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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: Expediente No. 05.102.559

Solicitud de patente de invención titulada: "MÉTODOS Y COMPOSICIONES FARMACÉUTICAS PARA LA OBTENCIÓN CONFIABLE DE NIVELES ACEPTABLES DE TESTOSTERONA EN SUERO".

Solicitante: SCHERING AKTIENGESELLSCHAFT.

RESPUESTA A LA OPOSICIÓN NOTIFICADA POR FIJACIÓN EN LISTA No. 108
DE FECHA 30 DE MARZO DE 2007, OFICIO No. 3879

J. IAN RAISBECK, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante la oposición interpuesta por la Dra. Laura Catalina Silva Barrera, actuando como apoderada de la sociedad PROCAPS S.A.:

1. En primer lugar y con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un Capítulo Reivindicatorio Modificado que reemplaza en su totalidad el Capítulo Reivindicatorio Modificado allegado mediante mi memorial del 20-03-2007. Para tal efecto, adjunto un recibo de pago que cubre la tasa de modificación correspondiente.

El Capítulo Reivindicatorio Modificado, compuesto por 7 reivindicaciones, incluye las siguientes modificaciones:

- Se limita el alcance de la reivindicación principal a los alcanosatos C₉-C₁₅.
- Se eliminaron las antiguas Reivindicaciones 8 a 18.

Valga anotar que las anteriores modificaciones en ningún momento corresponden a una ampliación de la materia originalmente revelada por la presente solicitud, por el contrario, el Capítulo Reivindicatorio Modificado es una franca limitación de lo originalmente reclamado, cumpliendo así con lo dispuesto por el Artículo 34 de la Decisión 486.

2. a- El Oponente argumenta en su memorial del 27 de febrero de 2007, que las Reivindicaciones 7 a 29 se refieren a usos y métodos de tratamiento, por lo que corresponderían a materia no patentable.

b- Llamo la atención al hecho que el Capítulo Reivindicatorio Modificado adjunto no contiene reivindicaciones dirigidas a usos o métodos de tratamiento. Por lo tanto, considero que la anterior objeción ha sido superada.

3. El Oponente argumenta que el documento US 4.181.721 (D1) afectaría la novedad de la invención reivindicada.

El Oponente anota que el documento D1 (resumen, descripción y reivindicaciones), se refiere a una inyección intramuscular que comprende una cantidad eficaz de un esteroide lipofílico que tiene actividad premenstrual disuelto en un portador aceitoso (aceite de ricino), insaturado para alcanzar y mantener la actividad premenstrual durante un período deseado de tiempo de al menos varias semanas. D1 define que dicha composición consiste esencialmente en 50-500 mg. de una hormona de esteroidea lipofílica con un efecto de depósito premenstrual disuelto en 1-6 mL de una mezcla del aceite y bencil/benzoato en una proporción de volumen de 6:4. Según las reivindicaciones de D1, se revela una formulación intramuscular que incluye un éster de testosterona fisiológicamente hidrolizable que tiene una actividad premenstrual disuelto en un portador aceitoso de aceite de ricino, insaturado, el cual puede comprender una mezcla de aceite y un bencil/benzoato. Así, la solución propuesta en D1 comprende los mismos elementos que la presente invención, un éster de testosterona y un vehículo que comprende aceite de ricino y un co-solvente, por lo tanto, a los ojos de D1, la presente solicitud carece evidentemente de novedad.

4. a- En primer lugar, es importante resaltar que cuando del análisis de novedad se trata, debe comprobarse que existan anticipaciones en el estado de la técnica que contengan

explícitamente todas las características técnicas de la invención, evidenciadas al comparar elemento por elemento de ésta tal como está definida por las reivindicaciones.¹

Así las cosas, deseo subrayar que la presente invención se relaciona específicamente con formulaciones inyectables (intramuscular) que comprenden un éster de testosterona (alcanoatos C₉-C₁₃); en un vehículo compuesto de aceite de ricino. Estas formulaciones proporcionan perfiles farmacocinéticos *in-vivo* superiores, manteniendo niveles aceptables de testosterona por lapsos ampliados de tal forma que permite mayores intervalos entre dosificaciones.

La anterioridad D1 citada por el Oponente se refiere a una formulación inyectable con efecto de depósito de una hormona lipofílica esteróidea, en donde el vehículo es una mezcla de aceite de ricino y benzoato de bencilo en una proporción 6:4, es decir, 60% de aceite de ricino y 40% de benzoato de bencilo (ver columna 5, líneas 27 y 47, columna 6, líneas 15 y 36, y Reivindicaciones 4, 5, 9, 10, 14 y 15). Sin embargo, este documento no hace mención de otras relaciones entre aceite de ricino y benzoato de bencilo. El Capítulo Reivindicatorio Modificado adjunto especifica que el aceite de ricino debe estar presente en una concentración de 25-45% en volumen, es decir, una concentración de aceite de ricino claramente inferior al 60% revelado por D1. Por consiguiente, la reivindicación 1 y sus reivindicaciones dependientes son claramente novedosas frente dicha anterioridad.

