



Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

07-3351

54. TÍTULO Trans-Clomifeno para el tratamiento
de Hipertrofia de próstata Benigna, cáncer de
próstata, hipogonadismo, triglicéridos elevados
y colesterol alto.

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15/08, 35/00

71. SOLICITANTE Repro Therapeutics, Inc.

DOMICILIO Woodlands, Texas.

74. APODERADO Olivia Maria Rodriguez D'Alema

22. BOGOTÁ, D. C., Enero 15/07.

53

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PCT
ENTRADA EN FASE NACIONAL

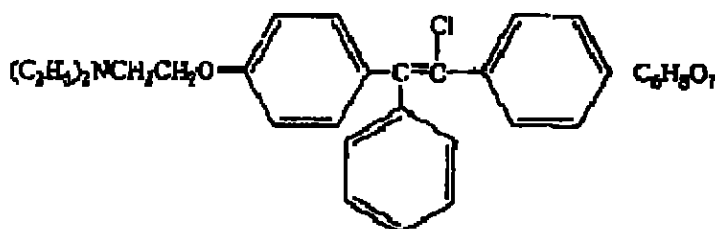
1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☒ Capítulo I.		☐ Capítulo II.	
2) SOLICITANTE (71)	Nombre: REPROS THERAPEUTICS, INC. Dirección: 2408 Timberloch Place, B-7 The Woodlands, Texas 77380 USA Nacionalidad o domicilio: Woodlands, Texas, USA Lugar de constitución: Delaware, Estados Unidos		IDENTIFICACIÓN C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO Cual _____
	Teléfono: _____ Fax: _____ E. Mail: _____		
3) REPRESENTANTE O APODERADO	Nombre: DILIA MARÍA RODRIGUEZ D'ALEMAN Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C. Teléfono: 6181088 Fax: 8350824 E. Mail: info@clarkemodet.com.co		IDENTIFICACIÓN C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ
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5) PCT (86) Solicitud Internacional No. PCT/US2005/025000 Fecha: Julio 14, 2005 Publicación Internacional No. WO2006/019916 A1 Fecha: Febrero 23, 2006			
6) Título (54) TRANS-CLOMIFENO PARA EL TRATAMIENTO DE HIPERTROFIA DE PRÓSTATA BENIGNA, CÁNCER DE PRÓSTATA, HIPOGONADISMO, TRIGLICERIDOS ELEVADOS Y COLESTEROL ALTO.			
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Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta página			

10)

ANEX S

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 8 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros:
 1. Reporte internacional de búsqueda
 2. Opinión escrita
 3. Cambios internacionales
 4. Solicitud PCT

11) FIGURA CARACTERÍSTICA:



12) Solicitud concesión de la patente,

NOMBRE: DILIA ROBRÍGUEZ D'ALEMAN

FIRMA:

C.C. 41.654.882 de Bogotá TP 20824 CSJ

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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POR AUT-UT-PA 428034 DEL 2001 BOLIVIANOS
TAL 91 TRATAMIENTO
EN 4/8 PASADUACIONES
A 1419 PIRENE TALAN 1000. A

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT 1 8001.6089 2

RECIBO OFICIAL DE CASH 06 - 99,833
FECHA 1 D CEMBRE 28 DE 2006

30306 C O N S I G N A C I O N 30306

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Mo PAGO	FECHA PGO	Ir PAGO
COMERCIO MINERO Y CO COLONIZACIONES S.A.	TRONCO POPULAR	050 00110-6	550534,9	28.12/2006	5,965,000 00	

30303 C O N C E P T O 30303

CANT	RENTISTAS	CONCEPTO	TOTAL CONCEPTO
1	50034-01-01 SOLICITUD	1 TRAMITES DE SOL DE PA EN E DE EN	463,000 00
		TOTAL	463,000 00

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RESPONSABLE _____

RECIBO DE CASH APLICADO AL EXPERIENTE No _____

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NIT : BGC176089-2

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

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(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.

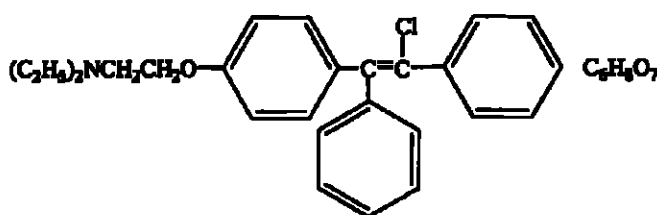
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(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 ($\pm$ SEM) mg/ml (17.0 nmol/L) while older men (age range 65yrs – 84 yrs. mean 70.7 yrs.) had a significantly lower mean 24 hrs. total serum testosterone level of 4.1 ± 0.4 mg/ml. ($P < 0.5$; 14.2 nmol/L). 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. Nonacrotal 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

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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

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 zuclophene) 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.

[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, 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

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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. Shamia, *et al.*, *Arch. Androl* 21:109 (1991). A WHO study showed no changes in semen quality or fertility after 6 months of treatment. (Anonymous *Androl.* 15:299 (1992).) A meta-analysis seems to confirm that testosterone levels go up in men with poor quality sperm but not fertility. (Vanderkerckhove, *et al.*, 2000). Studies have also suggested that long term treatment with clomiphene does not seem to have a drastic deleterious effect on health, although it did show that treatment resulted in poorer sperm quality after 4 months. Studies have kept men on clomiphene for as long as 18 months and at levels of 25 mg per day or 100 mg every other day.

[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)).

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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 azospermia, 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), Emcyte® (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 secretory total serum testosterone profile described in FIG. 1. For example, according to FIG. 1 a dosage of the preferred composition may be administered in a pharmaceutical formulation that would give rise to peak serum testosterone levels 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 Zuelomid (*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).

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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 Zucloimid on day 6 ($p = 0.03$ and $p = 0.00002$ respectively) and compared to Zucloimid on day 12 ($p = 0.047$). Zucloimid clearly did not raise total serum testosterone to any extent. Compared to the animals receiving Enclomid, the animals receiving Clomid exhibited more variable total testosterone levels on day 6 and later as judged by their coefficients of variations. When we looked at the time course of the effects (FIG. 3), we determined that only Enclomid significantly and statistically raised total serum testosterone on days 6 and 12 compared with either baseline or day 0 values. Moreover, cessation of Enclomid treatment, resulted in a significant drop in the level of total serum testosterone between day 12 and day 18 (washout). This indicates that Enclomid is readily cleared from the circulation consistent with the metabolic clearance seen for Enclomid in humans. Enclomid was clearly better and more consistent than Clomid itself and Zucloimid was ineffective.

Table I - 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 Zucloamid 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 Zucloamid resulted in a 22% increase in serum

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. 348 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

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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 Enclonud 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

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

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 [³H] dihydrotestosterone saturation analysis and by radioimmunoassay. Non-SHBG-bound testosterone levels (bioavailable testosterone) are also measured for example according to Tenover *et al.* J. Clin. Endocrinol. and Metab. 65:1118 (1987). See also Soderguard *et al.* J. Steroid. Biochem 16:801 (1982) incorporated herein by reference.

[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.

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 AndroxaTM 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 AndroxaTM (*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 AndroxaTM (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 AndroxaTM and placebo arms were randomized into cohorts that underwent in-clinic sessions on days 1 and 14 to determine pharmacokinetic parameters for AndroxaTM as well as cyclical changes in testosterone. The placebo and AndroxaTM 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 AndroxaTM 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 AndroxaTM 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

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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.

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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.

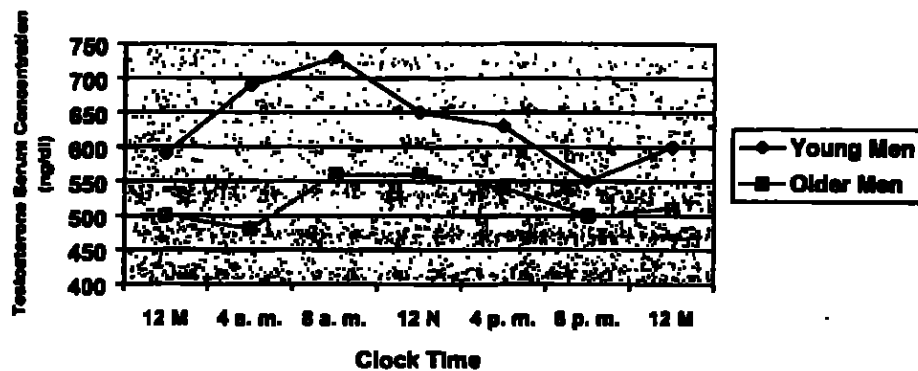
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16. The method of claim 12, wherein the patient is female.
17. The method of claim 1, wherein the composition is formulated for oral administration.
18. The method of claim 1, wherein the composition is formulated for extended release.

