this invention is the use of a compound binding to the sigma receptor in the production of a medicament for the treatment of metabolic syndrome.

[0006] The metabolic syndrome and definitions thereof are described in detail by Eckel et al., The Lancet, Vol. 365 (2005), 1415-1428, included herewith by reference. One of the respective definitions was established by the WHO in 1998 (as described in Alberti et al., Diabet. Med. 1998, 15, pages 539-53, the respective description thereof is herewith incorporated by reference and forms part of the present disclosure). The other, more widely accepted, definition of the metabolic syndrome was established by the Adult Treatment Panel (ATP III) of the US National Cholesterol Education Program (NCEP) in 2001, as described in JAMA 2001; 285; 2486-97, the respective description thereof is herewith incorporated by reference and forms part of the present disclosure.

[0007] The metabolic syndrome is characterized by an interaction of several physiological parameters such as triglycerides, lipids, blood pressure, glucose levels and insuline levels. Thus it includes especially hyperlipidemias and hypertriglyceridemia.

[0008] Even though obesity may play a critical role in the development of metabolic syndrome, many of its aspects are weight independent, especially some lipid parameters. Especially the positive influence on the weight independent aspects of the metabolic syndrome (see e.g. Fagotto and Pasquali, The Lancet, Vol. 365 (2005), 1363, 1364, included herewith by reference) like some blood parameters, especially lipid parameters is one of the major and surprising advantages of the inventively used compounds binding to the sigma receptor.

[0009] Hypertriglyceridemia can be categorized by the Fredrickson classification of lipid disorders (Fredrickson, 1971; Beaumont et al., 1970). All hyperlipidemias (types I, IIb, III, IV and V) except type IIa are characterized by elevated triglyceride levels. Thus, the present invention claims the use of sigma-1 receptor antagonists for treating the following types of hypertriglyceridemias:

- **Type I:** It is characterized by severe elevations in chylomicrons and elevated triglycerides. Because chylomicrons also contain a small amount of cholesterol, serum cholesterol levels also are quite high.
- **Type IIb:** It is the classic mixed hyperlipidemia (high cholesterol and triglycerides) caused by elevations in both low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL).
- **Type III:** It is also known as dysbetalipoproteinemia, remnant removal disease, or broad-beta disease. Typically, these patients have elevated total cholesterol and triglyceride levels and are easily confused with patients with type IIb hyperlipidemia. Patients with type III hyperlipidemia have elevations in intermediate-density lipoprotein (IDL), a VLDL remnant.
- **Type IV:** It is characterized by abnormal elevations of VLDL and triglycerides. Serum cholesterol levels are normal.
- **Type V:** It is the combination of types I and IV (elevations of both chylomicrons and VLDL). Serum cholesterol levels always are elevated, but the LDL cholesterol levels are normal. Given the rarity of type I disease, when elevated triglycerides are noted, the most likely cause is type V hyperlipidemia.

[0010] This/these compound/s may be in neutral form, the form of a base or acid, in the form of a salt, preferably a physiologically acceptable salt, in the form of a solvate or of a polymorph and/or in the form of in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable mixing ratio.

135

[0011] While working on compounds binding to the sigma receptor and with models like knock-out mice it was surprisingly found out that metabolic syndrome is connected to the sigma receptor so that compounds binding to the sigma receptor were acting on metabolic syndrome with a high potency.

[0012] The term "treatment" as used in the present application encompasses prevention, amelioration and/or complete recovery from the disease. Said term also includes the prevention, amelioration and/or complete recovery of one or more symptoms associated with the disease.

[0013] "The sigma receptor/s" as used in this application is/are well known and defined using the following citation: This binding site represents a typical protein different from opioid, NMDA, dopaminergic, and other known neurotransmitter or hormone receptor families (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)). Pharmacological data based on ligand binding studies, anatomical distribution and biochemical features distinguish at least two subtypes of σ receptors (R. Quiron et al., Trends Pharmacol. Sci. 13, 85-86 (1992); M.L.Leitner, Eur. J. Pharmacol. 259, 65-69 (1994); S.B. Hellewell and W.D. Bowen; Brain Res. 527, 244-253 (1990)); (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)). The protein sequence of sigma receptors (Sigma 1 (σ1) and Sigma 2 (σ2)) is known (e.g. Prasad, P.D. et al., J. Neurochem. 70 (2), 443-451 (1998)) and they show a very high affinity for e.g. pentazocine.

[0014] "Compound/s binding to the sigma receptor" or "sigma ligand" as used in this application is/are defined as having an IC_{50} value of ≤5000 nM, more preferably ≤1000 nM, more preferably ≤500 nM. More preferably, the IC_{50} value is ≤50 nM. More preferably, the IC_{50} value is ≤100 nM. Most preferably, the IC_{50} value is ≤ 50 nM. Additionally, the wording "Compound/s binding to the sigma receptor", as used in the present application is defined as having at least ≥50% displacement using 10 mM radioligand specific for the sigma receptor (e.g. preferably ^{1}H-pentazocine) whereby the sigma receptor may be any sigma receptor subtype. Preferably, said compounds bind to the sigma-1 receptor subtype.

[0015] Compounds binding to the sigma receptor generally also known as sigma ligands are well known in the art with many of them falling under the definition for "Compound/s binding to the sigma receptor" set up above. Still even though there are many uses known for sigma ligands such as antipsychotic drugs, anxiolytics, antidepressants, the treatment of stroke, antiepileptic drugs and many other indications there is nowhere any mentioning of these compounds being useful against metabolic syndrome.

[0016] Compounds binding to the sigma receptor known in the art and matching the criteria of sigma ligand (i.e. having an IC_{50} ≤ 5000 nM) as mentioned above, are listed below. Some of these compounds may bind to the sigma-1 and/or the sigma-2 receptor. Preferably, these compounds are in form of a salt, a base or an acid. Also preferably, the salts/bases/acids indicated in the list are to be understood as being exemplary and therefore may respresent any salt, base or acid of the compound.

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
(+)-HIMBACINE	(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester
(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester	(S)-Methamphetamine HCl
[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 1-(3-Benzyloxy-4-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester	[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 2-(Tert-Butoxycarbonyl-Naphthalen-1-Ylmethyl-Amino)-Ethyl Ester
[4-(4-Ethy)-3,5-Dimethyl-Pyrazol-1-Yl)- Phenyl]-[4-(3-Phenyl-Allyl)-Piperazin-1- Yl]-Methanone	1-(1,2-Diphenylethyl)Piperidine Maleate, (+/-)
1-(1-Naphthyl)Piperazine HCl	1-(3-Chlorophenyl)Piperazine HCl
1-(4-Bromo-Benzenesulfonyl)-4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine	2-(2-{[1-(3-Chloro-Benzyl)-Pyrrolidin-3-Yl]-Methyl-Carbamoyl)-3-Methyl-Propyl)-4,6-Dimethyl-Benzoic Acid
2-Chloro-11-(4-Methylpiperazino)Dibenz[B, F]Oxepin Maleate	3,3'-Diethylthiacarbocyanine Iodide
3-Mercapto-2-Methylpropanoic Acid 1,2-Diphenylethylamine Salt	3-Quinuclidinyl Benzilate
3-Tropanyl-3,5-Dichlorobenzoate	3-Tropanyl-Indole-3-Carboxylate HCl
4-(1 H-Indol-4-Yl)-Piperazine-1-Carboxylic Acid 2-(5-Bromo-2-Ethoxy-Phenylamino)-Cyclohexylmethyl Ester	4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine-1-Carboxylic Acid 2-Thiophen-2-Yl-Ethyl Ester

136

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
4-(3,5-Dimethoxy-Phenyl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-Benzyl)-Piperidin-2-Ylmethyl Ester	4-(3-Nitro-5-Sulfamoyl-Thiophen-2-Yl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-5-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-(5-Trifluoromethyl-Pyridin-2-Yl)-Piperazine-1-Carboxylic Acid Pent-2-Ynyl Ester
4,4'-Bis[4-(P-Chlorophenyl)-4-Hydroxypiperidino] Butyrophenone	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-Trifluoromethoxy-Benzenesulfonamide	4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-Yl)-Propyl]-Piperazin-1-Yl)-Ethyl Ester	4-Methoxy-N-[1-(7-Methoxy-Benzo[1,3]Dioxol-5-Ylmethyl)-Pyrrolidin-3-Yl]-Benzenesulfonamide
5-(N-Ethyl-N-Isopropyl)-Amiloride	7-Hydroxy-DPAT HBr, (±)-
8-Hydroxy-DPAT HBr, (R)-(+)-	8-Hydroxy-DPAT HBr, S(-)-
9-[4-(([4'-(trifluoromethyl)-1,1 1'-biphenyl-2-yl]carbonyl} amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide	Acepromazine Maleate
Acetophenazine Maleate	Acrinol
Ajmaline	Alaproclate HCl
Aloe-Emodin	Alprenolol D-Tartrate Salt Hydrate
Alprenolol HCl	AMI-193
Aminobenztropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Amoxapine	Anileridine HCl
Anisotropine Methylbromide	Anpirtoline
ARC 239 DIHCl	Astemizole
Auramine O HCl	Azaperone
Azatadine Maleate	Azelastine HCl
Bamethan sulfate	BD 1008 DiHBr
BD-1047	BD-1063
Benextramine TetraHCl	Benfluorex HCl
Benidipine HCl	Benoxathian HCl
Benoxinate HCl	Benperidol
Benproperine Phosphate	Benzododecinium bromide
Benzphetamine HCl	Benztropine Mesylate
Benzydamine HCl	Bephenium Hydroxynaphthoate
Bepridil HCl	Berberine chloride
Betaxolol HCl	Bifemelane
BMY 7378 DIHCl	Bopindolol Malonate
BP 554 Maleate	Bromhexine HCl

137

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
Bromodiphenhydramine HCl	Bromperidol
Brompheniramine Maleate	BTCP HCl
Bucllzine HCl	Buflomedil HCl
Bupropion HCl	Buspirone HCl
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Butoconazole Nitrate
BW 723C86 HCl	Carbetapentane Citrate
Carbinoxamine Maleate	Carpipramine DIHCl DIH2O
Carvedilol	Cephaplrin Benzathine
CGS-12066A Maleate	Chloroprocaine HCl
Chloroquine Phosphate	Chlorpheniramine Maleate
Chlorphenoxamine HCl	Chlorpromazine HCl
Chlorprothixene	Cinanserin HCl
Cinnarizine	Cirazoline HCl
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DIHCl
Cisapride Hydrate	Citalopram HBr
Clebopride Maleate Salt	Clemastine Fumarate
Clemizole HCl	Clenbuterol HCl
Clidinium Bromide	Clobenpropit 2HBr
Clofazimine	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Clozapine
CONESSINE	Cyclizine
Cyclobenzaprine HCl	Cycloheximide
Cyproheptadine HCl	Darrow Red HCl
Demecarium Bromide	Denatonium Benzoate
Deptropine Citrate	Desloratadine
Dexbrompheniramine Maleate	Dexchlorpheniramine Maleate
Dexfenfluramine HCl	Dibucaine HCl
Dicyclomine HCl	Diethylpropion HCl
Dimethisoquin HCl	Dimetindene Maleate
Diphemanil Methylsulfate	Diphenidol HCl
Diphenoxylate HCl	Diphenylpyraline HCl
Dipropyldopamine HBr	Dobutamine HCl
Donepezil HCl	Doxepin HCl
Droperidol	Duloxetine

138

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
Dyclonine HCl	Ebastine
Econazole Nitrate	Epinastine HCl
Etaverine HCl	Ethopropazine HCl
Etiolpride HCl, S(-)-	Etofenamate
Etonitazenyl Isothiocyanate	Femoxetine HCl
Fenfluramine HCl	Fentanyl Citrate
Fenticonazole Nitrate	Fipexide HCl
Flavoxate HCl	Flunarizine diHCl
Fluoxetine Related Compound B	Fluperlapine
Fluphenazine Decanoate DiHCl	Fluphenazine Enanthate DiHCl
Fluphenazine HCl	Fluphenazine N-Mustard DiHCl
Flurazepam Related Compound C	Fluspirilene
Fluvoxamine Maleate	GBR 12783 DiHCl
GBR 12909 DiHCl	GBR 13069 DiHCl
GBR-12935 DiHCl	GR 89696 Fumarate
Guanabenz Acetate	Guanadrel Sulfate
Guanethidine Sulfate	Halofantrine HCl
Haloperidol	HEAT HCl
Hexylcaine HCl	Hycanthone
Hydroxychloroquine Sulfate	Hydroxyzine HCl
Hyoscyamine Sulfate	IBZM, S(-)-
ICI-199,441 HCl	Ifenprodil Tartrate
Imipramine HCl	Indatraline HCl
Iofetamine HCl	Irinotecan HCl
Isamoltane Hemifumarate	Isopromethazine HCl
Isoxsuprine HCl	Ketanserin L-Tartrate
Ketoconazole	Ketotifen Fumarate Salt
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl
Labetalol HCl	Levetimide HCl, R(-)
Levobunolol HCl	Lidoflazine
Lisuride Hydrogen Maleate, R(+)-	Lobeline HCl
Iomerizine diHCl	Loperamide HCl
Loxapine Succinate	LY-53,857 Maleate
Maprotiline HCl	Mazindol
MDL 12,330A HCl	Mebhydroline 1,5-naphthalendisulfonate Salt
Meclizine HCl	Mefloquine HCl
Meprylcaine HCl	Mesoridazine Besylate