Es evidente que las características esenciales de la presente invención no fueron en ningún momento anticipadas por el arte previo que cita el Oponente; por ejemplo, D1 siempre utiliza una proporción mayor de aceite de ricino que de benzoato de bencilo, y por lo tanto, la presente invención es novedosa con respecto a D1.

b- De otra parte, aunque el Oponente no presenta argumentos en contra del nivel inventivo de la invención, deseo resaltar que la presente invención proporciona formulaciones con características mejoradas que superan las formulaciones convencionales del arte previo, como las ilustradas en D1.

c- Como fuera mencionado, la Reivindicación 1 del Capítulo Reivindicatorio Modificado Adjunto ahora especifica que el aceite de ricino debe estar presente en una

¹ Manual para el Examen de Solicitudes de Patentes de Invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina (Manual Andino de Patentes). Documento preparado por la Oficina Internacional de la OMPI. ISBN 9978-43-855-6. 2004. Sección 9.4.

concentración de 25-45% en volumen, es decir, que la concentración de aceite de ricino es significativamente inferior que la concentración descrita en D1.

Adicionalmente, me permito adjuntar datos suplementarios donde se compara la estabilidad del undecanoato de testosterona en diferentes mezclas de benzoato de bencilo y aceites (Anexo 1). Las mezclas oleosas difieren con respecto al tipo de aceite y la relación aceite y benzoato de bencilo. La estabilidad fue valorada sobre la base de la detección de ampollas conteniendo precipitados de undecanoato de testosterona siguiendo el almacenamiento en un refrigerador (2-8°C).

Sorprendentemente se encontró que la estabilidad de la formulación que comprende undecanoato de testosterona depende del tipo de aceite seleccionado. Como se concluye de los datos de estabilidad, se detectaron precipitados en todas las composiciones que comprenden aceite de arachis (aceite de mani) y migliol 812.

Por otro lado, se puede también concluir que la concentración de aceite de ricino tuvo un efecto pronunciado sobre la estabilidad del undecanoato de testosterona: mezclas que contienen 37% de aceite de ricino se mantuvieron perfectamente estables después de 34 días de almacenamiento, mientras que mezclas con 50% de aceite de ricino, y en particular 60% de aceite de ricino, no fueron lo suficientemente estables.

Los ejemplos suministrados en la anterioridad D1 se realizan sobre el ester enantanoato de testosterona (comprendiendo 7 átomos de Carbono), y el problema de estabilidad de los esteres de testosterona comprendiendo alcanos de C₉-C₁₅ no fue estudiado en dicha patente.

El hallazgo de los presentes inventores fue detectar que el aceite de ricino en una concentración inferior a 45% provee un efecto estabilizante, hecho que en ningún momento fue mostrado ni sugerido en la anterioridad D1.

Por lo expuesto anteriormente, llamo la atención al hecho que el presente Capítulo Reivindicatorio Modificado es inventivo sobre el arte previo citado por el Oponente.

Por último, me permito adjuntar copia de la Patente Europea EP1457208B9 (Anexo 2), que reclama la misma reivindicación principal que en la presente solicitud.

5. Con base en todo lo anterior, considero superadas las objeciones que el Oponente interpuso contra la novedad de la presente invención y solicito se declare infundada dicha oposición.

Atentamente,



J. IAN RAISBECK

C.C. 79'376.996 de Bogotá D.C.

T.P. . 135.799 del C. S. de la J.

Anexo:

- Capítulo Reivindicatorio Modificado.
- Recibo de pago.
- Anexo 1: datos que comparan la estabilidad del undecanoato de testosterona en diferentes mezclas de benzoato de bencilo y aceites.
- Anexo 2: copia de la Patente Europea EP1457208B9.

CAPÍTULO REIVINDICATORIO MODIFICADO*(en respuesta a oposiciones)*

1. Una composición formulada para inyección intramuscular que comprende un éster de testosterona seleccionado del grupo de ésteres que consiste en noncanoatos, decanoatos, undecanoatos, dodecanoatos, tridecanoatos, tetradecanoatos y pentadecanoatos lineales y ramificados; y un vehículo que comprende aceite de ricino en una concentración de 25 a 45 % en volumen y un co-solvente.

2. La composición de acuerdo con la reivindicación 1, en la cual el éster de testosterona es undecanoato de testosterona.

3. La composición de acuerdo con la reivindicación 2, en la cual el undecanoato de testosterona está en una dosis de 150 a 500 mg/ml.

4. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, en la cual el vehículo comprende el aceite de ricino en una concentración de 25 a 40 % en volumen.

5. La composición de acuerdo con cualquiera de las reivindicaciones 1 a 3, en la cual el co-solvente se encuentra en una cantidad en el rango de 55 a 65 % en volumen del vehículo.

6. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, en la cual el co-solvente es benzoato de bencilo.

7. Una formulación farmacéutica que contiene 1000 mg de undecanoato de testosterona en un vehículo de 4 ml de una mezcla de aceite de ricino y benzoato de bencilo en una relación 1:1,7 por volumen.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 07 - 49,161
FECHA : JUNIO 20 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBECK	CONSIGNACION	BANCO POPULAR	050-00110-6	52331062	19/06/2007	3,603,000.00

***** CONCEPTO *****

CANT. REENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	
	12 MARCAS Y LENAS COMERCIALES	99,000.00
	TOTAL :	\$ 99,000.00

SUM: NOVENTA Y NUEVE MIL PESOS



RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Solubilidad de undecanoato de testosterona (UT) en diferentes aceites**Objetivo**

Diferentes mezclas de benzoato de bencilo/aceite que contienen 250 mg de UT por ml fueron estudiadas por su cristalizabilidad en refrigerador a 2-8 °C. Determinar qué aceite particular y relación de concentraciones de benzoato de bencilo/aceite tienen la mayor capacidad de disolver UT.

Materiales

Aceite de ricino refinado para uso parenteral: DAB [Farmacopea Aleman]

Aceite de maní para uso parenteral: Ph. Eur.

Migliol 812: Ph Eur.

Benzoato de bencilo: Ph. Eur., USP

Undecanoato de testosterona: Monografía interna

Preparación

Para preparar cada solución, se disolvieron 25 g de UT a 50°C en la cantidad respectiva de benzoato de bencilo, con lo cual la cantidad de aceite respectivo fue adicionada. La mezcla resultante entonces fue agitada. Una solución clara fue formada. Fueron llenadas ampollas con 4 ml de parte de la solución y entonces fueron cerradas. 8 ampollas fueron guardadas en refrigerados (a 2-8°C) y 4 ampollas fueron mantenidas a 25°C. Las ampollas fueron chequeadas a tiempos específicos en busca de presencia de precipitados (cristales).

Relaciones

25 g UT en una mezcla de 40% de benzoato de bencilo + 60% de aceite de ricino refinado

25 g UT en una mezcla de 50% de benzoato de bencilo + 50% de aceite de ricino refinado

25 g UT en una mezcla de 63% de benzoato de bencilo + 37% de aceite de ricino refinado

25 g UT en una mezcla de 40% de benzoato de bencilo + 60% de aceite de maní

25 g UT en una mezcla de 50% de benzoato de bencilo + 50% de aceite de maní

25 g UT en una mezcla de 63% de benzoato de bencilo + 37% de aceite de maní

25 g UT en una mezcla de 40% de benzoato de bencilo + 60% de aceite de migliol 812

25 g UT en una mezcla de 50% de benzoato de bencilo + 50% de aceite de migliol 812

25 g UT en una mezcla de 63% de benzoato de bencilo + 37% de aceite de migliol 812

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Resultados

Estabilidad de las soluciones oleosas a temperatura ambiente (25°C)
No aparecieron precipitados en ningún ampolla después de 34°C
Estabilidad de soluciones oleosas durante almacenamiento en
refrigerador (a 2-8°C)

Formulaciones que comprenden aceite de ricino refinado para uso parenteral	Número de ampollas con precipitación (cristales)								
	0 d	1 d	2 d	3 d	6 d	8 d	10 d	21 d	34 d
40% de benzoato de bencilo	0	5	6	6	6	6	6	6	6
50% de benzoato de bencilo	0	0	1	3	3	3	3	4	5
63% de benzoato de bencilo	0	0	0	0	0	0	0	0	0

Formulaciones que comprenden aceite de maní para uso parenteral	Número de ampollas con precipitación (cristales)						
	0 d	1 d	4 d	6 d	8 d	19 d	32 d
40% de benzoato de bencilo	0	5	6	6	7	8	8
50% de benzoato de bencilo	0	2	5	5	5	7	8
63% de benzoato de bencilo	0	0	5	5	5	7	8

Formulaciones que comprenden miglitol 812 para uso parenteral	Número de ampollas con precipitación (cristales)							
	0 d	1 d	2 d	5 d	7 d	9 d	20 d	33 d
40% de benzoato de bencilo	0	4	4	7	8	8	8	8
50% de benzoato de bencilo	0	1	1	8	8	8	8	8
63% de benzoato de bencilo	0	0	1	1	1	1	5	6

Se puede decir en conclusión que la formulación que contiene aceite de ricino refinado para uso parenteral con un porcentaje de 63% de benzoato de bencilo (= composición de la formulación original Nebido ©) es la única formulación en la cual UT no precipita durante el almacenamiento por más de 34 días en refrigerador a 2-8°C. Todos los otros aceites y respectivas relaciones dieron un producto inestable.