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FIG. 1

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



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FIG. 2

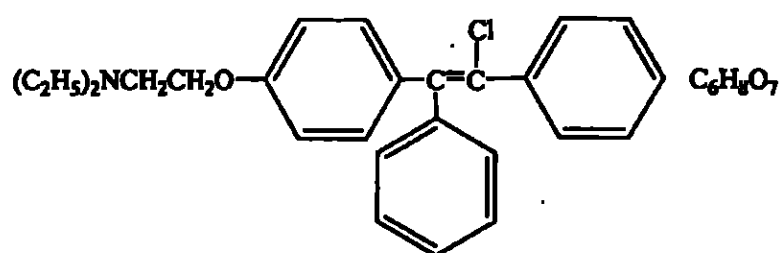
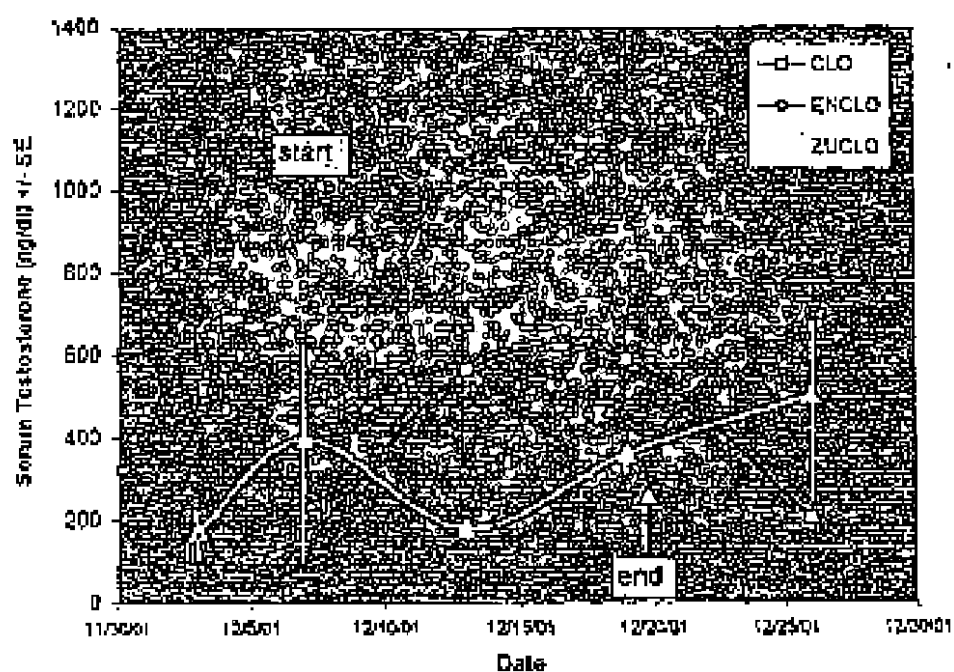
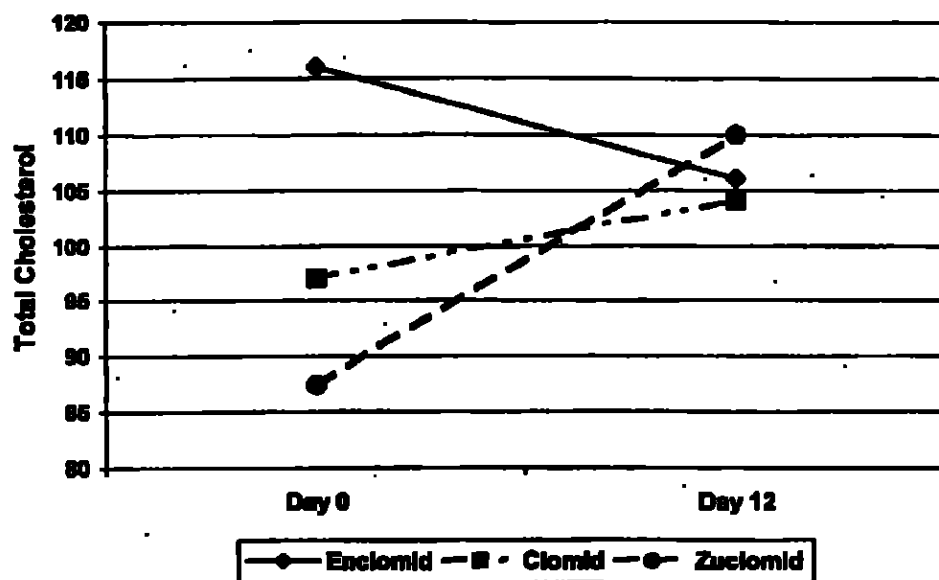


FIG. 3



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FIG. 4



Form FGT/BA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US2005/025000

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Classification 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+androxa1+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
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Y	abstract & IGAKU NO AYUMI , 115(9), 662-70 CODEN: IGAYAY; ISSN: 0367-7826, 1980,	2,3
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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. ☒ 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/025000

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			NO 20022221	A	28-06-2002
			PL 354726	A1	09-02-2004
			SK 8162002	A3	04-03-2003

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TRANS-CLOMIFENO PARA EL TRATAMIENTO DE HIPERTROFIA DE
PRÓSTATA BENIGNA, CÁNCER DE PRÓSTATA, HIPOGONADISMO,
TRIGLICERIDOS ELEVADOS Y COLESTEROL ALTO

PREFERENCIA CRUZADA A SOLICITUDES RELACIONADAS

[0001] La presente solicitud reivindica el beneficio de la Solicitud Provisional Estadounidense Número 60/588,123 presentada en Julio 14, 2004, la Solicitud Provisional Estadounidense Número 50/588,223 presentada en Julio 14, 2004, y la Solicitud Provisional Estadounidense Número 60/588,130 presentada en Julio 14, 2004, cada una de las cuales se incorpora aquí en su totalidad.

CAMPO DE LA INVENCION

[0002] La presente invención se relaciona con el uso de una composición que comprende clomifeno.

ANTECEDENTES

[0003] La testosterona es el andrógeno masculino principal, que juega un papel vital en la salud masculina general. La testosterona es esencial para el desarrollo y mantenimiento de tejidos reproductivos específicos (testículos, próstata, epididimis, vesícula seminal, y pene) y las características sexuales secundarias masculinas. Este juega un papel clave en la libido y la función eréctil y es necesario para la iniciación y mantenimiento de la espermatogénesis. La testosterona también tiene funciones importantes no relacionadas con tejidos reproductivos. Por ejemplo, este afecta positivamente la composición corporal al

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incrementar la retención de nitrógeno, que soporta la masa corporal magra, tamaño y resistencia del músculo. Este también actúa sobre el hueso para estimular la formación ósea.

[0004] La secreción de testosterona es el producto final de una serie de procesos hormonales. La hormona de liberación de Gonadotropina (GnRH), que se secreta en el hipotálamo, controla la secreción pulsátil de hormona luteinizante (LH) y la hormona de estímulo de folículo (FSH), que se secreta por la pituitaria anterior. El LH, en cambio, regula la producción y secreción de testosterona en células Leydig de los testículos, mientras que el FSH asiste en la inducción de la espermatogénesis. La testosterona es muy a menudo medida como "testosterona total". Esta medición incluye la testosterona que se une a la globulina de unión a hormona sexual (SHBG) (~44%) y por lo tanto no está biodisponible y la testosterona que está libre (~2%) o unida de forma ligera a otras proteínas (sin unión-SHBG) (~54%).

[0005] Los resultados de un estudio WHO indican que la testosterona se secreta normalmente en un ritmo circadiano, con niveles mayores en la mañana y niveles nadir que ocurren aproximadamente 8 a 10 p.m. Ver FIG. 1. Esta variación en la secreción de testosterona a través del día llega a ser mucho menos pronunciada en hombres mayores (edad promedio igual 71 años). La importancia de este ritmo no se conoce en este tiempo. Se obtienen muestras de pacientes jóvenes y mayores cada 10 minutos durante 24 horas por vía de una cánula de aspiración permanente. De acuerdo con Tenover (1987) los niveles promedio de testosterona de suero total en 24 horas en hombre jóvenes saludables (rango de edad 22 años – 35 años media 27.3 años) es de 4.9 ± 0.3 ($\pm$ SEM) mg/ml (17.0 nmol/L) mientras que los hombres mayores (rango de edad 65 años – 84 años

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media 70.7 años) tienen una media significativamente más baja nivel de testosterona en suero total en 24 horas de 4.1 ± 0.4 mg/ml ($P < 0.5$; 14.2 nmol/L). Los niveles de testosterona en suero obtenidos de muestras aleatorias únicas también son significativamente más bajo en hombres mayores (4.0 ± 0.2 mg/ml [13.9 nmol/L]) según se compara con 4.8 ± 0.2 mg/ml [16.6 nmol/L]) en hombres jóvenes saludables.

[0006] La deficiencia de testosterona puede resultar de trastornos genéticos o enfermedades subyacentes y también es frecuente una complicación con la edad. Por ejemplo, el hipogonadismo primario resulta de la falla testicular primaria. En esta situación, los niveles de testosterona son bajos y los niveles de gonadotropinas de pituitaria son elevados (LH y FSH). El hipogonadismo secundario se debe a la secreción inadecuada de las gonadotropinas de pituitaria. Adicionalmente a un bajo nivel de testosterona, los niveles LH y FSH son bajos o bajos – normales. Algunas de las secuelas de la deficiencia de testosterona en adultos incluyen una amplia variedad de síntomas que incluyen: pérdida de la libido, disfunción eréctil, oligospermia o asospermia, ausencia o regresión de características sexuales secundarias, reducción progresiva en masa muscular, fatiga, humor depresivo y riesgo incrementado de osteoporosis. Muchos de estos trastornos se refieren generalmente como menopausia masculina.

[0007] Existen varias formas de terapia de testosterona hoy en los Estados Unidos. Recientemente, las preparaciones transdérmicas han ganado favor en el mercado. Sin embargo, un parche de testosterona escrotal en niveles suprafisiológicos de 5α -dihidrotestosterona (DHT) debido a la alta concentración de 5α -reductasa en la piel del escroto. Los sistemas no escrútales se consideran más convenientes y la mayoría de los pacientes logra concentraciones de suero

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promedio dentro del rango normal y tienen niveles normales de DHT. La terapia de testosterona oral no se recomienda debido a que las dosis requeridas para terapia de reemplazo se asocian con riesgo significativo de hepatotoxicidad.

RESUMEN

[0008] La presente invención se relaciona con métodos y composiciones que comprenden *trans*-clomifeno. Esta composición también puede comprender *cis*-clomifeno. La composición puede comprender más de 1/1 v/v de *trans*-clomifeno. La composición puede comprender 0% a 29% en peso/peso de (*cis*, -Z-, *trans*-clomifeno) ("*cis*-clomifeno" o "Zuclomid") y 100% a 71% v/v (*trans*-, E-, *cis*-clomifeno) ("*trans*-clomifeno" o "Enclomid") o sales farmacéuticamente aceptables o solvatos de estos. La composición puede contener *cis*-clomifeno y *trans*-clomifeno, y la proporción de *trans*-clomifeno y *cis*-clomifeno puede ser mayor de 71/29. La composición puede comprender adicionalmente excipientes farmacéuticamente adecuados, diluyentes, portadores, y similares. La composición también puede comprender análogos de isómeros de *cis*-clomifeno y *trans*-clomifeno.

[0009] La composición se puede formular para una variedad de métodos de administración que incluyen administración oral, intravenosa, subcutánea, bucal, transmucosal, intratecal, intradérmica e intracisternal la composición también se puede formular para liberación extendida. En algunos métodos, las composiciones se pueden administrar de tal forma que dan aumento a los niveles de testosterona en suero generalmente similares a los niveles de testosterona en suero de un paciente normal. Las dosis de la composición se pueden administrar en una formulación farmacéutica que puede dar aumento a los picos en los niveles de

testosterona de suero entre aproximadamente 4 a.m. y en la noche. La composición también se puede administrar para dar aumento al pico de niveles de testosterona en suero en aproximadamente 8 a.m. Alternativamente, la composición se puede administrar para elevar a picos de niveles de testosterona en suero en cualquier tiempo del día que parezca adecuado al paciente y/o al medico que prescribe.