139

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
Metaphit Methanesulfonate	Metergoline
Methantheline Bromide	Methdilazine
Methiothepin Mesylate	Methixene HCl
Methoctramine	Methotrimeprazine Maleate
Methylene Violet 3Rax HCl	Metipranolol
Mexiletine HCl	Mianserin HCl
Miconazole	ML-9 HCl
Morantel Hydrogen L-Tartrate	MR 16728 HCl
N-(2-Chloroethyl)-N-Ethyl-2-Bromobenzylamine HCl	N'-[2-(Benzo[1,2,5]Thiadiazole-4-Sulfonylamino)-Acetyl]-Hydrazinecarboxylic Acid 2-(2-{4-[(4-Chloro-Phenyl)-Phenyl-Methyl]-Piperazin-1-Yl}-Ethoxy)-Ethyl Ester
Nafronyl Oxalate Salt	Naftifine
Naftopidil diHCl	Naltriben Mesylate
NAN-190 HBr	NE-100
Nefazodone	Nefopam HCl
Nicardipine HCl	Nicergoline
Niguldipine HCl, (+/-)-	Nisoxetine HCl
Nortriptyline HCl	Nylidrin HCl
Octoclothepin Maleate, (±)-	Orphenadrine Citrate
Oxamniquine	Oxamniquine Related Compound A
Oxamniquine Related Compound B	Oxatomide
Oxiconazole Nitrate	Oxybutynin HCl
Panaxatriol	PAPP
Paroxetine	Paxilline
p-Chlorobenzhydrylpiperazine	Penbutolol Sulfate
Pentamidine Isethionate	Pentazocine, (±)-
Pergolide Methanesulfonate	Perhexiline Maleate Salt
Perospirone	Perphenazine
Perphenazine Sulfoxide	Phenamil Methanesulfonate
Phencyclidine HCl	Phenoxafranin HCl
Phenoxybenzamine HCl	Phenyltoloxamine Citrate Salt
Piboserod	Pimozide
Pinacyanol Chloride	Pindobind, (+/-)-
Piperacetazine	Piperazine-1,4-Dicarboxylic Acid Benzyl Ester 2-[4-(4-Dimethylamino-Benzyl)-Piperazin-1-Yl]-Ethyl Ester
Piperidolate HCl	Pirenperone
PPHT HCl, (±)-	Pramoxine HCl

140

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
Prenylamine Lactate Salt	Pridinol Methanesulfonate Salt
Prochlorperazine Maleate	Procyclidine HCl
Proflavine Hemisulfate Salt	Progesterone
Promazine HCl	Promethazine HCl
Propafenone HCl	Proparacaine HCl
Propericyazine	Proplomazine
Propranolol HCl	Protokylol
Protriptyline HCl	Pyrilamine Maleate
Pyrimethamine	Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester
Pyrvinium Pamoate	Quetiapine Fumarate
Quinacrine HCl	Quinaldine Red
Quipazine Dimaleate	Quipazine, 6-Nitro-, Maleate
Raloxifene	Rimantadine HCl
Risperidone	Ritanserin
Ritodrine HCl	RS 23597-190 HCl
RS 67333 HCl	RS 67506 HCl
Safranin O HCl	Salmeterol
SB203186	SCH-23390 HCl, R(+)-
Sertaconazole Nitrate	Sertindole
Sertraline	Sibutramine HCl
SKF-525A HCl	SKF-96365 HCl
SNC 121	Spiperone HCl
Sufentanil	T-226296
Tamoxifen Citrate	Tamsulosin HCl
Tegaserod Maleate	Terbinafine HCl
Teroconazole	Terfenadine
Terfenadine Related Compound A	Tetracaine HCl
Tetrindole Mesylate	Thiethylperazine Malate
Thioperamide Maleate	Thioproperazine
Thioridazine	Thiothixene
Thiothixene, (E)-	Thonzonium Bromide
Tioconazole Related Compound A	TMB-8 HCl
Tolterodine L-Tartrate	Toremifene Citrate
Tramazoline HCl	Trans-U-50488 Methanesulfonate, (±)-
Trazodone HCl	Tridihexethyl Chloride
Trifluoperazine HCl	Trifluperidol HCl
Triflupromazine HCl	Trihexyphenidyl HCl

141

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
Trimebutine	Trimeprazine Hemi-L-Tartrate
Trimipramine Maleate	Tripelennamine HCl
Triprolidine HCl	Triprolidine HCl Z Isomer
Tropanyl 3,5-Dimethylbenzoate	Tropine 2-(4-Chlorophenoxy)Butanoate, Maleate
U-50488 HCl, (-)-	U-62066
UH 232 Maleate, (+)-	Vecuronium Bromide
Verapamil HCl	Verapamil Related Compound B
Vesamicol HCl	Vinpocetine
W-7 HCl	WB-4101 HCl
Xylazine	Xylometazoline HCl

[0017] Unless otherwise stated, the compounds of the invention are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon or ^{15}N-enriched nitrogen are within the scope of this invention.

[0018] A preferred embodiment of the invention includes the use of at least one compound binding to the sigma receptor for the production of a medicament for the treatment of elevated triglyceride levels. Also preferred is the use of at least one compound binding to the sigma receptor for the production of a medicament for treatment of chylomicronemia, hyperlipoproteinemia, hyperlipidemia (especially mixed hyperlipidemia), hypercholesterolemia, lipoprotein disorders and dysbetalipoproteinemia. An especially preferred embodiment is drawn to the use of at least one compound binding to the sigma receptor for the production of a medicament for the treatment hypertriglyceridemia including both the sporadic and familial disorder (inherited hypertriglyceridemia).
and dysbetalipoproteinemia

[0019] Generally the use of compounds binding to the sigma-1 receptor antagonist to produce a medicament for the treatment of metabolic syndrome does not have to cover the treatment of all its aspects. Thus a treatment reducing plasma levels of triglycerides for treating excess triglycerides in plasma (hypertriglyceridemia), does not necessarily include treatment of plasma cholesterol and glucose levels, that may be also concomitantly be elevated (hypercholesterolemia and hyperglycemia, respectively) in metabolic syndrome.

[0020] In addition the use of sigma-1 receptor antagonists to produce a medicament for the treatment of hypertriglyceridemia includes also treatment of elevated levels of triglycerides, which exist as a consequence of an abnormal diet or diseases such as diabetes, obesity or any disease or disturbance causing elevations in triglyceride levels.

[0021] Finally the use of sigma-1 receptor antagonists to produce a medicament for the treatment of hypertriglyceridemia includes also the treatment of different pathological conditions involving elevated triglyceride levels, such as chylomicronemia, hyperlipoproteinemia, mixed hyperlipidemia and dysbetalipoproteinemia.

[0022] The term "salt" is to be understood as meaning any form of the active compound according to the invention in which this assumes an ionic form or is charged and is coupled with a counter-ion (a cation or anion) or is in solution. By this are also to be understood complexes of the active compound with other molecules and ions, in particular complexes which are complexed via ionic interactions.

[0023] The term "physiologically acceptable salt" is understood in particular, in the context of this invention, as salt (as defined above) formed either with a physiologically tolerated acid, that is to say salts of the particular active compound with inorganic or organic acids which are physiologically tolerated - especially if used on humans and/or mammals - or with at least one, preferably inorganic, cation which are physiologically tolerated - especially if used on humans and/or mammals. Examples of physiologically tolerated salts of particular acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, hydrobromide, monohydrobromide, monohydrochloride or hydrochloride, methiodide, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, hippuric acid picric acid and/or aspartic acid. Examples of physiologically tolerated salts of particular bases are salts of alkali metals and alkaline earth metals and with NH_4.

[0024] The term "solvate" according to this invention is to be understood as meaning any form of the active compound according to the invention in which this compound has attached to it via non-covalent binding another molecule (most likely a polar solvent) especially including hydrates and alcoholates, e.g. methanolate.

142

[0025] In a very preferred embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as an antagonist.

[0026] In a very preferred embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as an inverse agonist.

[0027] In a very preferred embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as a partial antagonist.

[0028] In another possible embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as an agonist.

[0029] In another embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as a mixed agonist/antagonist, a partial agonist or a partial antagonist.

[0030] In another embodiment of the invention the sigma receptor to which the "compound binding to the sigma receptor" is binding to is the sigma-1 receptor. Under this embodiment "Compound/s binding to the sigma receptor" as used in this application is/are defined as having an IC50 value ≤ 5000 nM, more preferably ≤ 1000nM, more preferably ≤500 nM. More preferably, the IC_{50} value is ≤ 250 nM. More preferably, the IC_{50} value is ≤ 100 nM. Most preferably, the IC_{50} value is ≤ 50 nM. Additionally, the wording "Compound/s binding to the sigma receptor", as used in the present application is defined as having at least ≥ 50% displacement using 10 nM radioligand specific for the sigma receptor (e.g. preferably ^{3}H-pentazocine) whereby the sigma recepor may be any sigma receptor subtype.

[0031] In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of ≤1000 nM.

[0032] In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of ≤500 nM.

[0033] In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of ≤250 nM.

[0034] In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of ≤100 nM.

[0035] In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of ≤50 nM.

[0036] Most preferably, "compounds highly specific for the sigma receptor" are defined as being "Compound/s binding to the sigma receptor", as defined above, having an IC_{50} value of ≤100 nM.

[0037] In a highly preferred embodiment of the present invention, the compound binding to the sigma receptor as defined above, is binding to the sigma-1 receptor subtype.

[0038] In another possible aspect of the invention, the compound binding to the sigma receptor as defined above, may bind to the sigma-2 receptor subtype.

[0039] In human therapeutics, the dose administered can be quite low depending on the route of administration and is well known in the art because sigma compounds are known therapeutics.

[0040] The daily dosage for humans and animals may vary depending on factors that have their basis in the respective species or other factors, such as age, sex, weight or degree of illness and so forth. The daily dosage for humans may preferably be in the range from1 to 2000, preferably 1 to 1500, more preferably 1 to 1000 milligrams of active substance to be administered during one or several intakes per day.

[0041] Any medicament according to the invention contains the active ingredient as well as optionally at least one auxiliary material and/or additive and/or optionally another active ingredient.

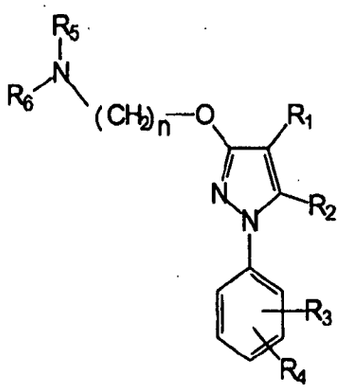
[0042] The auxiliary material and/or additive can be specifically selected from conserving agents, emulsifiers and/or carriers for parenteral application. The selection of these auxiliary materials and/or additives and of the amounts to be used depends upon how the pharmaceutical composition is to be applied. Examples include here especially parenteral like intravenous subcutaneous or intramuscular application formulations but which could also be used for other administration routes.

[0043] Routes of administration preferably include intramuscular injection, intraveneous injection, subcutaneous injection, sublingual, bucal, patch through skin, oral ingestion, implantable osmotic pump, collagen implants, aerosols or suppository.

[0044] Included in this invention are especially also methods of treatments of a patient or a mammal, including men, suffering from metabolic syndrome using compounds binding to the sigma receptor.

[0045] In another embodiment the use according to the invention; especially for the production of a medicament for the treatment of lipoprotein disorders; of a compound according to formula II

143



(II)

wherein

R_1 is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_8$ - $C=NR_8$, -CN, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_2 is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, -CN, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$,$-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_3 and R_4 are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, -CN, $-OR_8$,$-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, -NO2, $-N=CR_8R_9$, or halogen, or together they form a fused ring system,

R_5 and R_6 are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, -CN, $-OR_8$, - $OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen; together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted heterocyclyl group;

n is selected from 1, 2, 3, 4, 5, 6, 7 or 8;

t is 1,2 or 3;

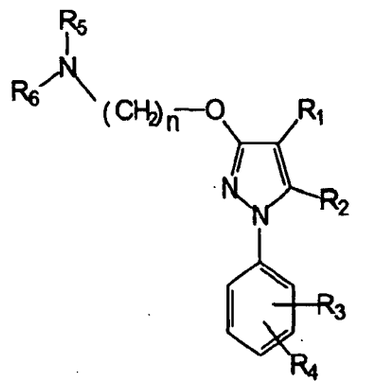
R_8 and R_9 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, or halogen;

or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

or

of a compound of the formula IIB:

144



(IIB)

wherein

R_1 is selected from the group formed by substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, -CN, $-OR_8$, $-OC(O)R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$ or halogen,

R_2 is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, -CN, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_3 and R_4 are independently selected from the group formed by substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, -CN, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen, or together they form a fused ring system,

R_5 and R_6 are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, -CN, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen; together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted heterocyclyl group;

n is selected from 1, 2, 3, 4, 5, 6, 7 or 8;

t is 1,2 or 3;

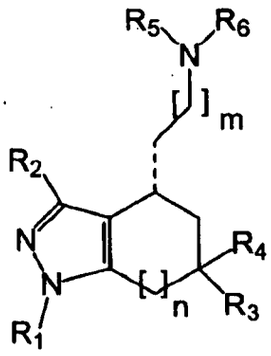
R_8 and R_9 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, or halogen;

or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof;

is excluded/disclaimed.