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(11) EP 1 457 208 B9

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**
Note: Bibliography reflects the latest situation

- (15) Correction information:
Corrected version no 2 (W2 B1)
Corrections, see page(s) 3,4,5,7,11,12

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28.02.2007 Bulletin 2007/09

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of the grant of the patent:
16.08.2006 Bulletin 2006/33

(21) Application number: 04075804.7

(22) Date of filing: 15.03.2004
- (51) Int Cl:
A61K 31/56^(2006.01) A61K 31/585^(2006.01)
A61K 31/583^(2006.01) A61K 47/14^(2006.01)
A61P 15/06^(2006.01) A61P 5/26^(2006.01)

(54) **Methods and pharmaceutical compositions for reliable achievement of acceptable serum testosterone levels**

Verfahren und Zusammensetzungen zum zuverlässigen Erreichen eines günstigen Serumentestosteronspiegels

Procédés et compositions pour atteindre avec fiabilité à un niveau de testostérone acceptable dans le sérum

(84) Designated Contracting States: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR Designated Extension States: AL LT LV MK (30) Priority: 14.03.2003 DK 200300399 (43) Date of publication of application: 15.09.2004 Bulletin 2004/38 (60) Divisional application: 06016949.7 / 1 743 646 (73) Proprietor: Schering Aktiengesellschaft 13342 Berlin (DE) (72) Inventors: • Hübler, Doris 07407 Schmiedlen (DE)	• Fricke, Sabine 07749 Jena (DE) • Ingwersen, Jan-Peter 13485 Berlin (DE) • Kuhn, Wilhelm 13589 Berlin (DE) (74) Representative: Plougmann & Vingtoft A/S Sundkrogsgade 9, P.O. Box 831 2100 Copenhagen (DK) (56) References cited: WO-A-00/59512 WO-A-97/40823 WO-A-98/36770 US-A- 4 212 883 • DATABASE WPI Section Ch, Week 199524 Derwent Publications Ltd, London, GB; Class B01, AN 1995-185577 XP002284337 & WO 95/12383 A (UNIV ZHEJIANG MEDICAL) 11 May 1995 (1995-05-11)
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Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 457 208 B9

Description

FIELD OF INVENTION

5 [0001] The present invention relates to the field of pharmaceutical formulation science as well as the field of therapeutic applications of hormones in hormone replacement therapy in men and in male contraception. In particular, the invention relates to compositions of testosterone esters in castor oil that upon intramuscular injection provides reliable physiological acceptable serum testosterone levels for a prolonged period.

10 BACKGROUND

[0002] For several decades, testosterone preparations have been used clinically to treat primary and secondary male hypogonadism in order to achieve normal physiologic levels of testosterone and to relieve symptoms of androgen deficiency. Furthermore, testosterone preparations have been used in male contraception as the sole active therapeutic agent for suppressing spermatogenesis or as an active agent in combination with progestins or further gonadotropin suppressive agents.

15 [0003] Male hypogonadism is characterised by a deficiency of endogenous testosterone production resulting in abnormally low levels of circulating testosterone, i.e. serum testosterone levels below 10 nmol/l.

[0004] Male hypogonadism may be classified in primary and secondary causes: primary or hypogonadotropic hypogonadism, congenital or acquired, may be derived from testicular failure due to cryptorchidism, bilateral testicular torsion, orchitis, orchidectomy, Klinefelter syndrome, chemotherapy or toxic damage from alcohol or heavy metals. Secondary or hypogonadotropic hypogonadism, congenital or acquired, is caused by idiopathic gonadotropin releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury from tumours, trauma, or radiation. In the vast majority of cases, hypogonadism is related to a primary defect of the testes.

25 [0005] The clinical picture of hypogonadal adult men varies a lot. For example, testosterone deficiency is accompanied by symptoms of different severity, including sexual dysfunction, reduced muscle mass and muscle strength, depressed mood and osteoporosis.

[0006] Current standard therapies aims at restoring physiologically relevant levels of testosterone in serum, which applies to concentrations of about 12 nmol to about 36 nmol. Intramuscular injection of testosterone esters, such as testosterone enanthate or testosterone cypionate, administered every two to three weeks, still represents the standard of testosterone replacement therapy in most countries of the world. Apart from the inconvenience of frequent visits to the doctor's office, the patients complain about variations in well-being due to short-term fluctuations of serum testosterone levels resulting from the pharmacokinetic profile after intramuscular injection of for example testosterone enanthate.