[0010] La composición se puede utilizar para tratar condiciones tales como cáncer de próstata e hipertrofia de próstata benigna. En el tratamiento del cáncer de próstata, la composición se puede administrar en un régimen de tratamiento que también incluye un quimioterapéutico. Quimioterapéuticos de ejemplo incluyen Taxotere® (doxetacel), Novantrone® (clorhidrato de mitoxantrona), Emcyt® (fosfato de sodio estramustina) doxorubicina, ketoconazol y vinblastina aunque también se pueden utilizar otros quimioterapéuticos. En algunos casos, el quimioterapéutico se puede administrar cerca al tiempo de la dosis de la composición. En otros casos el quimioterapéutico se puede administrar al paciente durante el mismo periodo de tiempo en el que el paciente está experimentando el tratamiento con la composición. El tratamiento con la composición puede preceder o seguir al tratamiento con el quimioterapéutico.

[0011] La composición también se puede utilizar para incrementar niveles de testosterona en suero en mamíferos machos hipogonadales, y para mejorar o evitar la secuela de niveles de testosterona bajos. Algunos síntomas, o secuelas, de niveles bajos de testosterona, que la presente invención puede utilizar para tratar, incluyen reducción de masa muscular, limitación de la capacidad de desempeño corporal, reducción de la densidad ósea, reducción de la libido, y/o reducción de potencia.

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[0012] La composición también se puede utilizar para reducir niveles de triglicéridos en mamíferos, y más específicamente en mamíferos machos, y para mejorar o evitar la secuela de altos niveles de colesterol. La composición también se puede utilizar en el tratamiento de niveles altos de colesterol en mamíferos, y más específicamente en mamíferos machos. Aunque los métodos de reducción de los niveles de triglicéridos y la mejora o prevención de las secuelas de niveles altos de colesterol se utilizan preferiblemente para tratar machos, ellos se también se pueden utilizar para tratar hembras.

BREVE DESCRIPCION DE LOS DIBUJOS

[0013] La Figura 1 es una gráfica representativa de perfiles de testosterona de suero total secretores normales en hombres saludables (jóvenes y viejos).

[0014] La Figura 2 muestra una estructura química de citrato de clomifeno.

[0015] La Figura 3 es una demostración gráfica del curso de tiempo de niveles de testosterona en suero con Clomid, Enclomid y Zuclomid.

[0016] La Figura 4 es una demostración gráfica del curso de tiempo de los niveles colesterol en babuinos machos tratados con Clomid, Enclomid y Zuclomid.

DESCRIPCIÓN DETALLADA

[0017] La administración del clomifeno puede resultar en un incremento en niveles de testosterona. Como se muestra en el ejemplo 3, la administración de una composición que comprende *trans*-clomifeno puede incrementar los niveles de

testosterona y puede suministrar una terapia efectiva para mejorar o prevenir uno o más síntomas de niveles bajos de testosterona. Sorprendentemente, la administración de una composición que comprende *trans*-clomifeno a machos afecta favorablemente la proporción del DHT con testosterona. Como un resultado, las composiciones que comprenden *trans*-clomifeno se pueden utilizar para tratar hipertrofia de próstata benigna y cáncer de próstata en machos al reducir la proporción relativa de DHT con testosterona. Adicionalmente, la administración de una composición que comprende *trans*-clomifeno se puede utilizar para reducir niveles de triglicéridos.

1. Composiciones de Clomifeno

[0018] La presente invención se relaciona con una composición que comprende clomifeno. El clomifeno (figura 2) es un antiestrógeno relacionado con el tamoxifen que bloquea la retroalimentación del estrógeno normal en el hipotálamo y la posterior retroalimentación negativa en la pituitaria, que puede conducir un incremento en la hormona luteinizante (LH) y la hormona de estímulo de folículo (FSH). Se ha utilizado el clomifeno para la intervención terapéutica en hombres con bajos niveles de testosterona. Tenover *et.al.*, J. Clin. Endocrinol. Metab. 64:1103, (1987) y Tenover *et. al.*, J. Clin. Endocrinol. Metab. 64:1118 (1987) incremento encontrado en FSH, LH en hombres jóvenes y viejos después de tratamiento con clomifeno. Ellos también encuentran aumento en testosterona libre y total en hombres jóvenes que muestran aumentos significativos. En los hombres, estos niveles incrementados de gonadotropinas estimulan las células Leydig de los testículos y resulta en la producción de niveles mayores de testosterona.

[0019] El clomifeno es una mezcla de dos isómeros geométricos *cis*, -Z-, clomifeno (*cis*-clomifeno o zuclomifeno) y *trans*-, E-, clomifeno (*trans*-clomifeno o enclomifeno). El HCl *trans*-clomifeno tiene un punto de fusión de 149°C-150.5°C, mientras que el *cis*-clomifeno HCl tiene un punto de fusión de 156.5°C-158°C. Los isómeros también se reportan por tener diferente vida medio in vivo. El clomifeno está actualmente aprobado como una mezcla de *cis*- y *trans*-isómeros, el *cis*-isómero está presente como aproximadamente 30% a 50% (Manual Merck) para mejoramiento de fertilidad en el paciente anovulatorio. Cuando se administra al paciente anovulatorio, el clomifeno mejora la ovulación al iniciar una serie de eventos endocrinos que culminan en un surgimiento de gonadotropina preovulatoria y posterior ruptura folicular. La droga se recomienda se administre durante 5 días en una dosis de hasta 100 mg diariamente. El clomifeno también se ha asociado con numerosos efectos colaterales que incluyen: visión turbia, incomodidad abdominal, ginecomastia, tumores testiculares, flujos vasomotores, náusea, y jaquecas. Adicionalmente, otros estudios sugieren que el clomifeno posee efecto de mejoramiento genotóxico y de tumor. El resultado neto de estas observaciones es que el clomifeno en su formato actual que tiene entre 30% y 50% del isómero *cis*, debe ser inaceptable para terapia crónica en hombres para el tratamiento de deficiencia de testosterona.

[0020] El *trans*-isómero de clomifeno es antiestrogénico (AE) mientras que el *cis*-isómero es la forma más potente y más estrogénica y también se ha reportado que tiene actividad anti-estrogénica. El efecto del clomifeno en la actividad ovulatoria se atribuye a ambas formas en razón a que la mezcla es más efectiva que el *trans*-clomifeno solo. El *trans*-isómero ayuda a la ovulación en el nivel del hipotálamo. El isómero *cis*-clomifeno estrogénico contribuye a la ovulación mejorada en cualquier parte en la que la trayectoria fisiológica conduzca

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a la ovulación. Los isómeros también se reporta que tienen diferente vida media in vivo. Adicionalmente, la forma *cis* ha reportado que deja niveles sanguíneos residuales en exceso de un mes luego de una dosis única.

[0021] Vandekerckhove, *et. al.* (Cochrane Database Syst Rev 2000; (2): CD000151 (2000)) nota que diez estudios que involucran 738 hombres han sugerido que los anti-estrógenos parecen tener un efecto benéfico en los resultados endocrinos, es decir testosterona, pero no hubo suficiente evidencia para evaluar los efectos de fertilidad. A pesar de eso, la administración de clomifeno puede mejorar los niveles de testosterona luego que uno pueda concluir fácilmente que la droga pueda impactar positivamente los efectos colaterales de la privación de testosterona tanto tiempo como los testículos todavía retengan la capacidad de responder a la estimulación de la gonadotropina.

[0022] La composición de clomifeno puede comprender trans-clomifeno o una sal farmacéuticamente aceptable de ésta. El cis-clomifeno o una sal farmacéuticamente aceptable de ésta también puede estar presente en la composición. La proporción de trans-clomifeno con cis-clomifeno puede ser mayor de 1/1 p/p. La proporción de trans-clomifeno con cis-clomifeno también puede ser mayor de 71/29. La composición puede comprender aproximadamente 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 o 100% p/p de ingredientes activos de trans-clomifeno. Análogos de isómeros trans- y cis- de clomifeno tales como aquellos descritos en Ernst et al., J. Pharmaceut. Sci. 65:148 (1976) también se pueden utilizar.

a. Formulaciones

[0023] La composición de clomifeno se puede formular para administración oral, intravenosa, subcutánea, bucal, transmucosal, intratecal, intradérmica, intracisternal, u otras rutas de administración. Las composiciones farmacéuticas adecuadas o formas de dosis unitarias pueden estar en la forma de sólidos, tales como tabletas o cápsulas llenas o líquidos tales como soluciones, suspensiones, elixires o cápsulas llenas con la misma, todas para uso oral. La composición también puede estar en la forma de soluciones inyectables estériles o emulsiones para uso parenteral (que incluye uso subcutáneo). La composición también puede estar en la forma de parches, ungüentos, supositorios, inhalantes o pastillas. Otras formulaciones para administración también pueden ser apropiadas y serán entendidas por un experto en la técnica. Tal composición farmacéutica y formas de dosis unitarias de éstas pueden comprender ingredientes farmacéuticamente aceptables adicionales tales como adyuvantes, diluyentes, portadores, o excipientes en proporciones convencionales.

[0024] Las formulaciones farmacéuticas pueden estar en la forma reformulaciones de liberación sostenida preparadas como se describe por ejemplo en la Patente Estadounidense No. 6,221,399, Patente Japonesa 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); Patentes Estadounidenses Nos. 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.

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2. Métodos de Tratamiento

[0025] Como se utiliza aquí, "tratamiento" o "tratar" o "que trata" cuando se refiere a la protección de un mamífero de una condición, significa evitar, suprimir, reprimir, o eliminar el trastorno. Evitar que la condición involucre administrar la composición a un mamífero antes del inicio de la condición. Suprimir la condición involucra administrar la composición a un mamífero después de la inducción del trastorno pero antes de su aparición clínica. Reprimir la condición involucra administrar la composición a un mamífero después de aparición clínica del trastorno de tal forma que el trastorno se reduce o mantiene. Eliminar el trastorno involucra administrar la composición a un mamífero después de la aparición clínica del trastorno de tal forma que el mamífero no sufra más la condición.