[0046] In another embodiment the use according to the invention; especially for the production of a medicament for the treatment of lipoprotein disorders, hyperlipidemia, hypertriglyceridemia or hypercholesterolemia,; of compounds according to general formula I

145



(I)

wherein

R_1 is selected from the group formed by hydrogen, susbtituted or unsubstituted alkyl, susbtituted or unsubstituted cycloalkyl, susbtituted or unsubstituted heterocyclyl, susbtituted or unsubstituted aryl, susbtituted or unsubstituted arylalkyl, and susbtituted or unsubstituted heterocyclylalkyl;

R_2 is selected from the group formed by hydrogen, susbtituted or unsubstituted alkyl, susbtituted or unsubstituted cycloalkyl, susbtituted or unsubstituted alkoxy, susbtituted or unsubstituted aryl, susbtituted or unsubstituted heterocyclyl, susbtituted or unsubstituted arylalkyl, and susbtituted or unsubstituted heterocyclylalkyl;

R_3 and R_4 are independently selected from the group formed by hydrogen, susbtituted or unsubstituted alkyl, susbtituted or unsubstituted cycloalkyl, susbtituted or unsubstituted heterocyclyl, susbtituted or unsubstituted aryl, susbtituted or unsubstituted arylalkyl and susbtituted or unsubstituted heterocyclylalkyl or, together, R_3 and R_4 form a 3 to 8 substituted or unsubstituted member ring;

R_5 and R_6 are independently selected from the group formed by hydrogen, susbtituted or unsubstituted alkyl, susbtituted or unsubstituted cycloalkyl, susbtituted or unsubstituted heterocyclyl, susbtituted or unsubstituted aryl, susbtituted or unsubstituted arylalkyl and susbtituted or unsubstituted heterocyclylalkyl or, R_5 and R_6 together, form a substituted or unsubstituted heterocyclyl having 3 to 7 atoms in the ring;

n is selected from 0, 1 and 2;

m is selected from 0, 1, 2, 3, 4;

the dotted line ------ is either a single or a double bond;

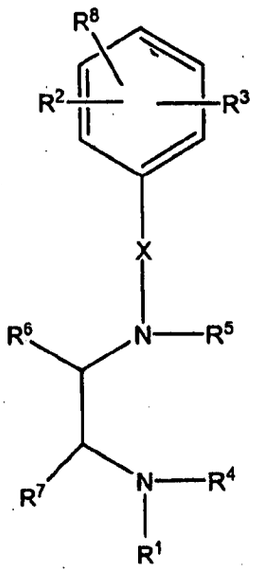
with the proviso that when R_1 is phenyl, R_2 is H, the dotted line ------ is a double bond, m is 1, and R_5 and R_6 form a 2,5-dioxopyrrolidine or a 5-ethoxy,2-oxo-pyrrolidine; then R_3 and R_4 are not both at the same time H or methyl;

or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof

is excluded/disclaimed.

[0047] In another embodiment the use according to the invention of compounds according to general formula IA

146



IA

wherein
R^1 is selected from C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;
R^2, R^3 and R^8 are independently of each other selected from H; OH, SH, NH_2, C_{1-6}Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; O-C(O)-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; C(O)-O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; or NH-C(O)-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;
R^4 and R^5 are independently of each other selected from H; OH, SH, NH_2, C_{1-6}Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;
or
R^4 and R^5 taken together are -$(CHR^9)_n$- forming a ring with n is selected from 1, 2 or 3 and each R^9 independently selected from H; OH, SH, NH_2, C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;
R^6 and R^7 are independently of each other selected from H; OH, SH, NH_2, C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; or O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;
X is -(CHR^{10})m-
with m selected from 0, 1, 2, 3 or 4 and
(if applicable) each R^{10} independently selected from H; OH, SH, NH_2, C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;
optionally in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable ratio; in the form shown or in form of the acid or base or in form of a salt, especially a physiologically acceptable salt, or in form of a solvate, especially a hydrate,
is excluded/disclaimed.

[0048] The examples and figures in the following section describing pharmacological trials are merely illustrative and the invention cannot be considered in any way as being restricted to these applications.

Examples

[0049] **Rationale:** The present invention provides evidence supporting the use of sigma-1 receptor antagonist to

147

reduce plasma levels of triglycerides. From the experimental point of view, both genetic and pharmacological approaches support the use of sigma-1 receptor antagonist to reduce plasma levels of triglycerides.

Example 1:

Genetic approach: Knockout mice deficient for the sigma-1 receptor ($\sigma1^{-/-}$) show reduced plasma levels of triglycerides respect to wild type mice.

[0050] Male and female mice from the C57BL/6J strain, including wild type and knockout for the sigma-1 receptor, were used in these experiments. The number of animals per group ranged from 16 to 23. Age ranged from 9-15 weeks. All mice had free access to water ad food (standard diet for rodents SAFE A04C; Scientific Animal Food and Engineering, 91360-Villemoisson sur Orge, France; Batch 40123). After a fasting period of 3-5 hours, mice were slightly anesthetized with isofluorane, blood samples were obtained from the retroorbital sinus and plasma was obtained by centrifugation.
[0051] Triglyceride levels in plasma were determined using the GPO/peroxidase method. Student t test was applied to determine statistical significance.
The results are presented below. Values are means ± standard deviation.
Units are expressed as mg/100 mL.

- Triglyceride levels in male mice:
  - Wild type (C57BL/6J $\sigma1^{+/+}$; n=20): 105.9 ± 38.39
  - Knockout sigma-1 receptor (C57BL/6J $\sigma1^{-/-}$; n=16): 71.5 ± 18.58 **
    ** p<0.01 compared to the control wild type group
- Triglyceride levels in female mice
  - Wild type (C57BL/6J $\sigma1^{+/+}$; n=20): 76.7 ± 29.08
  - Knockout sigma-1 receptor (C57BL/6J $\sigma1^{-/-}$; n=23): 58.2 ± 12.41 *
    * p<0.05 compared to the control wild type group

Example 2:

Pharmacologic approach: Treatment of obese (diet-induced obesity) wild type mice with a sigma-1 receptor antagonist results in a significant reduction in the concentration of triglycerides in blood.

[0052] Wild type male mice from the C57BL/6J strain were used in these experiments. Mice of 8-10 weeks of age were fed for two months with high fat diet (49 % fat content; Harlan Ibérica, TD97366). Treatment was administered subcutaneously, once a day, for 9 days. Treated animals received daily (for 9 days) a single dose of 50 mg/kg of BD-1063, a sigma-1 receptor antagonist. Control animals received daily vehicle (saline). During the period of treatment, mice had free access to water and food (high fat diet). At the end of the treatment, on day 10, blood samples were obtained through intracardiac puncture and triglyceride levels were measured using the Cholestech LDX blood analyzer. Student t test was applied to determine statistical significance.
The results are presented below. Values are means ± standard deviation.
Units are expressed as mg/100 mL.

- Triglyceride levels:
  - Control untreated (vehicle treated) mice: 91.75 ± 32.83
  - Treated (50 mg/kg BD-1063, s.c., once a day, 9 days): 56.8 ± 9.41 *
    * p<0.05 compared to the control wild type group

References

[0053] Fredrickson DS. An international classification of hyperlipidemias and hyperlipoproteinemias. Ann Intern Med. 1971 Sep;75(3):471-2.
[0054] Beaumont JL, Carlson LA, Cooper GR, Fejfar Z, Fredrickson DS, Strasser T. Classification of hyperlipidaemias and hyperlipoproteinaemias. Bull World Health Organ. 1970;43(6):891-915.

148

Claims

1. Use of at least one compound binding to the sigma receptor for the production of a medicament for the treatment of metabolic syndrome.

2. Use, according to claim 1, **characterized in that** said compound may be in neutral form, the form of a base or acid, in the form of a salt, preferably a physiologically acceptable salt, in the form of a solvate or of a polymorph and/or in the form of in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable mixing ratio.

3. Use, according to claim 1, **characterized in that** said compound binding to the sigma receptor has an IC50 value of ≤5000 nM.

4. Use, according to claim 1, **characterized in that** said compound binding to the sigma receptor has an IC50 value of ≤1000 nM.

5. Use, according to claim 1, **characterized in that** said compound binding to the sigma receptor has an IC50 value of ≤500 nM.

6. Use, according to claim 1, **characterized in that** said compound binding to the sigma receptor has an IC50 value of ≤250 nM.

7. Use, according to claim 1, **characterized in that** said compound binding to the sigma receptor has an IC50 value of ≤100 nM.

8. Use, according to claim 1, **characterized in that** said compound binding to the sigma receptor has an IC50 value of ≤50 nM.

9. Use, according to any of claims 1 to 8, **characterized in that** said compound binding to the sigma receptor used is acting on the sigma receptor as an antagonist.

10. Use, according to any of claims 1 to 8, **characterized in that** said compound binding to the sigma receptor used is acting on the sigma receptor as a partial antagonist.

11. Use, according to any of claims 1 to 8, **characterized in that** said compound binding to the sigma receptor used is acting on the sigma receptor as an inverse agonist.

12. Use, according to any of claims 1 to 11, **characterized in that** said compound binding to the sigma receptor is binding to the sigma-1 receptor subtype.

13. Use, according to claim 1, **characterized in that** said compound binding to the sigma receptor is selected from the group consisting of:

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
(+)-HIMBACINE	(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester
(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester	(S)-Methamphetamine HCl
[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 1-(3-Benzyloxy-4-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester	[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid2-(Tert-Butoxycarbonyl-Naphthalen-1-Ylmethyl-Amino)-Ethyl Ester
[4-(4-Ethyl-3,5-Dimethyl-Pyrazol-1-Yl)- Phenyl]-[4-(3-Phenyl-Allyl)-Piperazin-1-Yl]-Methanone	1-(1,2-Diphenylethyl)Piperidine Maleate, (+/-)
1-(1-Naphthyl)Piperazine HCl	1-(3-Chlorophenyl)Piperazine HCl

149

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
1-(4-Bromo-Benzenesulfonyl)-4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine	2-(2-[[1-(3-Chloro-Benzyl)-Pyrrolidin-3-Yl]-Methyl-Carbamoyl}-2-Methyl-Propyl)-4,6-Dimethyl-Benzoic Acid
2-Chloro-11-(4-Methylpiperazino)Dibenz[B, F]Oxepin Maleate	3,3'-Diethylthiacarbocyanine Iodide
3-Mercapto-2-Methylpropanoic Acid 1,2-Diphenylethylamine Salt	3-Quinuclidinyl Benzilate
3-Tropanyl-3,5-Dichlorobenzoate	3-Tropanyl-Indole-3-Carboxylate HCl
4-(1H-Indol-4-Yl)-Piperazine-1-Carboxylic Acid 2-(5-Bromo-2-Ethoxy-Phenylamino)-Cyclohexylmethyl Ester	4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine-1-Carboxylic Acid 2-Thiophen-2-Yl-Ethyl Ester
4-(3,5-Dimethoxy-Phenyl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-Benzyl)-Piperidin-3-Ylmethyl Ester	4-(3-Nitro-5-Sulfamoyl-Thiophen-2-Yl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-5-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-(5-Trifluoromethyl-Pyridin-2-Yl)-Piperazine-1-Carboxylic Acid Pent-2-Ynyl Ester
4,4'-Bis[4-(P-Chlorophenyl)-4-Hydroxypiperidino] Butyrophenone	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-Trifluoromethoxy-Benzenesulfonamide	4'-Chloro-8-Alpha-(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-Yl)-Propyl]-Piperazin-1-Yl}-Ethyl Ester	4-Methoxy-N-[1-(7-Methoxy-Benzo[1,3]Dioxol-5-Ylmethyl)-Pyrrolidin-3-Yl]-Benzenesulfonamide
5-(N-Ethyl-N-Isopropyl)-Amiloride	7-Hydroxy-DPAT HBr, (±)-
8-Hydroxy-DPAT HBr, (R)-(+)-	8-Hydroxy-DPAT HBr, S(-)-
9-[4-(([4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl} amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorène-9-carboxamide	Acepromazine Maleate
Acetophenazine Maleate	Acrinol
Ajmaline	Alaproclate HCl
Aloe-Emodin	Alprenolol D-Tartrate Salt Hydrate
Alprenolol HCl	AMI-193
Aminobenztropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Amoxapine	Anileridine HCl
Anisotropine Methylbromide	Anpirtoline
ARC 239 DiHCl	Astemizole
Auramine O HCl	Azaperone
Azatadine Maleate	Azelastine HCl
Bamethan sulfate	BD 1008 DiHBr
BD-1047	BD-1063
Benextramine TetraHCl	Benfluorex HCl