30 [0007] Recently, the use of testosterone esters with longer aliphatic chain length and/or higher hydrophobicity, such as testosterone undecanoate, has become interesting in terms of prolonging the interval between injections. Longer intervals between injections are advantageous from a patient's point of view.

[0008] For example Zhang G et al, 1998, report the injection of compositions comprising testosterone undecanoate in a concentration of 250 mg in 2 ml tea seed oil so as to administer a dose of 500 mg or 1000 mg of testosterone undecanoate (Zhang G et al., *A pharmacokinetic study of injectable testosterone undecanoate in hypogonadal men. J. Andrology*, vol 19, No 8, 1998). Zhang et al, 1999, relates to injectable testosterone undecanoate as a potential male contraceptive (Zhang et al, *J clin Endocrin & metabolism*, 1999, vol 84, no 10, p 3842-3848).

40 [0009] Furthermore, Behre et al, 1999, relates to testosterone undecanoate preparations for testosterone replacement therapy such as testosterone undecanoate 125 mg/ml in tea seed oil and testosterone undecanoate 250 mg/ml in castor oil (Behre et al, *Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies. European J endocrin*, 1999, 140, p 414-419).

[0010] Intramuscular injections of 250 mg testosterone undecanoate and 200 mg MPA every month have been suggested for male contraception (Chen Zhao-dian et al, *clinical study of testosterone undecanoate compound on male contraception. J Clin androl*, 1998, vol 1, issue 1, abstract).

50 [0011] Wang Lie-zhen et al. report testosterone replacement therapy using monthly intramuscular injections of 250 mg testosterone undecanoate (Wang Lie-zhen et al. *The therapeutic effect of domestically produced testosterone undecanoate in Klinefelter syndrome. New Drugs Market* 8: 28-32, 1991).

[0012] WO 95/12383 (Chinese application) relates to injectable compositions of testosterone undecanoate in vegetable oils selected from tea seed oil, sesame oil, arachis oil, olives oil and soyabean oil. The oil is optionally in admixture with benzyl benzoate. The compositions are injected monthly when applied for male contraception and substitution therapy.

55 [0013] US 4 212 863 is a patent which relates to a lipid formulation of steroids for oral or parenteral administration various oil carriers, optionally including benzyl benzoate, which is said to lower the viscosity of the lipid carrier and/or enhance the solubility.

[0014] Eckardtstein and Nieschlag, 2002, report the treatment of hypogonadal men with testosterone undecanoate,

wherein physiological relevant levels of testosterone may be achieved for an extended period of time upon initially injecting testosterone undecanoate four times in intervals of 6-weeks followed by subsequent injections of longer intervals (Eckardtstein and Nieschlag, *treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks*, *J Andrology*, vol 23, no 3, 2002)

[0016] However, it is well known that therapies with testosterone esters, such as testosterone undecanoate, still need to be improved in terms of achieving reliable serum testosterone levels in the physiologically acceptable range for a prolonged period of time. There is a need of providing reliable standard regimens acceptable for a broad population of men in need thereof, preferably regimens without the need of occasional control of serum testosterone levels, and regimens wherein steady state conditions are achieved within a shorter time period.

SUMMARY OF INVENTION

[0016] The present invention relates to injectable compositions comprising long-term acting testosterone esters for use in testosterone replacement therapy. Upon injecting the compositions, physiologically normal levels of testosterone in serum are reached within a short time period. Furthermore, the physiologically normal serum levels of testosterone are maintained for an extended period of time, without showing fluctuations in the hypogonadal range. The compositions are chemically stable with respect to the testosterone ester as well as physically stable with respect to the vehicle for a prolonged time.

[0017] Therefore, in a first aspect the present invention relates to a composition intended for injectable administration, such as by intramuscular injections, the composition comprises a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates preferably testosterone undecanoate; and a vehicle, which comprises castor oil and a co-solvent.

[0018] Furthermore, in a second aspect the invention relates to a method of treating diseases and symptoms associated with deficient endogenous levels of testosterone in a man. For example methods of treating primary and secondary hypogonadism; hypophyseal diseases; symptoms of sexual dysfunction; symptoms of reduced muscle mass and muscle strength; symptoms of depressed mood; or symptoms of osteoporosis. The method comprises administering by injection a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates, such as testosterone undecanoate, according to a particular scheme comprising:

- i) an initial phase of 2 to 4 injecting a dose of said testosterone ester with an interval of 4 to 8 weeks between each administration, each dose is in an amount therapeutically equivalent to a dose of testosterone undecanoate of between 500 mg and 2000 mg; followed by
- ii) a maintenance phase of subsequent injecting a dose of said testosterone ester with an interval of at least 9 weeks between each subsequent administration, each dose is in an amount therapeutically equivalent to a dose of testosterone undecanoate of between 500 mg and 2000 mg.