[0026] Varios estudios se han conducido sobre los efectos del tratamiento con clomifeno para trastornos diferentes a la anovulación descrita anteriormente. Por ejemplo, se han conducido estudios para determinar si o no el clomifeno se puede utilizar para mejorar la fertilidad en hombres al mejorar la calidad del semen. Homonnai et al., *Fertil. and Steril.* 50:801 (1988) dio aumento en la concentración de esperma y conteo pero otros no. (Ver, por ejemplo, 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); y Breznik, *Arch. Androl.* 21:109 (1993)). Un grupo vio el deterioro en el porcentaje de esperma normal con tratamiento a largo plazo. Shamis, et al., *Arch. Androl* 21:109 (1991). Un estudio WHO no mostró cambios en la calidad del semen o fertilidad después de 6 meses de tratamiento (Anonymous *Androl.* 15:299 (1992)). Un meta-análisis parece confirmar que los niveles de testosterona aumentan en los hombres con pobre calidad de esperma pero no fertilidad. (Vanderkerckhove, et al., 2000). Los estudios también han sugerido que el tratamiento a largo plazo con clomifeno no parece tener un efecto

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deletéreo drástico en la salud, aunque este mostró que el tratamiento resulta en calidad pobre de espermatozoides después de 4 meses. Los estudios han mantenido hombres en clomifeno durante 18 meses y en niveles de 25 mg por día o 100 mg cada tercer día.

[0027] En 1991, Guay et al (Urology 38:377 (1991)) sugiere que el clomifeno puede tratar la disfunción sexual en hombres. Su hipótesis parece ser que la función sexual sigue los niveles de la testosterona. Esto se soporta por estudios previos que muestran la influencia positiva de los andrógenos y la función sexual, Davidson, et al., J. Clin. Endocrinol. Metab 48:955 (1979), y los estudios que clasifican erecciones relacionadas con el sueño como una respuesta fuerte para T, Cunningham, et al., J. Clin. Endocrinol. Metab 70:792 (1990). Sin embargo, en 1995, Guay et al. (Gray, et al., J. Clin. Endocrinol. Metab. 80:3546 (1995)) publica un estudio en el que ellos ven un incremento el LH, FSH, y testosterona después de 2 meses clomifeno pero no muestran efectos en disfunción eréctil. Eso puede ser muy ventajoso para hombres jóvenes y grupos específicos de hombres mayores, pero parece que el nivel de testosterona no es suficiente. Efectos de testosterona en erecciones relacionadas con el sueño pueden haber sido tomadas muy seriamente (Herskowitz, et al., J. Psychosomat. Res. 42:541 (1997)).

a. Hipogonadismo

[0028] El hipogonadismo se puede tratar al administrar a un paciente en necesidad de este una cantidad efectiva de una composición de clomifeno. El trastorno asociado con el hipogonadismo puede incluir, pero no se limita a, reducción de masa muscular, limitación de la capacidad del desempeño corporal, reducción de la densidad ósea, reducción del alivio, reducción de potencia,

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hiperplasia prostática benigna, oligospermia, o azoospermia, ausencia o regresiones de características sexuales secundarias, reducción de la masa muscular, fatiga y depresión.

b. Hipertrofia de Próstata Benigna (BPH)

[0029] El BPH se puede tratar al administrar a un paciente en necesidad de este una cantidad efectiva de la composición de clomifeno. Los niveles de testosterona se pueden incrementar al administrar la composición de clomifeno mientras que afecta positivamente la proporción de testosterona con DHT comparado con complementos de testosterona.

c. Cáncer de Próstata

[0030] El cáncer de próstata se puede tratar al administrar una cantidad efectiva de una composición de clomifeno. La administración de las composiciones puede reducir la proporción de testosterona con DHT comparado con complementos de testosterona. Preferiblemente, en el tratamiento de cáncer de próstata, la composición de puede administrar en un régimen de tratamiento que también incluye un quimioterapéutico. Quimioterapéuticos de ejemplo incluye Taxotere® (docetaxel), Novantrona® (clorhidrato de mitoxantrona), Emcyt® (fosfato de sodio estramustina) doxorubicina, quetoconazol y vinblastina aunque otros quimioterapéuticos también se pueden utilizar. En algunos casos, el quimioterapéutico se puede administrar cercanamente al tiempo de la dosis de la composición. En otros casos el quimioterapéutico se puede administrar al paciente durante el mismo período de tiempo en el que el paciente está experimentando tratamiento con la composición de clomifeno. En todavía otros casos, el

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tratamiento con la composición de clomifeno puede preceder o seguir a tratamiento con el quimioterapéutico.

d. Triglicéridos Elevados

[0031] Se pueden tratar los triglicéridos elevados al administrar una cantidad efectiva de una composición de clomifeno. El paciente puede ser macho o hembra.

e. Métodos de Administración

[0032] Las composiciones de clomifeno se pueden administrar oralmente. Ellas también se pueden administrar por rutas de administración intravenosa, subcutánea, bucal, transmucosal, intratecal, intradérmica, intracisternal u otras rutas de administración. Dependiendo de las necesidades del paciente, y el juicio del médico que prescribe, el DHT y los niveles de testosterona en suero se pueden medir y la dosis se pueden alterar para alcanzar niveles benéficos de DHT y testosterona. Los niveles de testosterona también se pueden medir para un aumento suficiente en los niveles de testosterona en suero para alcanzar los resultados fisiológicos deseados asociados con testosterona normal descritos anteriormente. De forma similar, se pueden medir los niveles de triglicéridos antes y/o después de administración para determinar la dosis apropiada.

f. Dosis

[0033] En general, la composición de clomifeno se puede administrar como parte de un régimen de dosis diseñado para elevar los niveles de testosterona en

suero que imiten o correspondan al perfil de testosterona de suero total secretado normal descrito en la Figura 1. Por ejemplo, de acuerdo con la Figura 1 una dosis de la composición preferida se puede administrar en una formulación farmacéutica que pueda aumentar a niveles pico de testosterona en suero entre aproximadamente 4 a.m. y en la noche. Más específicamente la composición se puede administrar para elevar a picos en niveles de testosterona en suero aproximadamente 8 a.m. Alternativamente, las composiciones se pueden administrar para elevar a picos de niveles de testosterona en suero en cualquier tiempo del día considerado adecuado para un paciente y/o el médico que prescribe. En otra alternativa, tal como en alguno de los casos en donde el paciente, tiene triglicéridos elevados, pero también en otros casos dependiendo de la condición del paciente y los síntomas, el médico que prescribe puede desear administrar las composiciones sin respecto a los niveles de testosterona en suero.

[0034] La composición de clomifeno se puede administrar en una o más dosis de aproximadamente un mg a aproximadamente 200 mg (aunque la determinación de la dosis óptima es con el nivel de un experto en la técnica.

[0035] Los siguientes ejemplos son ilustrativos de la invención y no se pretenden limiten al alcance de la invención como se establece en las reivindicaciones adjuntas.

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EJEMPLO 1

Efecto de Clomid en Testosterona en Suero y Colesterol en Babuinos

Machos

[0036] Machos babuinos adultos se les da 1.5 mg/kg de Clomid, Enclomid (*trans*-Clomid) o Zuclomid (*cis*-Clomid) durante 12 días consecutivos. Las muestras se analizan y se toma suero en el día de primer tratamiento antes de darse el artículo de ensayo (día 0), después 12 días de tratamiento (día 12) y 7 días después del último tratamiento (fin o lavado).

1 .Efectos sobre el Peso Corporal y LH, FSH, PRL de Suero y Testosterona

[0037] Hubo incremento significativo en testosterona total en suero en el grupo que recibe Enclomid. Ver Tabla 1. No hubo diferencias entre los grupos en el período de línea base o en el día 0. Tampoco hubo diferencias entre los tres grupos de 7 días después de tratamiento (el período de lavado). Sin embargo, el Enclomid produce niveles mayores de testosterona comparados con el Clomid y Zuclomid en el día 6 ($p=0.03$ y $p=0.00002$ respectivamente) y comparado con el Zuclomid en el día 12 ($p=0.047$). El Zuclomid claramente no eleva la testosterona total en suero en ningún alcance. Comparado con los animales que reciben Enclomid, los animales que reciben Clomid exhiben más niveles de testosterona total variables en el día 6 y luego se juzga por los coeficientes de variaciones. Cuando observamos al tiempo del curso de los efectos (la FIGURA 3), determinamos que solo el Enclomid significativa y estadísticamente eleva la testosterona total en suero en los días 6 y 12 comparados con la línea base o los valores en el día 0. Más aún, la cesación el tratamiento con Enclomid resulta en

una caída significativa en el nivel de testosterona total en suero entre el día 12 y el día 18 (lavado). Esto indica que el Enclomid es fácilmente retirado de circulación consistente con la circulación metabólica vista para Enclomid en humanos. El Enclomid fue claramente mejor y más consistente que el Clomid en si mismo y el Zuclomid fue inefectivo.

Tabla 1 Niveles de Testosterona en Suero (ng/dl)

Grupo	ID	Línea Base 12/3/01	0 días 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
	ED	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
	ED	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
	ED	97.3	448.0	45.8	46.0	316.8

[0038] No hubo cambios en LH o FSH en suero. La proporción de testosterona total en suero para el LH siguió el mismo patrón como la testosterona total en suero, lo que sugiere una falta de dependencia (datos no mostrados). Tampoco hubo cambio en el peso corporal durante el estudio de 12 días. Hubo una reducción en la prolactina en suero (PRL) durante el estudio en el grupo que recibe Enclomid, lo que sugiere un efecto de antiestrógeno que se ha descrito en parte (Ben-Jonathan y Hnasko, 2001) y esperado sobre la base del hecho de que como en un hombre de edad la testosterona declina y se incrementa la Prolactina (Feldman et al., 2002).

2. Efectos sobre los niveles de Colesterol

[0039] El tratamiento con Enclomid tiende a reducir el colesterol en suero y el Zucloimid tiende a incrementar el mismo parámetro. El análisis preliminar indica que los cambios en los niveles de colesterol no fueron estadísticamente significativos y que los cambios están dentro del rango normal. Debido a la tendencia observada para los dos isómeros para demostrar efectos opuestos sobre los niveles de colesterol durante un período corto de tiempo, se conducen, análisis adicionales.

[0040] Análisis detallados indican que el Enclomid resulta es una reducción de 8% en niveles de colesterol en suero. Por el contrario, el tratamiento con Zucloimid resulta en un incremento del 22% en niveles de colesterol en suero. El tratamiento con Clomid resulta en un ligero incremento en niveles de colesterol en suero. El efecto opuesto del Enclomid y Zucloimid en niveles de colesterol en suero no se espera dado que los isómeros tienen, alternativamente agonista de estrógeno o actividad antagonista. Estos resultados indican que el Enclomid se

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puede utilizar para tratar pacientes con altos niveles de colesterol. Estos resultados también indican que el Enclomid puede ser más benigno que el Zuvlomid con respecto al colesterol en suero si se utiliza crónicamente para incrementar niveles de testosterona.