150

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
Benidipine HCl	Benoxathian HCl
Benoxinate HCl	Benperidol
Benproperine Phosphate	Benzododecinium bromide
Benzphetamine HCl	Benztropine Mesylate
Benzydamine HCl	Bephenium Hydroxynaphthoate
Bepridil HCl	Berberine chloride
Betaxolol HCl	Bifemelane
BMY 7378 DiHCl	Bopindolol Malonate
BP 554 Maleate	Bromhexine HCl
Bromodiphenhydramine HCl	Bromperidol
Brompheniramine Maleate	BTCP HCl
Bucilzine HCl	Buflomedil HCl
Bupropion HCl	Buspirone HCl
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Butoconazole Nitrate
BW 725C86 HCl	Carbetapentane Citrate
Carbinoxamine Maleate	Carpipramine DiHCl DiH2O
Carvedilol	Cephapirin Benzathine
CGS-12066A Maleate	Chloroprocaine HCl
Chloroquine Phosphate	Chlorpheniramine Maleate
Chlorphenoxamine HCl	Chlorpromazine HCl
Chlorprothixene	Cinanserin HCl
Cinnarizine	Cirazoline HCl
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DiHCl
Cisapride Hydrate	Citalopram HBr
Clebopride Maleate Salt	Clemastine Fumarate
Clemizole HCl	Clenbuterol HCl
Clidinium Bromide	Clobenpropit 2HBr
Clofazimine	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Clozapine
CONESSINE	Cyclizine
Cyclobenzaprine HCl	Cycloheximide
Cyproheptadine HCl	Darrow Red HCl
Demecarium Bromide	Denatonium Benzoate
Deptropine Citrate	Desloratadine

151

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
Dexbrompheniramine Maleate	Dexchlorpheniramine Maleate
Dexfenfluramine HCl	Dibucaine HCl
Dicyclomine HCl	Diethylpropion HCl
Dimethisoquin HCl	Dimetindene Maleate
Diphemanil Methylsulfate	Diphenidol HCl
Diphenoxylate HCl	Diphenylpyraline HCl
Dipropyldopamine HBr	Dobutamine HCl
Donepezil HCl	Doxepin HCl
Droperidol	Duloxetine
Dyclonine HCl	Ebastine
Econazole Nitrate	Epinastine HCl
Ethaverine HCl	Ethopropazine HCl
Eticlopride HCl, S(-)-	Etofenamate
Etonitazenyl Isothiocyanate	Femoxetine HCl
Fenfluramine HCl	Fentanyl Citrate
Fenticonazole Nitrate	Fipexide HCl
Flavoxate HCl	Flunarizine diHCl
Fluoxetine Related Compound B	Fluperlapine
Fluphenazine Decanoate DiHCl	Fluphenazine Enanthate DiHCl
Fluphenazine HCl	Fluphenazine N-Mustard DiHCl
Flurazepam Related Compound C	Fluspirilene
Fluvoxamine Maleate	GBR 12783 DiHCl
GBR 12909 DiHCl	GBR 13069 DiHCl
GBR-12935 DiHCl	GR 89696 Fumarate
Guanabenz Acetate	Guanadrel Sulfate
Guanethidine Sulfate	Halofantrine HCl
Haloperidol	HEAT HCl
Hexylcaine HCl	Hycanthone
Hydroxychloroquine Sulfate	Hydroxyzine HCl
Hyoscyamine Sulfate	IBZM, S(-)-
ICI-199,441 HCl	Ifenprodil Tartrate
Imipramine HCl	Indatraline HCl
Iofetamine HCl	Irinotecan HCl
Isamoltane Hemifumarate	Isopromethazine HCl
Isoxsuprine HCl	Ketanserin L-Tartrate
Ketoconazole	Ketotifen Fumarate Salt
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl

152

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
Labetalol HCl	Levetimide HCl, R(-)
Levobunolol HCl	Lidoflazine
Lisuride Hydrogen Maleate, R(+)-	Lobeline HCl
Lomerizine diHCl	Loperamide HCl
Loxapine Succinate	LY-53,857 Maleate
Maprotiline HCl	Mazindol
MDL 12,330A HCl	Mebhydroline 1,5-naphthalendisulfonate Salt
Meclizine HCl	Mefloquine HCl
Meprylcaine HCl	Mesoridazine Besylate
Metaphit Methanesulfonate	Metergoline
Methantheline Bromide	Methdilazine
Methiothepin Mesylate	Methixene HCl
Methoctramine	Methotrimeprazine Maleate
Methylene Violet 3Rax HCl	Metipranolol
Mexiletine HCl	Mianserin HCl
Miconazole	ML-9 HCl
Morantel Hydrogen L-Tartrate	MR 16728 HCl
N-(2-Chloroethyl)-N-Ethyl-2-Bromobenzylamine HCl	N'-[2-(Benzo[1,2,5]Thiadiazole-4-Sulfonylamino)-Acetyl]-Hydrazinecarboxylic Acid 2-(2-{4-[(4-Chloro-Phenyl)-Phenyl-Methyl]-Piperazin-1-Yl}-Ethoxy)-Ethyl Ester
Nafronyl Oxalate Salt	Naftifine
Naftopidil diHCl	Naltriben Mesylate
NAN-190 HBr	NE-100
Nefazodone	Nefopam HCl
Nicardipine HCl	Nicergoline
Niguldipine HCl, (+/-)-	Nisoxetine HCl
Nortriptyline HCl	Nylidrin HCl
Octoclothepin Maleate, (±)-	Orphenadrine Citrate
Oxamniquine	Oxamniquine Related Compound A
Oxamniquine Related Compound B	Oxatomide
Oxiconazole Nitrate	Oxybutynin HCl
Panaxatriol	PAPP
Paroxetine	Paxilline
p-Chlorobenzhydrylpiperazine	Penbutolol Sulfate
Pentamidine Isethionate	Pentazocine, (±)-
Pergolide Methanesulfonate	Perhexiline Maleate Salt
Perospirone	Perphenazine

153

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
Perphenazine Sulfoxide	Phenamil Methanesulfonate
Phencyclidine HCl	Phenosafranin HCl
Phenoxybenzamine HCl	Phenyltoloxamine Citrate Salt
Piboserod	Pimozide
Pinacyanol Chloride	Pindobind, (+/-)-
Piperacetazine	Piperazine-1,4-Dicarboxylic Acid Benzyl Ester 2-[4-(4-Dimethylamino-Benzyl)-Piperazin-1-Yl]-Ethyl Ester
Piperidolate HCl	Pirenperone
PPHT HCl, (±)-	Pramoxine HCl
Prenylamine Lactate Salt	Pridinol Methanesulfonate Salt
Prochlorperazine Maleate	Procyclidine HCl
Proflavine Hemisulfate Salt	Progesterone
Promazine HCl	Promethazine HCl
Propafenone HCl	Proparacaine HCl
Properciazine	Propiomazine
Propranolol HCl	Protokylol
Protriptyline HCl	Pyrilamine Maleate
Pyrimethamine	Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-3-Ylmethyl] Ester 2-Benzyl Ester
Pyrvinium Pamoate	Quetiapine Fumarate
Quinacrine HCl	Quinaldine Red
Quipazine Dimaleate	Quipazine, 6-Nitro-, Maleate
Raloxifene	Rimantadine HCl
Risperidone	Ritanserin
Ritodrine HCl	RS 23597-190 HCl
RS 67333 HCl	RS 67506 HCl
Safranin O HCl	Salmeterol
SB203186	SCH-23390 HCl, R(+)-
Sertaconazole Nitrate	Sertindole
Sertraline	Sibutramine HCl
SKF-525A HCl	SKF-96365 HCl
SNC 121	Spiperone HCl
Sufentanil	T-226296
Tamoxifen Citrate	Tamsulosin HCl
Tegaserod Maleate	Terbinafine HCl
Terconazole	Terfenadine
Terfenadine Related Compound A	Tetracaine HCl
Tetrindole Mesylate	Thiethylperazine Malate

154

(continued)

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
Thioperamide Maleate	Thioproperazine
Thioridazine	Thiothixene
Thiothixene, (E)-	Thonzonium Bromide
Tioconazole Related Compound A	TMB-8 HCl
Tolterodine L-Tartrate	Toremifene Citrate
Tramazoline HCl	Trans-U-50488 Methanesulfonate, (±)-
Trazodone HCl	Tridihexethyl Chloride
Trifluoperazine HCl	Trifluperidol HCl
Triflupromazine HCl	Trihexyphenidyl HCl
Trimebutine	Trimeprazine Hemi-L-Tartrate
Trimipramine Maleate	Tripelennamine HCl
Triprolidine HCl	Triprolidine HCl Z Isomer
Tropanyl 3,5-Dimethylbenzoate	Tropine 2-(4-Chlorophenoxy)Butanoate, Maleate
U-50488 HCl, (-)-	U-62066
UH 232 Maleate, (+)-	Vecuronium Bromide
Verapamil HCl	Verapamil Related Compound B
Vesamicol HCl	Vinpocetine
W-7 HCl	WB-4101 HCl
Xylazine	Xylometazoline HCl

14. Use, according to claim 1, **characterized in that** the medicament produced is for the treatment of elevated triglyceride levels, chylomicronemia, hyperlipoproteinemia; hyperlipidemia, especially mixed hyperlipidemia; hypercholesterolemia, lipoprotein disorders and dysbetalipoproteinemia.

15. Use, according to claim 1, **characterized in that** the medicament produced is for the treatment hypertriglyceridemia including both the sporadic and familial disorder, inherited hypertriglyceridemia.

155

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 06 38 4003

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	ECKEL R H ET AL: "The metabolic syndrome" LANCET THE, LANCET LIMITED. LONDON, GB, vol. 365, no. 9468, 16 April 2005 (2005-04-16), pages 1415-1428, XP004840990 ISSN: 0140-6736 * the whole document *	1-15	INV. A61K31/00 A61P3/00 A61P3/06 A61P3/04
X	BAYS H ET AL: "PHARMACOTHERAPY OF OBESITY CURRENTLY MARKETED AND UPCOMING AGENTS" AMERICAN JOURNAL OF CARDIOVASCULAR DRUGS, ADIS INTERNATIONAL,, NZ, vol. 2, no. 4, 2002, pages 245-253, XP008028337 ISSN: 1175-3277 * abstract * * the whole document * * page 246, left-hand column, paragraph 3 * * page 246, right-hand column, last line - page 247, left-hand column, line 15 * * page 247, right-hand column, paragraph 4 - paragraph 6 * * page 248, left-hand column, line 3 - line 23 * * page 249, line 3 - line 10 * * page 251, right-hand column, paragraph 3 *	1-15	

-/--

TECHNICAL FIELDS SEARCHED (IPC)

A61K
A61P

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	1 June 2006	Economou, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

156

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 06 38 4003

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	S. KLEIN ET AL.: "Clinical Implications of Obesity With Specific Focus on Cardiovascular Disease" CIRCULATION, vol. 110, no. 18, 2 November 2004 (2004-11-02), pages 2952-2967, XP002383495 usa * abstract * * the whole document * * page 2958, right-hand column, paragraph 2 - page 2960, left-hand column, paragraph 2 * * table 4 *	1-15	
E	WO 2006/021462 A (LABORATORIOS DEL DR. ESTEVE, S.A; LAGGNER, CHRISTIAN; CUBERES-ALTISENT) 2 March 2006 (2006-03-02) * the whole document * * page 20, line 22 * * claims 14,15 *	1-12,14, 15	
E	WO 2006/021463 A (LABORATORIOS DEL DR. ESTEVE, S.A; CORBERA ARJONA, JORDI; CUBERES-ALTIS) 2 March 2006 (2006-03-02) * the whole document * * page 5, lines 13,14 * * claims 12,13 *	1-12,14, 15	
E	EP 1 634 872 A (LABORATORIOS DEL DR. ESTEVE, S.A) 15 March 2006 (2006-03-15) * the whole document * * claims 13,14 *	1-12,14, 15	
E	EP 1 634 873 A (LABORATORIOS DEL DR. ESTEVE, S.A) 15 March 2006 (2006-03-15) * the whole document * * claims 10,11 *	1-12,14, 15	

TECHNICAL FIELDS SEARCHED (IPC)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	1 June 2006	Economou, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

157

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 06 38 4003

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

01-06-2006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006021462 A	02-03-2006	NONE	
WO 2006021463 A	02-03-2006	NONE	
EP 1634872 A	15-03-2006	US 2006106060 A1	18-05-2006
EP 1634873 A	15-03-2006	US 2006047127 A1	02-03-2006

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

158

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

- **ECKEL et al.** *The Lancet*, 2005, vol. 365, 1415-1428 **[0006]**
- **ALBERTI et al.** *Diabet. Med.*, 1998, vol. 15, 539-53 **[0006]**
- *JAMA*, 2001, vol. 285, 2486-97 **[0006]**
- **PAGOTTO ; PASQUALI.** *The Lancet*, 2005, vol. 365, 1363, 1364 **[0008]**
- **G. RONSISVALLE et al.** *Pure Appl. Chem.*, 2001, vol. 73, 1499-1509 **[0013] [0013]**
- **R. QUIRON et al.** *Trends Pharmacol. Sci.*, 1992, vol. 13, 85-86 **[0013]**
- **M.L.LEITNER.** *Eur. J. Pharmacol.*, 1994, vol. 253, 65-69 **[0013]**
- **S.B. HELLEWELL ; W.D. BOWEN.** *Brain Res.*, 1990, vol. 527, 244-253 **[0013]**
- **PRASAD, P.D. et al.** *J. Neurochem.*, 1998, vol. 70 (2), 443-451 **[0013]**
- **FREDRICKSON DS.** An international classification of hyperlipidemias and hyperlipoproteinemias. *Ann Intern Med*, September 1971, vol. 75 (3), 471-2 **[0053]**
- **BEAUMONT JL ; CARLSON LA ; COOPER GR ; FEJFAR Z ; FREDRICKSON DS ; STRASSER T.** Classification of hyperlipidaemias and hyperlipoproteinaemias. *Bull World Health Organ*, 1970, vol. 43 (6), 891-915 **[0054]**

159

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2008/075433	05.09.2008	16.10.2007

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/138 A61P3/00 A61P3/04 A61P3/06 A61P3/10

Applicant
REPROS THERAPEUTICS INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Terenzi, Carla Telephone No. +49 89 2399-7707

Form PCT/ISA/237 (Cover Sheet) (April 2005)

160

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2008/075433

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

161

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1, 16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1 Reference is made to the following documents:

D1: EP-A-1 829 534 (ESTEVE LABOR DR [ES]) 5 September 2007 (2007-09-05)
D2: WO 2006/019916 A (ZONAGEN INC [US]; PODOLSKI JOSEPH [US]; WIEHLE RONALD [US]) 23 February 2006 (2006-02-23)

For what concerns the most important passages of the above-mentioned documents, please see citations in the International Search Report, unless otherwise stated.