[0019] Further aspects relate to the use of the above-mentioned compositions for male contraception.

[0020] Still further aspects relate to the use of a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates for the preparation of medicaments that are in a form for parenteral administration, such as in a form for intramuscular injection and further comprises a vehicle comprising castor oil and a co-solvent. The medicaments in question are primarily for treating primary and secondary hypogonadism in a male for treating diseases and symptoms associated with deficient levels of testosterone in a male who are in therapy with a progestin or a further gonadotropin suppressive agent.

DETAILED DESCRIPTION OF THE INVENTION

[0021] The present inventors provide, herein, standard methods resulting in superior pharmacokinetic profiles of testosterone in vivo. Physiologically normal serum levels of testosterone are achieved quickly after initiating the therapy with the testosterone preparations of the invention and reliable testosterone serum levels within the normal physiological range is maintained for an extended period of time. Advantageously, the standard methods reported herein, allows for significant prolonged intervals between injections, and the serum testosterone levels may not necessarily need to be controlled.

[0022] According to the invention, the standard method includes combining the suitable formulation of a composition comprising slowly degradable testosterone esters, such as testosterone undecanoate, and suitable injection schemes of well defined doses of such testosterone esters.

[0023] Without being adapted to a particular theory, a number of parameters will influence the pharmacokinetic profile

of a testosterone ester that is injected intramuscularly, in particular if a depot effect is desirable. A depot effect can in general be achieved by selecting a testosterone ester that slowly degrades into free testosterone once it has entered the blood circulation. An additional factor contributing to the depot effect is the diffusion rate of the testosterone ester from the site of injection to the circulating blood system. The diffusion rate may depend on the dose and the volume injected in that the concentration gradient of the testosterone ester at the site of administration is thought to affect the diffusion rate. Furthermore, the type of vehicle injected together with the testosterone esters will influence the rate of diffusion of testosterone esters from the vehicle into the surrounding tissues and the rate of absorption into the blood circulation. Therefore, the partition coefficient (n-octanol-water partition coefficient) of the testosterone ester in the vehicle as well as the viscosity of the vehicle should be considered in order for adapting a depot effect following intramuscular injection of testosterone esters.

[0024] Moreover, for safety reasons and ease of handling, the testosterone ester should be properly dissolved in a vehicle. Often it is impossible to predict which kind of vehicles that both can dissolve the testosterone ester and provide the needed depot effect. Therefore, mixtures of various solvents may be required, although undesirable from a manufacturing point of view.

[0025] The present inventors have recognised that an effective depot effect in vivo of testosterone esters, such as testosterone undecanoate, is achieved when injecting the testosterone esters intramuscularly in a vehicle comprising castor oil and a suitable co-solvent. The co-solvent may lower the viscosity of the castor oil and then solve the problem with high viscosity of the castor oil when being injected. On the other hand, the co-solvent may increase the diffusion rate of the testosterone ester, resulting in a lower depot effect following intramuscular injection.

[0026] As may be understood, a first aspect of the invention relates to a composition comprising a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates and a vehicle comprising castor oil and a co-solvent.

[0027] The composition is formulated for parenteral administration, preferably intramuscular injection. In suitable embodiments of the invention, the testosterone ester is selected from esters, wherein the ester group is a nonanoate, a decanoate, an undecanoate, a dodecanoate, a tridecanoate, a tetradecanoate, or a pentadecanoate. Preferably, the ester group may be placed in the 17 β -position of the testosterone molecule. In a presently interesting embodiment, the testosterone ester is testosterone undecanoate, a testosterone ester with an aliphatic side chain in 17 β position. The chemical name is 17 β -hydroxyandrost-4-en-3-one undecanoate.

[0028] The term "castor oil" is meant to encompass castor oil refined for parenteral use, for example as described in DAB, wherein the castor oil is provided in a form without antioxidants and obtained with the first pressure of ricinus communis without using extraction processes. It should also be understood that the castor oil are not hydrogenated or at least in part not hydrogenated. In some embodiments, a minor part of the double bonds may be hydrogenated. For example, less than 20% w/w of the double bonds may be hydrogenated. Preferably less than 10% w/w of the double bonds may be hydrogenated, more preferably less than 5% w/w, even more preferably less than 2% w/w, most preferably less than 1% w/w of the double bonds are hydrogenated. Castor oil appears as a liquid at room temperature.

[0029] As stated, the co-solvent of the vehicle is, at least in part, an essential element of the compositions of the invention. Such co-solvents may in general be defined by its capability of reducing the viscosity of castor oil, as determined by a Höppler viscosimeter.