3. Efectos sobre los Parámetros Químicos Clínicos

[0041] Los valores promedio para cada parámetro no difieren entre los tres grupos para cualquier parámetro de ensayo al inicio del estudio según se determina por ANOVA o mediante el ensayo Kruzkal-Wallis. Todos los grupos exhiben valores normales en cada parámetro excepto para sodio suero (1); un parámetro calculado relacionado, espacio aniónico, que fue bajo para todos los nueve babuinos a través del ensayo; (2) glucosa en suero; y (3) BUN que fue alto en el día 0 para el grupo que se trató con Enclomid. En el día 12 del tratamiento y 7 días después de tratamiento (lavado), no hubo diferencia entre grupos para cualquier parámetro excepto el espacio aniónico que mostró que los grupos Clomid y Zuclomid tienen bajos valores a diferencia del grupo Enclomid. Los valores de sodio suero y espacio aniónico parecen ser anomalías asociadas con este grupo de babuinos.

[0042] Hubo efectos sustantivos en la población de células rojas con Enclomid y Zuclomid y en hematocritos con Zuclomid. Todos los compuestos reducen la concentración de hemoglobina celular promedio (MCHC) en el día 0 o en el punto final. Sin cambio en la media de hemoglobina celular (MCH) y un incremento en la media de volumen celular (MCV), la reducción del (MCHC) es predecible. Aunque se puede esperar que la testosterona eleve los hematocritos, solo el tratamiento de Zuclomid, que no incrementa la testosterona total en suero,

demuestra una diferencia estadística. Claramente, los hombres en un ensayo clínico que utilizan Zuclomid se deben monitorear para las características de su población de células sanguíneas rojas. Se predice que el Enclomid tiene menos de un efecto.

[0043] Parece que hay un efecto claro del Enclomid en el tratamiento de 12 días sobre las plaquetas aunque los valores encontrados permanecen dentro del rango normal. Una cosa para considerar aquí es el dimorfismo sexual en los conteos de plaquetas entre babuinos macho y hembras (279 para machos vs. 348 para hembras). Esto se debe probablemente a las hormonas. En razón a que el grupo Enclomid demuestra testosterona incrementada, la reducción de conteo de plaquetas puede ser secundaria al cambio en testosterona en este grupo. Más aún, el tratamiento con Enclomid empuja al conteo de plaquetas a su nivel masculino normal de un nivel de día 0 que es el extremo alto del rango normal para este grupo. El Enclomid no predecirá necesariamente un efecto deletéreo sobre las plaquetas.

[0044] Se ensayan todos los Clómidos que tienen efecto sobre la población de células sanguínea blanca (WBC), lo más llamativo es que el Enclomid eleva los conteos de linfocitos y eosinófilos. Los efectos no son tan directos como ellos pudieran ser. Parece ser un efecto fuerte del Enclomid sobre la reducción del porcentaje de granulocitos en la sangre. Los efectos son muy fuertes después del período de lavado de 7 días cuando los valores se reducen por debajo del rango normal. (Este curso de tiempo puede reflejar el relativamente largo tiempo requerido para afectar el cambio de la población WBC). Existe poco dimorfismo sexual en babuinos con respecto a las poblaciones de células sanguíneas blancas, de tal forma que los efectos son más probablemente debidos al

compuesto en si mismo que cambia en la testosterona. Sin embargo, cuando observamos en el conteo calculado de granulocitos utilizando el conteo WBC, no hallamos diferencias en el conteo de granulocitos debido a cualquier compuesto. Concomitantemente, es la historia de linfocito que es más interesante. Ambos, el conteo y el porcentaje de linfocitos en la población se incrementan con el tratamiento de Enclomid. Mientras que los valores medio de porcentaje de linfocitos permanece en el rango normal, dada la tendencia de un incremento en conteo WBC, el efecto neto es un incremento en conteo de linfocitos con Enclomid. Este resultado de eosinófilo es análogo. Existe una clara implicación para tratar hombres que tienen bajos linfocitos, tal como hombres que son VIH positivos. En razón a que el Enclomid es poco probable que reduzca los linfocitos basados en estos resultados, se puede hacer un caso para su uso en la población de hombres con SIDA. Estos individuos a menudo se tratan con agentes que están destinados a elevar la testosterona debido a los efectos residuales de la enfermedad. Baja toxicidad de hígado y riñón y efectos favorables sobre el colesterol y los lípidos también son atributos altamente favorables para cualquier medicación destinada para uso en hombres VIH positivos quienes ya están comprometidos por su enfermedad.

[0045] El incremento en glucosa de suero con Clomid o Zucloimid está dentro del rango normal. En el caso del Enclomid en donde los valores promedio de glucosa en suero fueron altos en el día 0, no hubo incremento con el tratamiento. No hubo evidencia de que el Enclomid tenga un efecto deletéreo en la glucosa sanguínea.

[0046] Ningún efecto claramente adverso en la función del hígado es evidente según se juzga por las enzimas AST y ALT. La tendencia en estos

valores es una reducción con el tratamiento. Un incremento en el nivel de enzimas en el suero indicará daño de hígado. El ALT/SGPT está fuera del rango bajo en el extremo del estudio para el grupo Clomid aunque las diferencias sobre el período de tratamiento no fueron significativas estadísticamente. Los cambios con el Enclomid y Zucloimid están dentro del rango normal. El AST se reduce en embarazo; así la reacción de un agonista estrógeno tal como el Zucloimid en la reducción del nivel AST marginal puede ser racionalizado. También se encuentra fosfatasa alcalina (ALP) en el hígado y se eleva varios estados de la enfermedad. La reducción del ALP arguye adicionalmente contra el daño hepático. No hubo cambios en la albúmina de suero, tampoco un producto del hígado. Una fuerte supresión de la albúmina de suero sobre un período de tiempo extendido puede contribuir a liberar niveles de hormona esteroide en suero en humanos aunque un papel más importante se juega por la hormona sexual que se une a la globulina. Como una línea de fondo, ninguno de los compuestos se puede ligar a daño de hígado sobre la base de los parámetros ensayados.

[0047] La actividad osteoblástica y las enfermedades del hueso se acompañan por altos valores de ALP en suero. El ALP no se eleva luego de tratamiento con Zucloimid y se reduce en valores que siguen el tratamiento de Enclomid. La tendencia podría predecir un resultado más benigno para el uso de Enclomid comparado con el Zucloimid.

[0048] Aunque el BUN y BUN/creatinina se alteran durante el estudio en los grupos Clomid y Enclomid, la falta de cambio definitivo en creatinina arguye contra la disfunción renal. Una pérdida de capacidad de filtración glomerular podría resultar en un incremento en BUN. La reducción de BUN ocurre en humanos debido a la pobre nutrición (probablemente no en una configuración controlada), o

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alta toma de fluidos (presumiblemente acompañada por edema). También, a pesar de un incremento en la testosterona de suero total entre el día 0 y el día 12 con Enclomid, no hay diferencias entre los valores de creatinina en suero, lo que arguye contra un incremento en la masa muscular durante este corto intervalo de tiempo.

[0049] Los niveles de sodio en suero fueron más bajos que los valores de referencia para todos los animales durante el estudio. El dióxido de carbono en suero fue mayor que los valores de referencia en el día 12 para los grupos Clomid y Zucloimid. El espacio de anión en suero fue menor para todos los animales durante el estudio, haciendo un paralelo con los resultados de sodio. El Enclomid eleva este parámetro hacia valores normales. Los desbalances de electrolitos detectados en los ensayos de animales durante todos los periodos de tratamiento permanece elusivo pero puede ser parte del mismo fenómeno de trastorno de fluidos sugerido por los resultados BUN.

[0050] Los anteriores resultados indican que el Enclomid es más efectivo que el Clomid o el Zucloimid en mejoramiento de la testosterona total en suero. El zucloimid claramente no es efectivo y esa deficiencia limita cualquier uso del Clomid para hipogonadismo, particularmente en razón al componente del Zucloimid de Clomid puede predominar en la circulación durante el tiempo dado que es mayor de vida media.

[0051] El Enclomid parece ser relativamente benigno en todos los aspectos cuando se compara con el Zucloimid y, a menudo, aún con el Clomid. Esto es particularmente cierto cuando se da consideración a la tendencia del Enclomid para reducir el colesterol, y las enzimas del hígado opuesto a la tendencia del

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Zuclomid para elevar los mismos parámetros. La tendencia sorprendente del Enclomid para elevar el conteo de linfocitos puede ser útil para hombres con SIDA si se puede mostrar que la subpoblación CD4+ de linfocitos no se reduce o se mejora.

EJEMPLO 2

Método para Incrementar Nivel de Testosterona en Hombres que Utilizan Trans-clomifeno y Mezclas de Trans-clomifeno y Cis-clomifeno en Proporciones Mayores de 1.

[0052] Antes de la administración del trans-clomifeno, se toman muestras sanguíneas de sujetos machos y se mide los niveles de testosterona utilizando las metodologías descritas para el ejemplo en Matsumoto, et al. Clin. Endocrinol. Metab. 56; 720 (1983) (incorporada aquí como referencia). La globulina de unión a hormona sexual (SHBG) libre y unida a la testosterona, también se puede medir como se describe en el ejemplo Tenover et al. J. Clin. Endocrinol Metab. 65:1118 (1987) que describe mediciones de SHBG mediante un análisis de saturación de dihidrotestosterona [^3H] y mediante radioinmunoensayo. Los niveles de testosterona no unidos al SHBG (testosterona biodisponible) también se miden para el ejemplo de acuerdo con Tenover et al. J. Clin. Endocrinol y Metab. 65:1118 (1987). Ver también Soderguard et al. J. Steroid. Biochem 16:801 (1982) incorporado aquí como referencia.

[0053] Se le dan dosis diarias a los pacientes de 1.5 mg/kg de clomifeno, en donde la proporción de trans-clomifeno a cis-clomifeno es mayor de 1. Los pacientes se monitorean para niveles de testosterona de tal forma que la cantidad

de dosis y frecuencia de dosis se puede ajustar para lograr niveles terapéuticos de testosterona en el paciente.

EJEMPLO 3

Método para Reducir Niveles de Triglicérido en Hombres que Utilizan Trans-clomifeno y Mezclas de Trans-clomifeno y Cis-clomifeno en Proporciones Mayores de 1.