2. Claims 1-28 relate to a subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT. Their patentability is *inter alia* dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT. The EPO, for example, does not recognise as patentable claims to the use of a compound in a medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

3. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 and 16 is not new in the sense of Article 33(2) PCT.

Document D1 discloses the use of clomiphene citrate for treating metabolic syndrome and its symptoms. Therefore, the subject-matter of claims 1 and 16 is not novel over D1.

4. Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims or 1-23 does not involve an inventive step in the sense of Article 33(3) PCT.

4.1 The applicant will agree that claims which are not new cannot be considered as involving any exercise of an inventive step.

4.2 The document D1 is regarded as being the **closest prior art** to the subject-matter of claims 2, 3, 4, 17 and 18 and discloses the use of clomiphene (which is a mixture of *cis* and *trans* clomiphene) for treating metabolic syndrome and its symptoms.

The subject-matter of claims 2, 3, 4, 17 and 18 therefore differs from this known D1 in that, compositions comprising 0% to about 29% w/w of *cis*-clomiphene and about 100% to about 71% *trans*-clomiphene or compositions consisting essentially of *trans*-clomiphene have been used.

The **problem to be solved** by the present invention may therefore be regarded as the provision of the most appropriate ratio of *cis* and *trans* clomiphene in the compositions for the treatment of metabolic syndrome and its symptoms.

The solution proposed in the present application, namely the use of compositions comprising 0% to about 29% w/w of *cis*-clomiphene and about 100% to about 71% *trans*-clomiphene or compositions consisting essentially of *trans*-clomiphene, cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

Document D2 already describes compositions comprising 0% to about 29% w/w of *cis*-clomiphene and about 100% to about 71% *trans*-clomiphene or compositions consisting essentially of *trans*-clomiphene.

As the present application, D2 shows the beneficial effects of said compositions in the treatment of elevated triglyceride levels and elevated cholesterol levels by increasing total serum testosterone, and demonstrates that *trans*-clomiphene is more effective than clomiphene and *cis*-clomiphene.

In view of this known prior art, the skilled person would regard it as a normal routine procedure to try and use the compositions of the claimed solution in order to solve the problem posed. Thus, an inventive step cannot be acknowledged for the subject-matter of claims 2, 3, 4, 17 and 18.

4.3 Claims 8-10 are directed to the use of an antiestrogen, specifically of compositions comprising 0% to about 29% w/w of *cis*-clomiphene and about 100% to about 71% *trans*-clomiphene or compositions consisting essentially of *trans*-clomiphene, for

treating impaired fasting glucose.

The objective **technical problem faced** in claims 8-10 may therefore be regarded as the provision of a treatment for impaired fasting glucose.

However, the present application shows the ability of the claimed compositions to reduce blood glucose levels only in a specific group of patients, namely hypogonodal men. Therefore, since in order to fulfil the requirements of Article 33(3) PCT, it is foreseen that the claimed invention is based on a technical effect achieved over the whole scope of the claims, no inventive step can be acknowledged for the subject matter of claim 8-10.

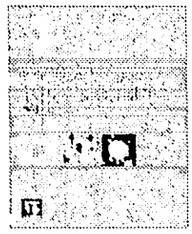
4.4 Dependent claims 5-7, 11-15, 19-23 do not add any features which might establish novelty/inventive step of the subject-matter of the independent claims over the prior art

Claims 24-28 appear to meet the requirements of Article 33 (1,2) PCT, because none of the documents of the available prior art discloses or suggests the use of compositions comprising 0% to about 29% w/w of *cis*-clomiphene and about 100% to about 71% *trans*-clomiphene or compositions consisting essentially of *trans*-clomiphene for treating impaired fasting glucose in a subject with secondary or idiopathic hypogonadotrophic hypogonadism.

EUROPEAN UROLOGY SUPPLEMENTS 6 (2007) 847–857

available at www.sciencedirect.com
Journal homepage: www.europeanurology.com

European Association of Urology



Testosterone Associations with Erectile Dysfunction, Diabetes, and the Metabolic Syndrome

T. Hugh Jones *

Robert Hague Centre for Diabetes and Endocrinology, Barnsley Hospital NHS Foundation Trust, Gawber Road, Barnsley, S75 2EP, United Kingdom
Academic Unit of Diabetes Endocrinology and Metabolism, University of Sheffield, Sheffield, United Kingdom

Article info

Keywords:
Erectile dysfunction
Hypogonadism
Metabolic syndrome
Testosterone
Type 2 diabetes

www.eu-acme.org/europeanurology

Please visit www.eu-acme.org/europeanurology to read and answer questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Hypogonadism and erectile dysfunction are common disorders seen in patients presenting to urology clinics. Increasing evidence indicates that both disorders have important associations with the metabolic syndrome, type 2 diabetes, and cardiovascular disease, all conditions with an increased morbidity and mortality. A low testosterone level is positively associated with the presence and severity of atherosclerosis. The early recognition of these clinical conditions is important to allow treatment and hence reduce cardiovascular risk. Recent publication of guidelines to aid the diagnosis of hypogonadism and a better understanding of how to interpret biochemical tests of androgen deficiency are helping to clarify which patients require testosterone substitution. Symptoms of hypogonadism are not specific and can be especially confounding in men with chronic diseases such as diabetes. Furthermore, convincing evidence shows that testosterone replacement, in addition to improving well-being and symptoms of hypogonadism, may have other vascular and metabolic benefits. Erectile dysfunction is associated with both diabetes and atherosclerosis. Men who fail to respond to phosphodiesterase type 5 inhibitors are more likely to have low testosterone levels and testosterone replacement improves the response. Testosterone substitution also can improve glycaemic control, insulin resistance, and waist circumference in hypogonadal men with type 2 diabetes and cardiac ischaemia in angina. The role of testosterone in these conditions requires further investigation; however, the identification of hypogonadism in its own right requires treatment. Larger studies are underway to investigate the additional potential benefits of testosterone therapy in men with diabetes and metabolic syndrome.

* Tel. +44 1226777047; Fax: +44 1226777771.
E-mail address: hugh.jones@nhs.net.

1569-9056/$ – see front matter doi:10.1016/j.eursup.2007.07.002

166

1. Introduction

It is recognised that erectile dysfunction (ED) is common in men with type 2 diabetes with more recent evidence of an increased prevalence in those with metabolic syndrome. However, it is less well known that there is a high prevalence of symptomatic testosterone deficiency (hypogonadism) in men with type 2 diabetes. Low testosterone levels are also found in men with the metabolic syndrome. It is important to recognise the coexistence of these conditions because, first, it may alter the management of the ED, and second, clinical detection of hypogonadism and treatment may lead to a significant improvement in quality of life.

Increasing evidence indicates that low testosterone levels are associated with cardiovascular disease as well as diabetes. Early clinical trials have shown that testosterone therapy can reduce some individual cardiovascular risk factors, which include visceral obesity, insulin resistance, hypercholesterolaemia, and inflammatory markers. Furthermore, animal studies have demonstrated beneficial effects of testosterone on atherogenesis. The importance of these findings has recently been emphasised by a study of 858 men that found increased mortality in men (male veterans) who had a low testosterone levels at baseline [1]. This is supported by data from the Massachusetts Male Aging Study (MMAS), which found that a low total testosterone level almost doubled the risk of all-cause mortality [2].

2. Diagnosis of hypogonadism

Hypogonadism is defined as a clinical syndrome that must comprise symptoms and biochemical confirmation with low circulating testosterone levels. The difficulties in making the diagnosis in borderline cases is confounded by the symptoms of hypogonadism being nonspecific and the lack of a consensus as to the level of testosterone considered to be consistent with the diagnosis as well as which fraction of testosterone should be assayed. The more common symptoms of hypogonadism include reduction or loss of libido, decreased erectile strength, fatigue, reduced physical strength and endurance, impaired cognitive function, and mood disturbances, including sadness, irritability, grumpiness, and depression.

The recent publication of two major sets of guidelines has provided some help in making the diagnosis. Recommendations for the diagnosis and management of late-onset hypogonadism (symptomatic men with low testosterone levels associated with ageing) were published by a group of international experts under the auspices of the International Society for Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM), and the European Association for Urology (EAU) [3]. These recommendations state that in the presence of symptoms a total testosterone level < 8 nmol/l requires testosterone substitution therapy, whereas a level > 12 nmol/l does not. In symptomatic men with total testosterone levels between 8 and 12 nmol/l a trial of testosterone therapy can be considered. The guidelines of the Endocrine Society of America recommend that testosterone levels < 10.4 nmol/l are consistent with hypogonadism [4]. Blood drawn for testosterone analysis should be taken before 1100 h because the hormone has a diurnal variation with levels reaching a peak between 0600 and 0800 h and a nadir between 1800 and 2000 h. It has been demonstrated that in some normal men testosterone levels can fall into the hypogonadal range in the afternoon. Therefore, blood for testosterone should not be taken during an afternoon clinic visit because this could lead to misdiagnosis. In some older men, but not all, the rhythm is less pronounced or lost, so it is still important to assess testosterone only in the morning. Testosterone levels can be low in the presence of intercurrent infection, infarction, and injury including the postsurgical period and can be higher the morning after sexual intercourse.

Total testosterone consists of three major fractions in the circulation. The majority (60–80%) of testosterone is bound to sex hormone-binding globulin (SHBG), whereas 2–3% is free and 20–40% is bound to albumin. The free plus the albumin-bound testosterone comprises the biologically active or bioavailable component, whereas that bound to SHBG is considered to be inactive although some reports show SHBG to bind to cells. In clinical practice total testosterone is routinely measured. Many studies have shown that bioavailable or free testosterone measurement correlates well with biologic end points of androgen action, for example, bone turnover and body composition. Free testosterone measured by radioimmunoassay is partly dependent on SHBG and hence provides no significant benefit over the use of total testosterone. Assays for free testosterone measured by equilibrium dialysis and for bioavailable testosterone by ammonium sulphate precipitation are time consuming and not readily available. Mathematical formulae for measurement of free and bioavailable testosterone have been produced using total testosterone and SHBG and some are available on the following Web sites: www.issam.org and www.him-link.com. Statin therapy can lower the

167

total testosterone but does not affect the bioavailable or free testosterone. It is important to recognise this because this is a confounding factor and can lead to the potential over-diagnosis of hypogonadism.

In clinical practice, total testosterone is a good screening test for biochemical hypogonadism; however, borderline levels can be difficult to interpret especially in men with diabetes and those who are older. If measured bioavailable testosterone is not used locally then the mathematical calculation of either free or bioavailable testosterone can be helpful but should be validated in-house because variations in total testosterone and SHBG assays between laboratories can occur.

Traditionally, hypogonadism has been classified as primary (testicular failure with elevated luteinising hormone [LH]) or secondary hypogonadism (hypothalamic-pituitary failure with low LH). Hypogonadism can, however, occur with normal gonadotrophin levels. The nomenclature for this is unclear. In some countries (eg, the United States), it is included with secondary hypogonadism; it is sometimes known as mixed hypogonadism (combination of primary and secondary hypogonadism) and also normogonadotrophic hypogonadism. Furthermore, the nomenclature for symptomatic and biochemical testosterone deficiency associated with ageing is not fully clear although the favoured terminology is late-onset hypogonadism, whereas others have suggested testosterone deficiency syndrome [5]. This review concentrates mainly on low testosterone levels found in men with the metabolic syndrome and type 2 diabetes mellitus. This can occur at any age although the incidence increases with age and the definitions of symptomatic testosterone deficiency associated with this group do not entirely apply.

It is imperative that the presence of overt prostate carcinoma is excluded before testosterone therapy is begun in men older than 45 yr [3,4]. It is also important that men older than 45 yr receiving testosterone substitution are followed every 3 mo for the first year and yearly thereafter for prostate carcinoma screening [3,4].