[0030] Injection of high viscous vehicles, such as castor oil, is associated with technical limitations to the size of cannula due to the resistance of the vehicle when passing the cannula. It is commonly recommended that the viscosity of an injection solution should be kept below 100 mPas. In certain instances, the viscosity of a final product, ready to be injected, such as a re-constituted product may be, e.g., less than 100 mPas, such as 90 mPas, 80 mPas, 70 mPas at room temperature. In some embodiments, the viscosity of the vehicle is less than 80 mPas, 50 mPas, 40 mPas or 30 mPas at room temperature.

[0031] Thus, suitable embodiments of the invention relate to those wherein the co-solvent is selected from those that when being mixed with castor oil in an oil:co-solvent volume ratio of between 1:0.2 to 1:3, the viscosity drops from 850-1100 mPas to 20 mPas at room temperature. Preferably, the co-solvent is selected from those, wherein the viscosity drops from 850-1100 mPas to about 80-100 mPas, when the co-solvent is being mixed with castor oil in an oil:co-solvent volume ratio of about 1:1 to 1:3. The viscosity of the vehicle may be determined with a Höppler type viscometer. The Höppler type viscometer consists of an inclined glass tube inside which a sphere with known density, mass and diameter glides through the liquid to be measured, and the falling time of the ball is measured. The viscosity is measured at a fixed temperature, often room temperature such as 20°C or 25°C. The measurements are repeated until the values are constant.

[0032] The co-solvent may be characterised by its ability to reduce the viscosity of a vehicle, such as castor oil, of the solvent in a ratio dependent manner.

[0033] In one interesting embodiment of the invention the viscosity of a mixture of castor oil and a co-solvent in a volume ratio of 1:0.1 to 1:1.7 is reduced from 90% to 5% to that of castor oil.

[0034] In a suitable embodiment of the invention, the viscosity of a mixture of castor oil and a co-solvent in a ratio of

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1:0.02 by volume is reduced by about 10 % relatively to the viscosity of castor oil. In other various embodiments, when the ratio between the oil and co-solvent is of 1:0.04 by volume the viscosity is reduced by 20% relatively to the viscosity of castor oil, when the ratio is of 1:0.08 by volume the viscosity is reduced by 25%, when the ratio is of 1:0.1 by volume the viscosity is reduced by 40%, when the ratio is of 1:0.2 by volume the viscosity is reduced by 50%, when the ratio is of 1:0.35 by volume the viscosity is reduced by 75%, when the ratio is of 1:0.5 by volume the viscosity is reduced by 80%, when the ratio is of 1:1 by volume the viscosity is reduced by 90%, or when the ratio is 1:1.6 by volume the viscosity is reduced by 95%.

[0035] In further interesting embodiments, the viscosity of the composition is below 100 mPas. Furthermore, in some embodiments the viscosity of vehicle, such as the mixture of castor oil and a co-solvent, such as benzyl benzoate is below 90 mPas, the viscosity of the vehicle is about 80 - 100 mPas, such as 70 to 100 mPas, such as 80-90 mPas at room temperature (20°C to 25°C).

[0036] As mentioned, the viscosity of the injected vehicle may determine the pharmacokinetic profile of an injected substance. Thus, in order to obtain a final product with a suitable depot effect in vivo, the castor oil and co-solvent is in a volume ratio ranging between 1:0.2 to 1:3, such as between 1:0.5 to 1:3, or between 1:0.75 to 1:2.5. Preferably, the volume ratio is in the range from 1:1 to 1:2.

[0037] In presently interesting embodiments of the invention, the co-solvent is benzyl benzoate. In principle, other types of co-solvents may be applicable for use in combination with castor oil, such as for example ethanol or benzyl alcohol. Interesting co-solvents of the present invention are those which are capable of dissolving the testosterone esters and is miscible with castor oil. Of special interest are co-solvents suitable for dissolving about 100-500 mg, such as 250 mg of testosterone undecanoate in 1 mL of the co-solvent within 50 minutes at 40°C or within 20 minutes at 60°C.

[0038] The solubility of the testosterone esters may be affected upon adding a co-solvent to the castor oil vehicle. Probably the solubility may be improved. Thus, in some embodiments, the testosterone ester is completely dissolved in the composition, and in other embodiments the testosterone ester is partly dispersed in the composition. Preferably, the testosterone esters are fully dissolved in the vehicle. That is to say that no particles of testosterone may be detected by X-ray diffraction analysis.

[0039] The present invention provides compositions, wherein the co-solvent is present in the vehicle at concentrations ranging from 55 to 85 vol%.

[0040] In other words, the vehicle comprises the castor oil in a volume concentration ranging between 25 to 45 vol% or 25 to 40 vol%.