[0054] Antes de la administración de trans-clomifeno, se toman muestras de sangre de sujetos machos y se miden los niveles de triglicéridos utilizando metodologías descritas por ejemplo en 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), que se incorpora aquí como referencia.

[0055] Se les dan dosis diarias a los pacientes de 1.5 mg/kg de clomifeno, en donde la proporción de trans-clomifeno a cis-clomifeno es mayor de 1. La cantidad de dosis y frecuencia de dosis de clomifeno se puede ajustar para lograr niveles terapéuticos de triglicéridos en el paciente al monitorear los niveles de triglicéridos en diferentes vías del tratamiento.

EJEMPLO 4

Método para Reducir Niveles de Triglicéridos en Mujeres Utilizando *Trans*-clomifeno y Mezclas de *Trans*-clomifeno y *Cis*-clomifeno en Proporciones mayores de 1

[0056] Antes de administración del *Trans*-clomifeno, se toman muestras de sangre de sujetos hembras y se miden los niveles de triglicéridos como en el Ejemplo 3.

[0057] Se le dan dosis diarias a las pacientes de 1.5 mg/kg de clomifeno, en donde la proporción de *Trans*-clomifeno a *Cis*-clomifeno es mayor de 1. La cantidad de dosis y la frecuencia de dosis de clomifeno se pueden ajustar para alcanzar niveles terapéuticos de triglicéridos en el paciente al monitorear niveles de triglicéridos en diferentes días del tratamiento.

EJEMPLO 5

Comparación de Androxal™ con Androgel®

[0058] Se conduce un estudio de inoculación controlada de placebo en el avance Biological Research, Inc. (ABR) Clinical Research Center in Hackensack, New Jersey para comparar la administración oral de Androxal™ (*Trans*-clomifeno) con Androgel® (testosterona) en hombres hipogonadales. El Androgel® (Solvay Pharmaceuticals, Inc.) consiste de una crema que administra 5testosterona exógena en una matriz transdérmica.

[0059] El estudio vincula 62 hombres hipogonadales con niveles de testosterona menores de 300 ng/dl (normal 298-1034 ng/dl) que se aleatorizan en 6 diferentes grupos, tres dosis de Androxal™ (12.5 mg, 25 mg, y 50 mg), placebo, y altas y bajas dosis de Androgel®. La mitad de los hombres en cada grupo Androxal™ y de placebo se aleatorizan en cohortes que experimentaron secciones en clínica en los días 1 y 14 para determinar los parámetro farmacocinéticos para

el Androxal™ así como también cambios clínicos en testosterona. La dosis de placebo y Androxal™ se administran en una forma de doble ciego. La crema Androgeol® se administra en una forma de etiqueta abierta. La mitad de los pacientes Androgeol® experimentaron secciones similares en clínica a otros pacientes en el estudio. Luego de las dos exposiciones de los pacientes a droga semanal se sigue de siete días adicionales a diez días para determinar el estado de nivel de testosterona.

[0060] No se notaron efectos colaterales en ninguno de los grupos Androxal™ o Androgeol® del estudio que fueran diferentes al placebo. Adicionalmente, todas las dosis producen cambios significativos estadísticamente en testosterona de los niveles de testosterona de línea base. Las bajas, medias y altas dosis de Androxal™ alcanzan incrementos promedio de 169, 247 y 294 mg/dl respectivamente, mientras que aquellos del Androgeol® 5G, la dosis más baja aprobada, y el Androgeol® 10G, la dosis más alta aprobada, produce cambios de la línea base que son de 212 y 363 ng/dl. Estos valores son estadísticamente indistinguibles de aquellos cambios alcanzados con el Androxal™. Esta incapacidad para mostrar diferencias entre el Androxal™ y el Androgeol® parece resultar de los resultados altamente variables encontrados cuando se utiliza Androgeol®. Por ejemplo la dosis de 50 mg de Androxal™ eleva la media total de testosterona a 589 ± 172 ng/dl después de 15 días, un coeficiente de variación (CV) de 29% es similar al grupo de placebo (36%). De otra parte el Androgeol® 5G y 10G produce valores de testosterona promedio totales de 473 ± 289 ng/dl y 608 ± 323 ng/dl, CV de 61% y 53% respectivamente.

[0061] Después de 14 días de terapia con Androxal™ todas las dosis se asocian con un patrón diurno de testosterona similar al grupo de placebo, es decir un pico en la mañana, al mediodía, y durante la noche. Sin estar ligado por la teoría, este patrón se puede deber a la forma de acción del Androxal™, que parece ser mediado a través de efectos en el eje hipotálamico-pituitaria. El patrón diurno para los hombres en Androge® fue casi plano. Sin embargo, picos en total de la testosterona para el Androge® se asocian con la dosificación y a menudo exceden el alto nivel normal de 1034 ng/dl. Ciertos individuos en Androge® son capaces de alcanzar niveles pico de testosterona total sobre 2500 ng/dl.

[0062] El efecto en los niveles de dihidrotestosterona en suero (DHT) también se mide. Los hombres con Androxal™ experimentaron un cambio favorable en su DHT para testosterona total. Por ejemplo hombre en dosis de 50 mg de Androxal™ experimentaron una proporción de DHT/TT de 0.83 con la proporción de grupo de placebo de 1.07. Por contraste la proporción DHT/TT para los grupos Androge® fue de >1.5. Los resultados indican que los hombres con Androge® ganaron DHT más rápido que el total de testosterona. Así, los niveles normales de DHT se interrumpieron con relación a la testosterona en hombres con terapia Androge®.

[0063] Los resultados de parámetros químicos clínicos también indican, inesperadamente, que los hombres en Androxal™ experimentaron una reducción no dependiente de dosis en triglicéridos. La reducción en triglicéridos promedió una reducción de 19.1% después de dos semanas de terapia. Esto comparado con una reducción de 5.9% del grupo de placebo e incrementos de 0.3% y 22% del Androge® 5G y 10G respectivamente.

[0064] Basado en este estudio inferimos un número de ventajas potenciales para el Androxal™ como una terapia potencial. Primero, el Androxal™ parece elevar la testosterona total en el rango normal en una forma altamente consistente sin picos anormalmente altos en testosterona en suero. Segundo, el Androxal™ parece mejorar la proporción de DHT/TT, una consideración poteancialmente importante desde el punto de vista del cáncer de próstata. Tercero, el mantenimiento de un patrón diurno normal mejora los niveles de testosterona en una forma más natural. Finalmente, la tendencia a reducir triglicéridos puede ser una ventaja para muchos hombres.

REIVINDICACIONES

1. Un método para tratar una condición seleccionada del grupo que consiste de hipertrofia de próstata benigna, cáncer de próstata, triglicéridos elevados, alto colesterol e hipogonadismo que comprende administrar a un paciente en necesidad de este una composición que comprende *Trans*-clomifeno o un análogo de este o una sal farmacéuticamente aceptable o solvato de este y opcionalmente uno o más diluyentes farmacéuticamente aceptables, adyuvantes, portadores o excipientes.
2. El método de la reivindicación 1, en donde la composición comprende adicionalmente *Cis*-clomifeno o un análogo de este o una sal farmacéuticamente aceptable o solvato de este y en donde la proporción de *Trans*-clomifeno a *Cis*-clomifeno es mayor de 71/29.
3. El método de la reivindicación 1, en donde la composición consiste esencialmente de una cantidad efectiva de *Trans*-clomifeno o un análogo de este o una sal farmacéuticamente efectiva o solvato de este, y opcionalmente uno o más diluyentes farmacéuticamente aceptables, adyuvantes, portadores, o excipientes.

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4. El método de la reivindicación 1, en donde la condición se selecciona del grupo que consiste de hipertrofia de próstata benigna, cáncer de próstata, e hipogonadismo.
5. El método de la reivindicación 4, en donde la composición se formula para administración oral.
6. El método de la reivindicación 4, en donde la composición se formula para liberación extendida.
7. El método de la reivindicación 4, en donde la composición se administra a niveles pico la testosterona en suero cerca de las 8 a.m.
8. El método de la reivindicación 4, en donde la condición es hipertrofia de próstata benigna.
9. El método de la reivindicación 4, en donde la condición es cáncer de próstata.
10. El método de la reivindicación 4, en donde la composición se administra en un régimen de dosis adicional que comprende un quimioterapéutico.

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11. El método de la reivindicación 7 en donde la condición es hipogonadismo y el paciente sufre de un síntoma seleccionado del grupo que consiste de reducción de masa muscular, limitación de la capacidad de desempeño corporal, reducción de la densidad ósea, reducción de la libido, reducción de potencia.
 12. El método de la reivindicación 4 en donde el paciente es un mamífero.
 13. El método de la reivindicación 4 en donde el paciente es un humano.
 14. El método de la reivindicación 1 en donde la condición se selecciona del grupo que consiste de triglicéridos elevados y colesterol alto.
 15. El método de la reivindicación 12, en donde el paciente es macho.
 16. El método de la reivindicación 12, en donde el paciente es hembra.
 17. El método de la reivindicación 1, en donde la composición se formula para administración oral.
 18. El método de la reivindicación 1, en donde la composición se formula para liberación extendida.
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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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

To:

HOWREY LLP
Attn. Scott, Teddy C., Jr.
2941 Fairview Park Drive, Box 7
Falls Church, VA 22042
UNITED STATES OF AMERICA

(PCT Rule 44.1)

Date of mailing
(day/month/year)

24/11/2005

Applicant's or agent's file reference

07189.0003.00PC01

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2005/025000

International filing date
(day/month/year)

14/07/2005

Applicant

XONAGEN, INC.

1. ☒ 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 18:

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 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

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 60bis.1 and 60bis.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 18 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 18 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.

Name and mailing address of the International Searching Authority

 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) 340-3018

Authorized officer

Angela Lopez Navarro

DOCKETED

(See notes on accompanying sheet)

12/01/05

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 07189.0003.00PC01	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/025000	International filing date (day/month/year) 14/07/2005	(Earliest) Priority Date (day/month/year) 14/07/2004
Applicant ZONAGEN, 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 6 sheets.

☒ 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 the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ 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 II).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

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

5. With regard to the abstract,

☒ 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. 2

☒ 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.

INTERNATIONAL SEARCH REPORT

International Application No.

CT/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 Androge1 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



Further documents are listed in the continuation of box C



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 documents 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.