3. Low testosterone: a risk factor for metabolic syndrome and diabetes

The metabolic syndrome is a cluster of cardiovascular risk factors that include visceral obesity, impaired glucose tolerance, dyslipidaemia, and hypertension, which has been shown to be associated with increased mortality. The situation is confounded by the several definitions of the condition, including those from the World Health Organisation (WHO), National Cholesterol Education Program (NCEP), and International Diabetes Federation (IDF) with the latter now being more commonly used in Europe [6–8]. There is persuasive epidemiologic evidence from several longitudinal population studies that a low testosterone level is an independent risk factor for the development of both the metabolic syndrome and type 2 diabetes in later life. The MMAS and the Multiple Risk Factor Intervention Trial (MRFIT) have shown that low levels of total testosterone and SHBG (which is associated with insulin resistance) were both independent risk factors in middle-aged men who later developed diabetes [9,10]. The Rancho-Bernado Study based in California demonstrated a significant inverse correlation between baseline total testosterone with long-term (8-yr follow-up) fasting glucose and insulin levels as well as glucose intolerance [11]. A Finnish study has shown that low testosterone and SHBG levels also predict the development of the metabolic syndrome (defined by NCEP) as well as diabetes [12]. Importantly, the MMAS has provided evidence that low testosterone is a risk factor for metabolic syndrome (NCEP definition) and diabetes in men who were not initially obese [13]. Recently the Third National Health and Nutrition Examination Survey (NHANES III) in a population of 1413 men after adjustment for age, race/ethnicity, and adiposity showed that those men initially in the lowest tertile of either free or bioavailable but not total testosterone were approximately four times more likely to have prevalent diabetes compared to those in the third tertile [14]. These finding support those of the MMAS in that the risk is independent of adiposity.

4. Low testosterone in metabolic syndrome and type 2 diabetes

Two studies have shown that in men the metabolic syndrome is associated with low circulating levels of free and total testosterone [12,15]. The Finnish study also found SHBG levels were lower in men with the metabolic syndrome. Conversely, higher levels of bioavailable and total testosterone and SHBG in the Quebec Family Study were found to have increased insulin sensitivity and a reduced risk of developing the metabolic syndrome [16]. These findings were independent of body composition and insulin levels.

Several cross-sectional studies have constantly found low testosterone levels in men with type 2 diabetes [17–22]. The majority of these studies have measured total testosterone and it has been argued that levels will be low in diabetic men because SHBG

levels are low. The Rancho-Bernado Study did report that bioavailable testosterone was also low [15]. This finding has been supported by two recent publications. Importantly, Dhindsa and coworkers assessed free testosterone measured using equilibrium dialysis in 103 diabetic men and found that one third had levels lower than the normal range [22]. The Barnsley Study in the United Kingdom found 14% of diabetic men with symptoms with very low bioavailable testosterone and a further 28% with symptoms and a borderline low level [23]. The prevalence is considerably greater than that of a normal population as demonstrated by the MMAS [24]. In the MMAS, using an arbitrary cutoff value of total testosterone of 11.3 nmol/l, the prevalence of hypogonadism (defined by testosterone levels alone) for each decade was as follows: 12%, 19%, 28%, and 49%, respectively, for men in their fifties, sixties, seventies, and eighties [24]. In the Barnsley Study using an arbitrary cutoff of total testosterone of 12 nmol/l alone, the rates were 50%, 52%, 48%, and 55% for men in their forties, fifties, sixties, and older than 70 yr, respectively [19]. With symptoms and total testosterone < 12 nmol/l, the percentages were 32%, 47%, 43%, and 52% for men in their forties, fifties, sixties, and older than 70 yr in Barnsley Study [19]. This is the first study to assess symptoms of hypogonadism as well as biochemical evidence of testosterone deficiency (Fig. 1). However, this study also clearly demonstrated that symptoms of hypogonadism occurred at a similar frequency in those with total testosterone levels > 12 nmol/l. This underlines the nonspecific nature of hypogonadal symptoms and the need to measure serum testosterone. The only way to assess whether the symptoms are related to testosterone deficiency is to give a trial of testosterone replacement therapy in symptomatic patients with low testosterone levels.

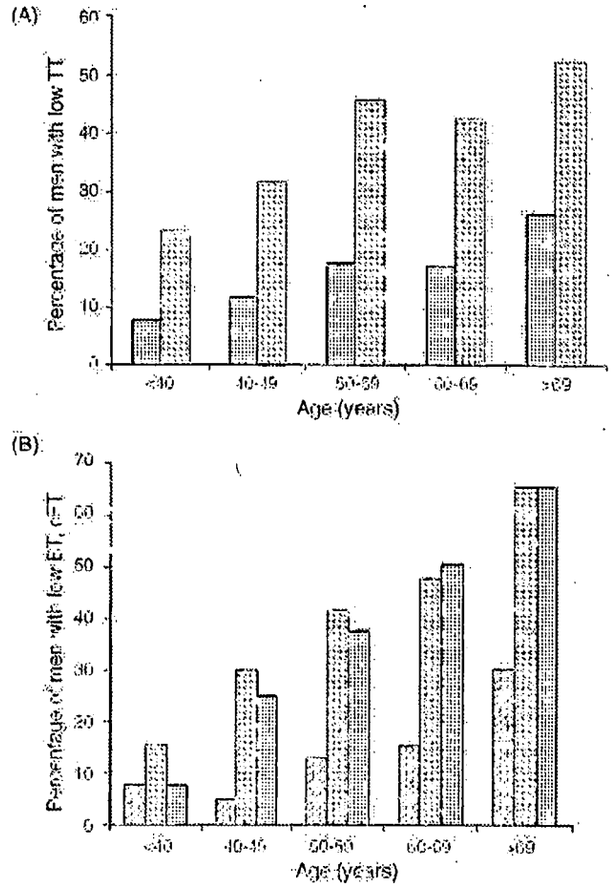


Fig. 1 – Prevalence of hypogonadism in men with type 2 diabetes. Incidence of positive symptom score in men with low testosterone by decades of age. (A) Total testosterone (TT). ▥, TT < 8 nmol/l; ▨, TT < 12 nmol/l. (B) Bioavailable testosterone (BT) and calculated free testosterone (cFT). ▨, BT < 2.5 nmol/l; ▨, BT < 4 nmol/l; ▥, cFT < 0.255 nmol/l. © (2007) American Diabetes Association From Diabetes Care, Vol. 33 (2007); pages 911–917.

5. Effect of androgen ablation therapy for prostate cancer

A powerful study of 73,196 men treated for locoregional prostate cancer with androgen ablation therapy has reported an increased risk of incident diabetes, myocardial infarction, and cardiovascular disease in men treated with gonadotrophin-releasing hormone (GnRH) agonists [25]. This finding is supported by smaller studies in men being started on prostate cancer therapy. Three months after initiation of either GnRH agonist or antiandrogen therapy men were found to have increased insulin levels as well as arterial stiffness [26,27]. A further study of men treated by surgical castration found elevated fasting and postprandial glucose and insulin levels 1 mo after surgery [28]. Hyperglycaemia and insulin resistance were also found in a longer-term study with a follow-up of 1 yr [29]. Furthermore, diabetic men treated with androgen ablation therapy for prostate cancer have worsening diabetic control and the need for a significant increase in their diabetic medication [30]. These findings are pertinent to the urologist and also again demonstrate the association of testosterone with carbohydrate metabolism.

6. ED with low testosterone levels

Men with low testosterone levels have an increased risk of severe ED [31]. A meta-analysis has demon-

169

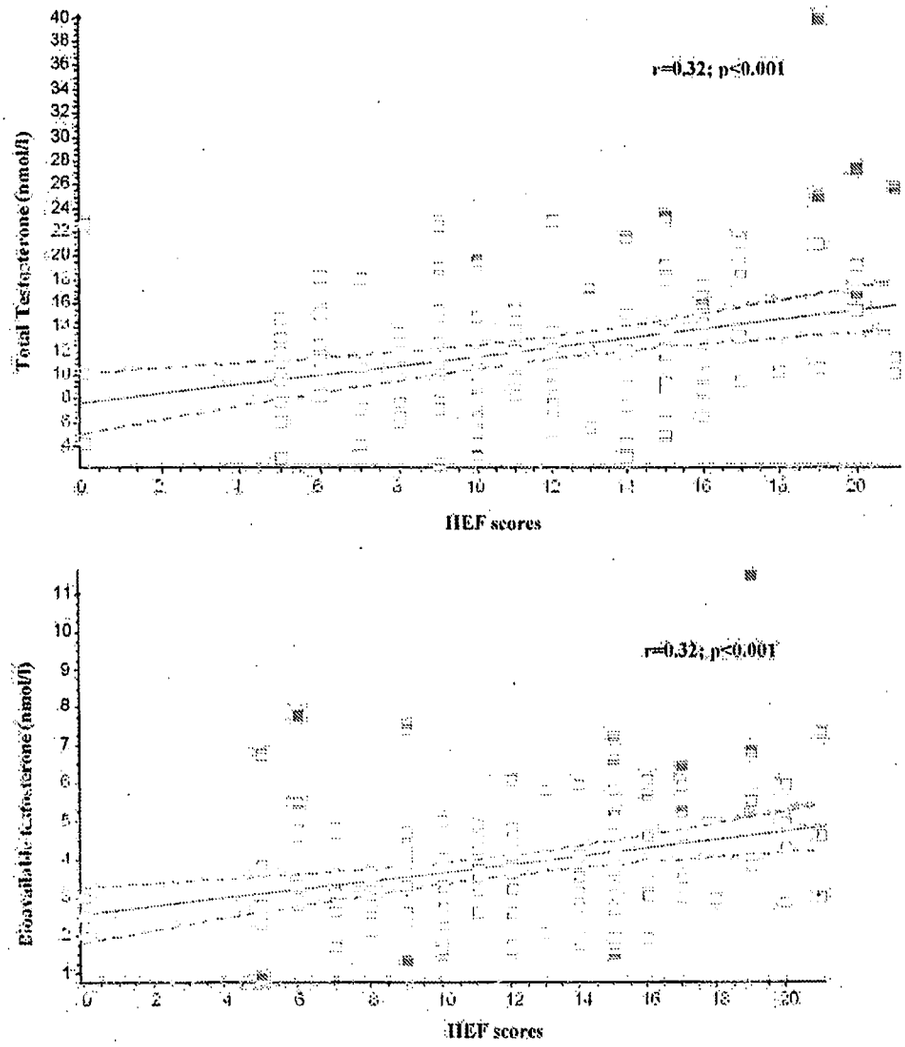


Fig. 2 – Correlation of total and bioavailable testosterone levels with erectile dysfunction as assessed by IIEF scores. From ref. [38]. © (2007) International Journal of Andrology, Online early articles doi:10.1111/j.1365-2605.2007.00744.x.

strated that approximately one third of men with ED have androgen deficiency [32]. There is a significantly higher prevalence of men with metabolic syndrome having ED compared to healthy controls (26.7% vs. 13%) [33]. Metabolic syndrome is associated with a more severe ED, which is further exacerbated by the coexistence of hypogonadism [34]. No studies have compared the prevalence of ED in men with the metabolic syndrome, with and without testosterone deficiency. It is well established that ED is common in diabetic men with prevalences of 30–90% [35–38]. The pathophysiology of ED is complex and multifactorial with vascular disease probably being the most common component. There is, however, a high prevalence, as described above, of testosterone deficiency in men with diabetes. A recent study has found that levels of bioavailable and free testosterone, but not total testosterone, are significantly lower in diabetic men with ED as opposed to those without [38]. Interestingly, the severity of ED as assessed by the International Index of Erectile Function (IIEF) scores correlated with total as well as bioavailable and free testosterone (Fig. 2) [38]. The implication is that total testosterone in those patients with milder forms of ED is not as sensitive as bioavailable or free testosterone measurements.

Kalinchenko and coworkers found that testosterone levels were significantly lower in men with type 2 diabetes who failed to respond to sildenafil when compared to responders and that when testosterone therapy was added, the response improved [39] The importance of testosterone in the physiology of the erection has been demonstrated in animal studies

[40,41]. The nitric oxide-mediated mechanism for erections is dependent on androgen [40]. Testosterone deficiency also produces adverse changes in the architecture of the corpus cavernosum including the arrangement of elastic fibres leading to pathologic alterations contributing to ED [42]. Furthermore, testosterone restores sildenafil responsiveness in animal models of diabetic-induced ED [43]. Interventional studies in men with low testosterone levels and ED have clearly demonstrated that testosterone replacement therapy improves erectile function in men who have failed to respond adequately to phosphodiesterase type 5 (PDE5) inhibitors alone [39,44,45]. No studies in men with diabetes alone have been performed. In a study of testosterone in hypogonadal men with ED, 63% regained normal function and increases in sexual desire with testosterone treatment alone [46]. One study, however, found only 2 of 28 sildenafil non-responders had low testosterone levels with the main cause being severe vascular abnormalities [47].

According to the EAU guideline update, all men presenting with ED should have their testosterone level measured [48]. Furthermore, combining testosterone replacement therapy with PDE5 inhibitors should be considered [49].