"Z" document member of the same patent family

Date of the actual completion of the international search

3 November 2005

Date of mailing of the international search report

24/11/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentplan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 851 epo nl
Fax (+31-70) 340-3016

Authorized officer

Albrecht, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/025000

G.(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

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 Ca ²⁺ 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. ☒ 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.

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

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.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.
PCT/US2005/025000

International filing date (day/month/year)
14.07.2005

Priority date (day/month/year)
14.07.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/138, A61P3/06, A61P15/08, A61P35/00

Applicant
ZONAGEN, 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 43bis.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"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(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 three 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:



European Patent Office
D-80288 Munich
Tel. +49 89 2369 - 0 Tx: 523656 epmu d
Fax: +49 89 2369 - 4485

Authorized Officer

Albrecht, S
Telephone No. +49 89 2369-7894



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/025000

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, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. 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:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ 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.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/025000

75 #

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-18

because:

- ☒ the said international application, or the said claims Nos. 1-18 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-18 (1-6, 8-18 in part) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ the claims, or said claims Nos. 16 are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the whole application or for said claims Nos.

- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished
☐ does not comply with the standard

the computer readable form ☐ has not been furnished
☐ does not comply with the standard

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- ☐ See separate sheet for further details

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

1. Statement

Novelty (N)	Yes: Claims	10
	No: Claims	1-6,8,9,11-15,17,18
Inventive step (IS)	Yes: Claims	
	No: Claims	1-6,8-15,17,18
Industrial applicability (IA)	Yes: Claims	-
	No: Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1. Claims 1-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

III.2. The term "analog" in claims 1-3 is considered not to meet the requirements of Art.6 PCT, because it lacks clear, explicit boundaries and the scope of it needs interpretation. In particular, it could mean salts, or chemically similar derivatives, but could also include all compounds having the same mode of action, independently from the chemical structure. As a result of this, the skilled person is unable to establish the scope of these claims, which therefore have to be considered as unclear. Mutatis mutandis dependent claims 4-18. Accordingly, the term "analog" will not be taken into account for the assessment of novelty and inventive step of claims 1-18.

III.3. Claim 7 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved ("[...] to give rise to peak serum testosterone levels at around 8 am"). Such a definition is only allowable under the conditions elaborated in the PCT Preliminary examination Guidelines, chapter 5.35. In this instance, however, such a formulation is not acceptable because the result cannot be achieved without undue in vivo experimentation. The same objection applies to dependent claim 11.

Accordingly, novelty and inventive step issues cannot be discussed for claim 7, whereas the examination of claim 11 will be limited to the treatment of hypogonadism in patients suffering 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.

III.4. Claim 16 is drafted as a dependent claim of claim 12, the latter being dependent of claim 4. However, the claimed uses indicated in claim 4 only apply to male patients (with respect to hypogonadism see p.3, paragraph 11 of the description). Claim 16 is therefore not supported

by the description as required by Article 6 PCT, and can not be further examined.

Re Item V

Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D1-D8) are referred to in this report; the numbering results from the order of citations found in the Search Report (SR) and will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

V.1. Novelty

V.1.1. Claims 1-6, 8, 9, 11-15, 17, 18 do not appear to be novel in the sense of Article 33 (2) PCT, the reasons being as follows:

a) D3 discloses the use of a composition comprising trans-clomiphene for the treatment of male hypogonadism. The composition may be for oral use, it may provide sustained-release of the active agent and it may further contain up to 29% of cis-clomiphene. The serum cholesterol lowering effect of trans-clomiphene is also mentioned in D3.

Thus, D3 anticipates the subject-matter of claims 1-6, 11-15, 17, 18.

b) D4 describes the use of an antiestrogen (clomiphene citrate) for the treatment of benign prostate hypertrophy. The composition may i.a. be administered orally or transdermally. Hence, D4 takes away the novelty of claims 1, 4-6, 8, 12, 13, 15, 17, 18.

c) D6 mentions the use of clomiphene in a clinical trial involving patients suffering from prostate cancer and prostate hypertrophy, and is therefore prejudicial to the novelty of claims 1, 4, 8, 9, 12, 13, 15.

V.1.2. Claim 10 appears to be novel over the available prior art.

V.2. Inventive step

V.2.1. Claims 1-6, 8, 9, 11-15, 17, 18:

Being not new, the subject-matter of present claims 1-6, 8, 9, 11-15, 17, 18 cannot be considered as inventive either.

V.2.2. Claim 10:

Dependent claim 10 does not contain any additional feature(s) which, in combination with the features of any claim to which it refers, meet(s) the requirements of the PCT with respect to inventive step. The further feature(s) disclosed therein represent selections from the usual range of possibilities (see D5) for which no unexpected effect can be seen.

V.3. Industrial Applicability

For the assessment of the present claims 1-18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

INTERNATIONAL BUREAU OF WIPO

Applicant(s): Zonagen, Inc.
Int. App. No.: PCT/US2005/025000
Int. Filing Date: July 14, 2005
Priority Date: July 14, 2004
Title: Trans-Clomiphene For The
Treatment of Benign Prostate
Hypertrophy, Prostate Cancer,
Hypogonadism, Elevated
Triglycerides and High
Cholesterol

Via Facsimile: 011 41 22 338 82 70

REQUEST FOR RECORDING OF CHANGE UNDER RULE 92BIS

International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20
Switzerland

Dear Sir:

Applicants hereby request under Rule 92bis.1(a), the International Bureau to record a change in connection with the above-identified international application to indicate that Zonagen, Inc. has formally changed its name to Repros Therapeutics Inc. We attach for your reference a copy of the official documentation from the Delaware Secretary of State certifying the name change.

Applicants respectfully requests that, pursuant to Administrative Instructions Section 422, the International Bureau provide notification of the above-requested change to all appropriate Offices.

Respectfully submitted,

HOWREY LLP

Dated: December 8, 2006

By:


David W. Clough, Ph.D.
Registration No. 36,107

HOWREY LLP
321 N. Clark Street, Suite 3400
Chicago, IL 60610
(312) 595-1239 (main)
(312) 595-1408 (direct)
(312) 595-2250 (fax)

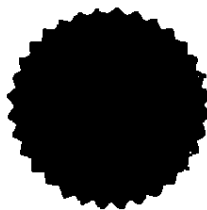
Delaware

PAGE 1

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF CORRECTION OF "REPROS THERAPEUTICS, INC.", CHANGING ITS NAME FROM "REPROS THERAPEUTICS, INC." TO "REPROS THERAPEUTICS INC.", FILED IN THIS OFFICE ON THE SECOND DAY OF MAY, A.D. 2006, AT 4:17 O'CLOCK P.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS.



2135473 8100

060409804

Harriet Smith Windsor
Harriet Smith Windsor, Secretary of State

AUTHENTICATION: 4713751

DATE: 05-02-06

**CERTIFICATE OF CORRECTION
TO THE
CERTIFICATE OF AMENDMENT TO THE
RESTATED CERTIFICATE OF INCORPORATION
OF
REPRO THERAPEUTICS, INC.**

Repro Therapeutics, Inc., organized and existing under and by virtue of the General Corporation Law of the State of Delaware,

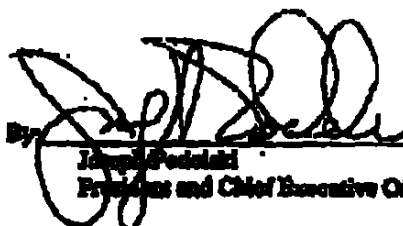
DOES HEREBY CERTIFY:

1. The name of the corporation is Repro Therapeutics, Inc.
2. That a Certificate of Amendment to the Restated Certificate of Incorporation was filed with the Secretary of State of Delaware on May 2, 2006 (the "Filing Date") and that said Certificate requires correction as permitted by Section 103 of the General Corporation Law of the State of Delaware.
3. The inaccuracy or defect of said Certificate of Amendment to be corrected is as follows: Article I of the Restated Certificate of Incorporation should be amended to correct the punctuation of the name of the Company. The name is incorrectly punctuated as Repro Therapeutics, Inc. and should be punctuated as Repro Therapeutics Inc.
4. Therefore, pursuant to this Certificate of Correction effective as of the Filing Date, Article I of the Restated Certificate of Incorporation shall now read as follows:

"ARTICLE I

The name of the corporation is Repro Therapeutics Inc."

IN WITNESS WHEREOF, I have hereunto set my hand this 2nd day of May, 2006.



Joseph Podolait
President and Chief Executive Officer

Delaware

PAGE 1

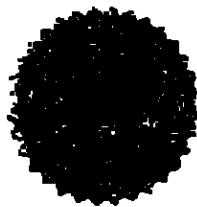
The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "ZENAGEN, INC.", CHANGING ITS NAME FROM "ZENAGEN, INC." TO "REPROX THERAPEUTICS, INC.", FILED IN THIS OFFICE ON THE SECOND DAY OF MAY, A.D. 2006, AT 12:58 O'CLOCK P.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS.

2135473 0100

060408178



Harriet Smith Windsor
Harriet Smith Windsor, Secretary of State

AUTHENTICATION: 4711448

DATE: 05-02-06

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84

State of Delaware
Secretary of State
Division of Corporations
Delivered 01:02 PM 05/02/2006
P2280 12:58 PM 05/02/2006
SW 660408178 - 2130473 F228

SOMAGEN, INC.

CERTIFICATE OF AMENDMENT
TO
REVISED CERTIFICATE OF INCORPORATION

Pursuant to the provisions of the Delaware General Corporation Law (the "DGCL"),
SOMAGEN, Inc., a Delaware corporation (the "Corporation"), does hereby certify as follows:

1. Pursuant to a written consent of the Board of Directors of the Corporation (the
"Board") executed on December 22, 2005, the Board adopted a resolution that the Revised
Certificate of Incorporation of the Corporation be amended and that such amendments be
submitted to the stockholders of the Corporation for their approval as follows:

Article I of the Revised Certificate of Incorporation is hereby amended to change the
name of the Corporation so that it shall hereafter read in its entirety as follows:

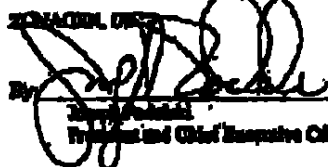
"ARTICLE I

The name of the corporation is Somagen Therapeutics, Inc."

2. At a meeting and vote of the stockholders held on May 2, 2006, a majority of the
stockholders entitled to vote therein approved said amendments to the Revised Certificate of
Incorporation.