7. Visceral obesity

Visceral obesity is an independent risk factor for cardiovascular disease [50]. Total testosterone levels are lower in men with obesity. The San Antonio Heart Study found that both total and free testosterone levels inversely correlated with body mass index and waist-to-hip ratio [51]. The HERITAGE Family Study however demonstrated that not all men with obesity are clinically hypogonadal [52]. There is also a tendency in younger men with type 2 diabetes who have low total testosterone to have normal bioavailable and free testosterone levels [24]. Although there are no large studies it has been shown in a small study that weight loss can lead to higher testosterone levels in obese men [53].

Hypotheses (the hypogonadal-obesity-adipocytokine cycle; Fig. 3) have been offered to explain the effect of adiposity on circulating testosterone based on known scientific findings [54,55]. Visceral adiposity correlates positively with the degree of insulin resistance. Aromatase has a high activity in adipocytes and metabolism of testosterone to oestradiol. The higher the number and volume of adiposities, the greater is the breakdown of testosterone. Testosterone inhibits the enzyme lipoprotein lipase, which is situated on the outer surface of the fat cell

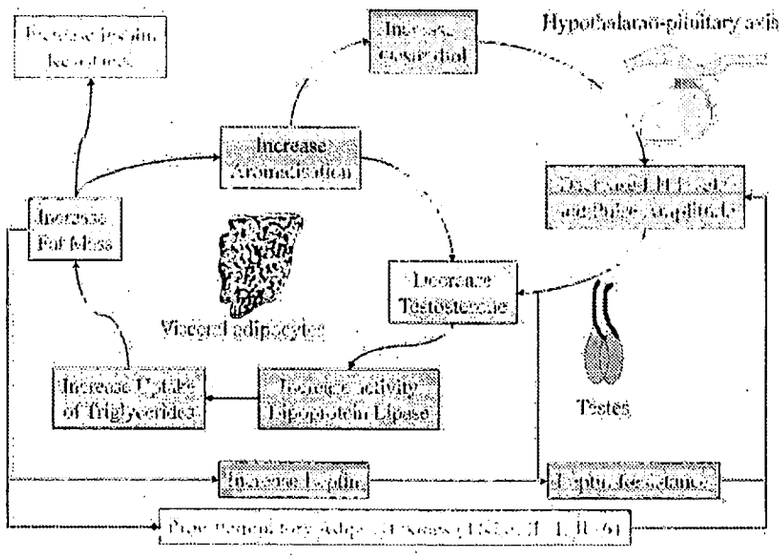


Fig. 3 – The hypogonadal-obesity-adipocytokine cycle. Increasing abdominal obesity leads to increased activity of the enzyme aromatase, present in adipose tissue, which converts testosterone to oestrogen. The resulting low testosterone level increases lipoprotein lipase enzyme activity and triglyceride uptake leading to increased obesity and insulin resistance. This in turn causes further androgen deficiency and visceral fat deposition. Oestradiol inhibits gonadotrophin release from the pituitary. Furthermore, testosterone levels are also lowered as a result of leptin resistance at the hypothalamic-pituitary level and the inhibitory effect of leptin on the testicular axis. Proinflammatory adipocytokines such as tumour necrosis α (TNF-α) and interleukin 6 (IL-6) could also potentially inhibit the pituitary axis resulting in low testosterone levels. This represents a form of secondary hypogonadism where the hypothalamic-pituitary axis cannot respond to low circulating testosterone levels.

171

that regulates the conversion of free fatty acids into triglyceride [56]. Lower testosterone levels would enhance the enzyme activity leading to greater uptake of triglyceride into the adipocytes, increasing fat storage and also stimulating the formation of new fat cells from pre-adipocytes. This exacerbates insulin resistance and drives the cycle to further reduce testosterone levels.

The normal homeostatic response is that the hypothalamic-pituitary axis would detect the falling testosterone level and increase gonadotrophin secretion to stimulate the testis. This response is potentially inhibited by at least three different mechanisms. (1) Oestradiol has an inhibitory action on LH production by the hypothalamic-pituitary axis [57]. (2) The inflammatory adipocytokines, tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6), also inhibit LH release. (3) Leptin normally stimulates LH release but in human obesity the hypothalamic-pituitary axis becomes leptin resistant [58,59]. This hypothesis would explain the high incidence of hypogonadism with normal LH levels in obese men. Leptin also directly inhibits the action of gonadotrophins on the testis.

8. Association of cardiovascular risk factors with testosterone

Low testosterone levels are associated with the independent cardiovascular risk factors of visceral obesity and insulin resistance found in the metabolic syndrome and type 2 diabetes [55,60 for review]. In addition, low testosterone levels are linked to a proatherogenic lipid profile, a hypercoagulable and proinflammatory milieu [60 for review]. Although there is no direct association of testosterone with hypertension there is a higher incidence of low testosterone levels in men with treated or untreated hypertension [60 for review].

The relationship between testosterone and lipid parameters is not fully clear, but the majority of reports have found that hypogonadism is associated with higher levels of total and low-density lipoprotein (LDL) cholesterol, and triglycerides and low levels of high-density lipoprotein (HDL) cholesterol [60 for review]. A meta-analysis of studies on lipid profiles has found that testosterone replacement therapy reduces total and LDL cholesterol but has no effect on HDL cholesterol levels [61]. In healthy and diabetic men a positive correlation is found between testosterone and HDL cholesterol levels [62,63].

Low testosterone levels are associated with higher levels of fibrinogen, plasminogen activator inhibitor type 1 (PAI-1), and clotting factor VII and low levels of tissue plasminogen activator (tPA) [64–66]. The overall effect of these associations theoretically would provide a hypercoagulable milieu. Unlike oestrogens, testosterone therapy has not been shown to have any adverse effects on coagulation [67].

It is well known that cardiovascular disease and diabetes are associated with elevated serum levels of inflammatory proteins which include C-reactive protein (CRP), IL-1, IL-6, and TNF-α. In diabetic subjects testosterone is inversely proportional to CRP and IL-6, but testosterone therapy in a short-term study had no effect on these proteins [68]. However, in a study of hypogonadal men of whom the majority had coronary heart disease testosterone therapy suppressed serum TNF-α and IL-1β and increased the antiatherogenic cytokine IL-10 [69]. Clearly there are interesting effects of testosterone on inflammatory and coagulation states that require further investigation.

9. ED as a marker of atherosclerosis

ED is strongly associated with several cardiovascular risk factors, including hypertension, obesity, ageing, and smoking as well as diabetes [70]. Furthermore, vascular disease is probably the most common cause of ED [71]. There is a strong relationship between ED and silent coronary heart disease in men with uncomplicated type 2 diabetes [72]. It is also understood that ED may precede or be a herald of a subsequent myocardial infarction. It is important therefore to assess the patient with ED holistically with analysis of overall cardiovascular risk. This will lead to patient awareness of impending cardiovascular disease and treatment, which would include advice on changes in lifestyle (eg, diet, exercise, and smoking cessation), and treatment of hyperlipidaemia, hypertension and consideration of antiplatelet therapy.

10. Effect of testosterone replacement therapy in diabetes

In hypogonadal men with type 2 diabetes, testosterone therapy increases physical activity and improves libido, ED, muscle strength, and mood [39]. Testosterone substitution in hypogonadal men also improves insulin sensitivity [73]. Furthermore, testosterone reduces insulin levels and insulin resistance in men with obesity [74]. Two studies in hypogonadal men with type 2 diabetes have shown that testosterone replacement also improves

172

glycaemic control although one of these studies was not blinded [75,76]. Kapoor and coworkers performed a randomised, double-blind, placebo-controlled, crossover study of testosterone replacement [76]. This, in addition to demonstrating beneficial effects on fasting blood glucose and glycated haemoglobin, significantly found an improvement in insulin resistance, visceral adiposity, and total cholesterol levels [76]. The exact mechanism by which testosterone mediates these effects is unclear but may be in part mediated in changes in visceral adiposity. A larger European multicentre study (TIMES2) is currently underway to determine if the benefits of testosterone replacement therapy in testosterone-deficient men with type 2 diabetes or the metabolic syndrome persist in the longer term and potentially improve cardiovascular risk [77].

11. Testosterone and cardiovascular disease

In men, testosterone levels are related to the presence and severity of atheroma. One study on aortic atherosclerosis [78] and three studies on carotid artery atherosclerosis [79–82] have demonstrated an inverse relationship between testosterone and degree of atherogenesis. Intima medial thickness (IMT) is a surrogate marker of atherogenesis, which can be measured in the carotid artery. A longitudinal study has found that carotid IMT in men with low circulating testosterone levels at baseline had the greatest progression of their disease over 4 yr [83].

Several cross-sectional studies have shown either an association of low testosterone or a neutral effect in men with cardiovascular disease [60 for review]. Similarly to ED, bioavailable and free testosterone measurements are better than total testosterone at delineating differences between those with and without coronary artery disease [84].

Animal studies have found that castration accelerates atherogenesis and testosterone is protective against the development of fatty streak formation an early stage of atherogenesis [85–88]. Furthermore, one of these models of testosterone replacement found that testosterone replacement ameliorated plaque formation.

Laboratory and clinical studies have found that testosterone is a rapidly acting vasodilator. Testosterone therapy has been found to increase coronary artery diameter and flow and to improve time to cardiac ischaemia in men with coronary heart disease [89,90]. The beneficial effects on cardiac ischaemia and symptoms of angina have been shown to improve over a 3-mo period [90].

12. Conclusions

Testosterone deficiency and ED individually and together are conditions commonly associated with type 2 diabetes, metabolic syndrome, and cardiovascular disease. These conditions commonly present to the urologist and it is important they are not taken in isolation. When urologists clinically assess these patients, they should consider the coexistence of diabetes, metabolic syndrome, and atherosclerosis. ED can be the herald of subsequent development of a myocardial infarction. Evidence from pilot studies indicates that treatment of testosterone deficiency in men with ED, diabetes, and cardiovascular disease leads to clinical benefits in addition to relieving classical symptoms of hypogonadism. Larger and longer-term studies will hopefully provide us with clearer information as to whether these improvements are sustained and if there is a reduction of cardiovascular risk and ultimately morbidity and mortality. For the time being, the current clinical indication for testosterone therapy remains a clinical diagnosis of hypogonadism as defined by international guidelines. All men with ED should have their testosterone levels measured. Patients treated with testosterone require careful monitoring especially of haematocrit value and surveillance for prostate carcinoma as recommended in clinical guidelines, although there is no currently accepted scientific basis or compelling evidence that testosterone has a causative role in prostate cancer [91,92].

Conflicts of interest

Professor Jones has received honoraria from Prostrakan advisory boards.

References

[1] Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. Arch Intern Med 2006;166:1660–5.

[2] Araujo AB, Handelsman D, McKinlay JB. Total testosterone as a predictor of mortality in men: results from the Massachusetts Male Aging Study. The Endocrine Society Annual Meeting, San Diego, CA, USA Program and Abstracts 2005;P1–561.

[3] Nieschlag E, Swerdloff R, Behre HM, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM and EAU recommendations. J Androl 2006;27:135–7.

[4] Androgen Deficiency Syndromes in Men Guideline Task Force. Testosterone therapy in adult men with androgen