3. The amended amendments to the Revised Certificate of Incorporation was duly
adopted in accordance with the applicable provisions of Section 242 of the DGCL.

IN WITNESS WHEREOF, this Certificate of Amendment has been executed as of the
2nd day of May, 2006.

SOMAGEN, INC.
By 
Robert J. Somagen
President and Chief Executive Officer

05/02/2006

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) 07189.0003.00PC01

Box No. I TITLE OF INVENTION METHODS AND COMPOSITIONS WITH TRANS-CLOMIPHENE	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.) ZONAGEN, INC. 2408 Timberloch Place, B-1 The Woodlands, Texas 77380 United States of America	
Telephone No. 281-719-3400	
Facsimile No. 281-719-3446	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.) PODOLSKI, Joseph 3 Pebble Hollow Court The Woodlands, Texas 77381 United States of America	
This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.)	
Applicant's registration No. with the Office	
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) SCOTT, Teddy C., Jr., Ph.D. Howray LLP 2941 Fairview Park Drive Box No. 7 Falls Church, VA 22042	
Telephone No. (312) 846-5821	
Facsimile No. (312) 595-2250	
Teleprinter No.	
Agent's registration No. with the Office 53,573	
☐ 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.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(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.)</i> WIEHLE, Ronald 13903 Viewfield Court Houston, Texas 77059 United States of America	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> 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: <i>(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.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> 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: <i>(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.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> 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: <i>(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.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> 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.	

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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 two persons are to be indicated as applicants and/or inventors 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 three 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)(iii) 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)(iv) and 49bis.1 (d)).*

Continuation of Box No. IV

Edward M. O'Toole, Reg. No. 22,477;
John F. Lynch, Reg. No. 22,504;
Albert P. Hailuin, Reg. No. 25,227;
Stephen H. Cagle, Reg. No. 28,445;
Floyd R. Nation, Reg. No. 27,580;
John D. Norris, Reg. No. 28,248;
J. Paul Williamson, Reg. No. 29,800;
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. 38,107;
Janelle D. Wasack, Reg. No. 38,300;
Robert J. McLaughan, Reg. No. 38,699;
Nicolas G. Barzoukas, Reg. No. 38,823;
Peter J. Chessman, Reg. No. 38,841;
Stephen E. Edwards, Reg. No. 38,885;
Connie Florae-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. 44,681;
Ira D. Finkelstein, Reg. No. 44,880;
Suzy Harblson, Reg. No. 45,138;
Matthew Madsen, Reg. No. 45,584;
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;
Christine M. Cochran, Reg. No. 52,757;
Teddy C. Scott, Jr., Reg. No. 53,573;
Kate G. Berazutskaya, Reg. No. 53,984;
Ryan A. Heck, Reg. No. P-51,795;

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

☐

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 be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

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) 14 July 2004 (14.07.2004)	80/588,130	US		
item (2) 14 July 2004 (14.07.2004)	80/588,223	US		
item (3) 14 July 2004 (14.07.2004)	80/588,123	US		

☐

Further priority claims are indicated in the Supplemental Box.

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

☒

all items

☐

item (1)

☐

item (2)

☐

item (3)

☐

other, see Supplemental Box

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

Box No. VII

INTERNATIONAL SEARCHING AUTHORITY

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

ISA / .EP.....

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

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

Box No. VIII

DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

		Number of declarations
☐	Box No. VIII (i) Declaration as to the identity of the inventor	:
☐	Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐	Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐	Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐	Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING																																																							
This international application contains: (a) on paper, the following number of sheets: <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">request (including declaration sheets) :</td> <td style="width: 20%; text-align: right;">5</td> </tr> <tr> <td>description (excluding sequence listing and/or tables related thereto) :</td> <td style="text-align: right;">17</td> </tr> <tr> <td>claims :</td> <td style="text-align: right;">2</td> </tr> <tr> <td>abstract :</td> <td style="text-align: right;">1</td> </tr> <tr> <td>drawings :</td> <td style="text-align: right;">4</td> </tr> <tr> <td>Sub-total number of sheets :</td> <td style="text-align: right;">29</td> </tr> <tr> <td>sequence listing :</td> <td></td> </tr> <tr> <td>tables related thereto :</td> <td></td> </tr> <tr> <td colspan="2"><i>(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)</i></td> </tr> <tr> <td>Total number of sheets :</td> <td style="text-align: right;">29</td> </tr> </table> (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: <i>(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)</i>	request (including declaration sheets) :	5	description (excluding sequence listing and/or tables related thereto) :	17	claims :	2	abstract :	1	drawings :	4	Sub-total number of sheets :	29	sequence listing :		tables related thereto :		<i>(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)</i>		Total number of sheets :	29	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">1. ☒ fee calculation sheet</td> <td style="width: 20%; text-align: right;">1</td> </tr> <tr> <td>2. ☐ original separate power of attorney</td> <td style="text-align: right;"></td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td style="text-align: right;"></td> </tr> <tr> <td>4. ☐ copy of general power of attorney; reference number, if any:</td> <td style="text-align: right;"></td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td style="text-align: right;"></td> </tr> <tr> <td>6. ☐ priority document(s) identified in Box No. VI as item(s):</td> <td style="text-align: right;"></td> </tr> <tr> <td>7. ☐ translation of international application into (language):</td> <td style="text-align: right;"></td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td style="text-align: right;"></td> </tr> <tr> <td>9. ☐ sequence listing in electronic form (indicate type and number of carriers)</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(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 13ter :</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column :</td> <td style="text-align: right;"></td> </tr> <tr> <td>10. ☐ tables in electronic form related to sequence listing (indicate type and number of carriers)</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(i) ☐ copy submitted for the purposes of international search under Section 802(b-quarter) only (and not as part of the international application) :</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(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-quarter) :</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :</td> <td style="text-align: right;"></td> </tr> <tr> <td>11. ☒ other (specify): TRANSMITTAL LETTER and return-receipt postcard</td> <td style="text-align: right;">1</td> </tr> </table>	1. ☒ fee calculation sheet	1	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 13ter 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 13ter :		(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-quarter) 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-quarter) :		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :		11. ☒ other (specify): TRANSMITTAL LETTER and return-receipt postcard	1
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(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :																																																							
11. ☒ other (specify): TRANSMITTAL LETTER and return-receipt postcard	1																																																						
Figure of the drawings which should accompany the abstract: 2	Language of filing of the international application: English																																																						
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>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).</i> Teddy C. Scott, Jr., Ph.D. Registration No. 58,573																																																							

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

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

PCT

FEE CALCULATION SHEET Annex to the Request

For receiving Office use only

International Application No.

Applicant's or agent's
file reference

07189.0003.00PC01

Date stamp of the receiving Office

Applicant
ZONAGEN, INC.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE USD 300 **F**

2. SEARCH FEE USD 2075 **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 } 29
Where items (b) and (c) of Box No. IX do not apply, enter Total number of sheets }

i1 first 30 sheets USD 1211 **i1**

i2 x = **i2**
number of sheets fee per sheet
in excess of 30

i3 additional component (only if a sequence listing and/or tables related thereto are filed in electronic form under Section 801(a)(1), or both in that form and on paper, under Section 801(a)(15)):

400 x = **i3**
fee per sheet

Add amounts entered at i1, i2 and i3 and enter total at **I** USD 1211 **I**

(Applicants from certain States are entitled to a reduction of 75% of the international filing fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at **I** is 25% of the international filing fee.)

4. FEE FOR PRIORITY DOCUMENT (if applicable) USD 60 **F**

5. TOTAL FEES PAYABLE USD 3646
Add amounts entered at T, S, I and P, and enter total in the TOTAL box

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

- ☒ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons
☐ cheque ☐ bank draft ☐ revenue stamps ☐ other (specify):

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all receiving Offices)

- ☒ Authorization to charge the total fees indicated above.
☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.
☒ Authorization to charge the fee for priority document.

Receiving Office: RO/ US
Deposit Account No.: 08-3038
Date: July 14, 2005
Name: Teddy C. Scott, Jr.
Signature: [Signature]



FORMATO DE DIGITALIZACION
RELACION DE ANEXOS



Royal
Technologies S.A.
Calle 100 No. 100, P.O. Box 100

Expediente No		No de Folios
07003351		
Item	No de Unidades	
1	CD	
2	DVD	
3	REVISTA	
4	LIBRO	
5	PERIODICO	
6	DISQUETES	
7	SOBRE DE MANILA	✓
8	SOBRE BLANCO TAMAÑO CARTA	
9	SOBRE BLANCO TAMAÑO OFICIO	
10	OTROS:	

Observaciones:

arte final

P

PCT

MODELO DE UTILIDAD

- 11

INCOMPLETA / 1

[1]

- | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|-----|
| 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 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 |
|---|---|---|---|---|---|---|---|---|-----|

INCOMPLETA I

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INCOMPLETA []

ble

Fecha _____

9

Copy for (DO-EP) 31
PATENT COOPERATION TREATY

PCT/US2005/025000

From the INTERNATIONAL BUREAU

PCT

**NOTIFICATION OF THE RECORDING
OF A CHANGE**

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

SCOTT, Teddy, C., Jr.
Howrey LLP
2941 Fairview Park Drive
Box No. 7
Falls Church, VA 22042
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
04 January 2007 (04.01.2007)

Applicant's or agent's file reference
07189.0003.00PC01

International application No.
PCT/US2005/025000

IMPORTANT NOTIFICATION

International filing date (day/month/year)
14 July 2005 (14.07.2005)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

ZONAGEN, INC.
2408 Timberloch Drive, B-1
The Woodlands, TX 77380
United States of America

State of Nationality

US

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

REPROS THERAPEUTICS INC.
2408 Timberloch Drive, B-1
The Woodlands, TX 77380
United States of America

State of Nationality

US

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

EPO-DG.1

12 01. 2007

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Giffa Schmitt Beate

94

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RODRIGUEZ DILIA MARIA

844

REFERENCIA	Radicación No.	07 3351
	Solicitud internacional	PCT/US2005/025000
	Fecha inicio fase nacional	14/02/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	1541

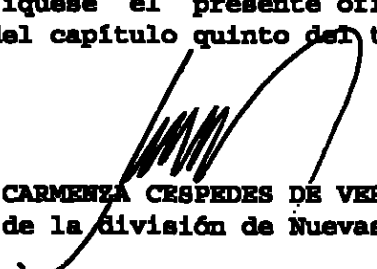
Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se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

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


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

El anterior requerimiento fue notificado por fijación en lista de fecha 02 FEB. 2007
adpa10