173

deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006;91:1995–2010.
[5] Morales A, Schulman C, Tostain J, Wu FCW. Testosterone deficiency syndrome (TDS) needs to be named appropriately—the importance of accurate terminology. Eur Urol 2006;50:407–9.
[6] World Health Organisation. Definition, diagnosis, classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Geneva: World Health Organization, 1999.
[7] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486–97.
[8] The IDF consensus worldwide definition of the metabolic syndrome 2005. http://www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf.
[9] Stellato RK, Feldman HA, Hamdy O, et al. Testosterone, sex hormone binding globulin and the development of type 2 diabetes in middle aged men: prospective results form the Massachusetts Male Aging Study. Diabetes Care 2000;23:490–4.
[10] Haffner SM, Shaten J, Stern MP, et al. Low levels of sex hormone binding globulin and testosterone predict the development of non insulin dependent diabetes mellitus in men. Am J Epidemiol 1995;145:859–97.
[11] Oh JY, Barrett-Connor E, Wedick NM, et al. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo Study. Diabetes Care 2002;25:55–60.
[12] Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care 2004;27:1036–41.
[13] Kupelian V, Page ST, Araujo AB, et al. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with the development of the metabolic syndrome in non-obese men. J Clin Endocrinol Metab 2006;91:843–50.
[14] Selvin E, Feinleib M, Zhang L, et al. Androgens and diabetes in men. Results from the third National Health and Nutrition Examination Survey. Diabetes Care 2007;30: 234–8.
[15] Muller M, Grobbee DE, den Tonkelaar I, et al. Endogenous sex hormones and metabolic syndrome in aging men. J Clin Endocrinol Metab 2005;90:2618–23.
[16] Blouin K, Despres JP, Couillard C, et al. Contribution of age and declining androgen levels to features of the metabolic syndrome in men. Metabolism 2005;54:1034–40.
[17] Ando S, Rubens R, Fottiere R. Androgen plasma levels in male diabetics. J Endocrinol Invest 1984;7:21–4.
[18] Barrett-Connor E, Khaw KT, Yen SS. Endogenous sex hormones in older men with diabetes mellitus. Am J Epidemiol 1990;132:895–901.
[19] Barrett-Connor E. Lower endogenous androgen levels and dyslipidemia in men with non-insulin-dependent diabetes mellitus. Ann Intern Med 1992;117:807–11.
[20] Andersson P, Marin P, Lissner L, et al. Testosterone concentrations in women and men with NIDDM. Diabetes Care 1994;17:405–11.
[21] Dietz E, Cuk A, Hughl S, et al. Association of increased C-peptide serum levels and testosterone in type2 diabetes. Eur J Intern Med 2000;11:322–8.
[22] Dhindsa S, Prabhakar S, Sethi M, et al. Frequent occurrence of hypogonadotrophic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 2004;89:5462–8.
[23] Kapoor D, Aldred H, Clark S, et al. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes. Correlations with bioavailable testosterone and visceral adiposity. Diabetes Care 2007;30:911–7.
[24] Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. J Clin Endocrinol Metab 2001;86: 724–31.
[25] Keating NL, O'Malley J, Smith ME. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–56.
[26] Smith JC, Bennett S, Evans LM, et al. The effects of induced hypogonadism on arterial stiffness, body composition and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab 2001;86:4261–7.
[27] Dockery F, Bulpitt CJ, Agarwal S, et al. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clin Sci (Lond) 2003;104:195–201.
[28] Xu T, Wang X, Hou S, et al. Effect of surgical castration on risk factors for arteriosclerosis of patients with prostate cancer. Chin Med J [Engl] 2002;115:1336–40.
[29] Basaria S, Muller DC, Carducci MA, et al. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. Cancer 2006; 106:581–8.
[30] Yassin A, Saad F, Guillame A, et al. Effect of androgen deprivation on glycaemic control and on biochemical cardiovascular risk factors in men with diabetes. J Urol 2006;175(Suppl):325.
[31] Kratzik CW, Schatzl G, Lunglmayr G, et al. The impact of age, body mass index and testosterone on erectile dysfunction. J Urol 2005;174:240–3.
[32] Isidori A, Giannetta E, Gianfrilli D, et al. Effect of testosterone on sexual function in men: results of meta-analysis. Clin Endocrinol (Oxf) 2005;63:229–43.
[33] Esposito K, Giugliano F, Martedi E, et al. High proportions of erectile dysfunction in men with the metabolic syndrome. Diabetes Care 2002;28:1201–3.
[34] Corona G, Mannucci E, Schulman C, et al. Psychobiologic correlates of the metabolic syndrome and associated sexual dysfunction. Eur Urol 2006;50:595–604.
[35] McCulloch DK, Campbell IW, Wu FC, et al. The prevalence of diabetic impotence. Diabetologia 1980;18:279–83.
[36] Fedele D, Coscelli C, Santeusanio F, et al. Erectile dysfunction in diabetic patients in Italy. Diabetes Care 1998;21: 1973–7.
[37] Cho NH, Ahn CW, Park JY, et al. Prevalence of erectile dysfunction in Korean men with Type 2 diabetes mellitus. Diabetic Med 2006;23:198–203.

174

[39] Kapoor D, Clarke S, Channer KS, Jones TH. Erectile dysfunction is associated with low testosterone levels and visceral adiposity in men with type 2 diabetes. Int J Androl. In press. doi:10.1111/j.1365-2605.2007.00744.x.
[39] Kalinchenko ST, Kozlov GI, Gontcharov NP, Katsiya GV. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. Aging Male 2003;6: 94–9.
[40] Mills TM, Reilly CM, Lewis RW. Androgens and penile erection. J Androl 1996;17:633–8.
[41] Shabsigh R. Testosterone therapy in erectile dysfunction. Aging Male 2004;7:312–8.
[42] Traish AM, Goldstein I, Kim NN. Testosterone and erectile dysfunction: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. Eur Urol 2007;52:54–70.
[43] Chang XH, Filippi S, Morelli A, et al. Testosterone restores diabetes-induced erectile dysfunction and sildenafil responsiveness in two distinct animal models of chemical diabetes. J Sex Med 2006;3:253–64.
[44] Aversa A, Isidori AM, Spera G, et al. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. Clin Endocrinol (Oxf) 2003;58:632–8.
[45] Shabsigh R, Kaufman J, Steidle J, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol 2004;172:658–63.
[46] Greenstein A, Mabjeesh NJ, Sofer M, et al. Does sildenafil combined with testosterone gel improve erectile dysfunction in hypogonadal men in whom testosterone therapy alone failed. J Urol 2003;175:530–2.
[47] Wespes E, Rammal A, Garbar C. Sildenafil non-responders: haemodynamic and morphometric studies. Eur Urol 2005;48:136–9.
[48] Wespes E, Amar E, Hatzichristou D, et al. EAU guidelines on erectile dysfunction: an update. Eur Urol 2006;49: 806–15.
[49] Greco EA, Spera G, Aversa A. Combining testosterone and PDE5 inhibitors in erectile dysfunction: basic rationale and clinical evidences. Eur Urol 2006;50:940–7. Corrigendum. Eur Urol 2007;51:872.
[50] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.
[51] Haffner SM, Valdez RA, Stern MP, et al. Obesity, body fat distribution and sex hormones in men. Int J Obes 1993;17:643–9.
[52] Couillard C, Gagnon J, Bergeron J, et al. Contribution of body fatness and adipose distribution to the age variation in plasma steroid hormone concentrations in men: the HERITAGE Family Study. J Clin Endocrinol Metab 2000;85:1026–31.
[53] Strain GW, Zumoff B, Miller LK, et al. Effect of massive weight loss on hypothalamic-pituitary-gonadal function in obese men. J Clin Endocrinol Metab 1988;66:1019–23.
[54] Cohen PG. The hypogonadal-obesity cycle. Med Hypotheses 1999;52:49–51.
[55] Kapoor D, Malkin CJ, Channer KS, et al. Androgens, insulin resistance and vascular disease in men. Clin Endocrinol (Oxf) 2005;63:239–50.
[56] Marin P, Oden B, Bjorntorp P. Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue in vivo in men: effects of androgens. J Clin Endocrinol Metab 1995;80:239–43.
[57] Guay AT, Bansal S, Heatley GJ. Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind-placebo controlled trial with clomiphene citrate. J Clin Endocrinol Metab 1995;80: 3546–50.
[58] Mantzoros CS. The role of leptin in human obesity and disease: a review of current evidence. Ann Intern Med 1999;130:671–80.
[59] Isidori AM, Caprio M, Strollo F, et al. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab 1999;84:3673–80.
[60] Jones RD, Nettleship JE, Kapoor D, et al. Testosterone and atherosclerosis in aging men: purported association and clinical implications. Am J Cardiovasc Drugs 2005;5: 141–54.
[61] Whitsel EA, Boyko EJ, Matsumoto AM, et al. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. Am J Med 2001;111:261–9.
[62] Van Pottelbergh I, Braeckman L, De Bacquer D, et al. Differential contribution of testosterone and estradiol in the determination of cholesterol and lipoprotein profile in healthy middle-aged men. Atherosclerosis 2003;166: 95–102.
[63] Stanworth RD, Kapoor D, Channer KS, et al. Testosterone levels correlate positively with HDL cholesterol levels in men with type 2 diabetes. Endocr Abstr 2007;14:P628.
[64] Caron P, Bennet A, Camare R, et al. Plasminogen activator inhibitor in plasma is related to testosterone in men. Metabolism 1989;38:1010–5.
[65] Yang XC, Jing TY, Resnick LM, et al. Relation of hemostatic risk factors to other risk factors for coronary heart disease and to sex hormones in men. Arterioscler Thromb 1993;13:467–71.
[66] De Pergola G, De Mitrio V, Sciaraffia M, et al. Lower androgenicity is associated with higher plasma levels of prothrombotic factors irrespective of age, obesity, body fat distribution, and related metabolic parameters in men. Metabolism 1997;46:1287–93.
[67] Smith AM, English KM, Malkin CJ, et al. Testosterone does not adversely affect fibrinogen or tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) levels in 46 men with chronic stable angina. Eur J Endocrinol 2005;152:285–91.
[68] Kapoor D, Clarke S, Stanworth R, et al. The effect of testosterone replacement therapy on adipocytokines and C-reactive protein in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2007;156:595–602.
[69] Malkin CJ, Pugh PJ, Kapoor D, et al. The effect of testosterone replacement on endogenous inflammatory cyto-

175

kines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab 2004;89:3313–8.
[70] Montorsi F, Pavagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease: matching the right target with the right test in the right patient. Eur Urol 2006;50:721–31.
[71] Kirby M. Identification, management of risk factors. In: Kirby M, editor. Erectile dysfunction and vascular disease. London, United Kingdom: Blackwell Publishing; 2006. p. 35–42.
[72] Gazzarusso C, Giordanetti S, De Amici E, et al. Relationship between erectile dysfunction and silent myocardial ischaemia in apparently uncomplicated type 2 diabetic patients. Circulation 2004;110:22–6.
[73] Simon D, Preziosi P, Barrett-Connor E, et al. Interrelation between plasma testosterone and plasma insulin in healthy adult men: the Telecom Study. Diabetologia 1992;35:173–7.
[74] Marin P, Holmang S, Jonsson L, et al. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. Int J Obes Relat Metab Disord 1992;16:991–7.
[75] Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male 2003;6:1–7.
[76] Kapoor D, Goodwin E, Jones TH, et al. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2006;154:899–906.
[77] Channer KS, Jones TH, TIMES2 Study Investigator. Reducing cardio-metabolic risk with testosterone replacement therapy (TRT)—a randomised, placebo-controlled trial of TRT in hypogonadal men with type 2 diabetes mellitus (DM) or metabolic syndrome (MS)—the TIMES2 study. 12th World Congress on Heart Disease, Vancouver, BC, Canada, 2007.
[78] Hak AE, Witteman JCM, De Jong FH, et al. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam Study. J Clin Endocrinol Metab 2002;87:3632–9.
[79] Fukui M, Kitagawa Y, Nakamura N, et al. Association between serum testosterone concentration and carotid atherosclerosis in men with type 2 diabetes. Diabetes Care 2003;26:1869–73.
[80] Van Den Beld AW, Bots ML, et al. Endogenous hormones and carotid atherosclerosis in elderly men. Am J Epidemiol 2003;57:25–31.
[81] Svartberg J, Von Muhlen D, Mathiesen E, et al. Low testosterone levels are associated with carotid atherosclerosis in men. J Intern Med 2006;259:576–82.
[82] De Pergola G, Pannacciulli N, Ciccone M, et al. Free testosterone plasma levels are negatively associated with the intima-media thickness of the common carotid artery in overweight and obese glucose-tolerant young adult men. Int J Obes Relat Metab Disord 2003;27:803–7.
[83] Muller M, Van Den Beld AW, Bots ML, et al. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. Circulation 2004;109:2074–9.
[84] English KM, Mandour O, Steeds RP, et al. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. Eur Heart J 2000;21:890–4.
[85] Eruck B, Brehme U, Gugel N, et al. Gender-specific differences in the effects of testosterone and estrogen on the development of atherosclerosis in rabbits. Arterioscler Thromb Vasc Biol 1997;17:2192–9.
[86] Larsen BA, Nordestgaard BG, Stender S, et al. Effect of testosterone on atherogenesis in cholesterol-fed rabbits with similar plasma cholesterol levels. Atherosclerosis 1993;99:79–86.
[87] Alexandersen P, Haarbo J, Byrjalsen I, et al. Natural androgens inhibit male atherosclerosis. Circ Res 1999;84:813–9.
[88] Nettleship JE, Jones RD, Biggins CM, et al. Testosterone replacement reduces aortic fatty streak formation in testosterone deficient Tfm mice following feeding on a cholesterol-enriched diet. Endocr Abstr 2006;11:P404.
[89] Webb CM, McNeill JG, Hayward CS, et al. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. Circulation 1999;100:1690–6.
[90] English KM, Steeds RP, Jones TH, et al. Low dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina. Circulation 2000;102:1906–11.
[91] Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Eng J Med 2004;350:482–92.
[92] Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. Eur Urol 2006;50:935–9.

176

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-040524- -00000-0000

Fecha: 2010-04-08 15:24:36 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eva: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 176

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☑ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita 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

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

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

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
RODRIGUEZ D' ALEMAN DILIA MARIA
Apoderado(a) y/o Representante de
REPROS THERAPEUTICS INC

REFERENCIA		
	Radicación No.	10 040524
	Solicitud internacional	PCT/US2008/075433
	Fecha inicio fase nacional	16/05/2010
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	107871

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:

1. El solicitante debe aclarar si la solicitud corresponde al capítulo I o II del PCT por que la indicación en el petitorio no corresponde a los documentos del expediente, en caso necesario adjuntar los documentos que corresponden.

2. 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, conforme a lo establecido por el artículo 26 literal b) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título V de la Circular Única de Superintendencia de Industria y Comercio.

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.

Continua en la página siguiente...

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 04 JUN. 2010.
adpa11

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5 , 7 y 10 PBX: 5870000
Sede CAN: Av. Cra 50 No. 26-55 int. 2 Tel: 5600070
Call Center 6513240. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co