[0041] It should be understood that intentionally the composition should not comprise another plant oil, such as for example tea seed oil. That is to say that castor oil is the only plant oil present in the composition or that castor oil makes up at least 50% by volume of the total content of the plant oil in the vehicle, such as at least 60%, 70%, 80% or 90% by volume.

[0042] It is generally considered that the needed concentration of the co-solvent depends on a number of factors, such as I) the amount of testosterone ester in the injection vehicle, II) the required reduction of viscosity and III) the release properties of the injection vehicle with respect to the testosterone ester at the site of injection (diffusion rate). In interesting embodiments of the invention, the co-solvent makes up at least 50 vol%. Interestingly, the co-solvent is in an amount ranging from about 40 to 80 vol% of the vehicle, such as about 50 to 70 vol%, most preferably the co-solvent is in an amount ranging from about 55 to 85 vol% of the vehicle.

[0043] In some embodiments of the invention, the concentration of the co-solvent in the vehicle should be limited in order to reduce the diffusion rate of the testosterone esters, for instance at the site of injection. Therefore in some embodiments the concentration of co-solvent in the vehicle should be less than 75 vol%.

[0044] The volume that can be injected intramuscularly is known to affect the release rate of an active principle from a vehicle. An injection volume of 5 mL is generally considered as the maximum volume that can be administered by one single intramuscular injection to one injection site. When intramuscular injection of volumes greater than 5 mL is required, the injection volume needs to be divided into two or more separate injections to different injection sites. However, multiple injections for the administering of one dose are generally not preferred because of the inconvenience conferred to the patient.

[0045] The injection of a single dose to one injection site offers great advantages in controlling the release rate of an active principle, rather than multiple injection of divided single doses. The present invention relates to injection schemes wherein a single dose of a testosterone ester is divided into no more than two separate injections to one or more injection sites. Most preferable, a single dose of a testosterone ester is injected as one single injection to one injection site. Therefore, in presently interesting embodiments of the invention the dose of the testosterone esters is administered as a single injection to one injection site, wherein the injected volume is of 1 to 5 mL, preferably of 1 to 4 mL, such as of 1.5 to 4 mL. Suitable injection volumes of the invention for ensuring reproducible administration volumes and uniform release of the testosterone esters is lower than 5 mL, such as about 5 mL, about 4 mL, about 3 mL, about 2 mL and about 1 mL.

[0046] In order for using single injections and low injection volumes, the concentration of the testosterone esters in

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the compositions need to be relatively high. Thus, a testosterone ester, such as testosterone undecanoate is in a concentration of 100 mg to 1000 mg per mL of the vehicle. In still interesting embodiments, the testosterone ester, such as testosterone undecanoate, is in a concentration of 130 to 750 mg per mL of the vehicle, more preferably of 150 to 500 mg per mL, most preferably of 175 to 400 mg per mL, such as about 250 mg/mL of the vehicle.

5 [0047] The composition may be suitable formulated as a unit dose form such as a unit dose intended for being injected as one single dose. In such embodiments, the testosterone ester, such as testosterone undecanoate, is in a dose of 500 to 4000 mg, preferably of 500 mg to 3000 mg, more preferably of 750 mg to 2000 mg, most preferably of 750 mg to 1500 mg, such as 1000 mg.

10 [0048] It is further contemplated that compositions of the invention comprise a further therapeutically active agent, such as a progestin and/or a further gonadotropin suppressive agent other than a testosterone ester.

[0049] As used herein, the term "progestin" encompasses all compounds with progestinic activity such as cyproterone, drospironone, etonogestrel, desogestrel, gestodene, levonorgestrel, norethisterones, norgestimate, norethindrone, norethindrone acetate, norethynodrel, norgestimate, norgestrel, medrogestone, medroxyprogesterone acetate and progesterone.

15 [0050] The compositions of the invention are chemically stable with respect to the testosterone esters. That is to say that degradation products could not be detected after long term storage (such as after 7 weeks or 17 weeks or even longer) at conditions normally known to accelerate degradation processes, such as variations in temperatures, high and low temperatures and various relative humidity. For example, less than 1% by weight of degradation products of testosterone esters is present after storage of the composition for at least 7 weeks, such as for 16 or 17 weeks, for 8 months, or for 9 or 12 months at 40 °C and 25 % RH in darkness. Preferably, less than 0.5 % w/w, such as less than 0.2 % w/w of degradation products of testosterone esters is present after storage at the above-mentioned conditions.

20 [0051] Moreover, the vehicle comprising castor oil and benzyl benzoate is also highly stable in that no sublimate of the solution is seen upon storage of the composition for a long time at various temperatures.

[0052] Compositions according to the invention may be prepared according to techniques known by the skilled person.

25 [0053] A first step in the preparation of a composition of the invention comprises dissolving the testosterone ester in the co-solvent. Then, the testosterone undecanoate/co-solvent solution is combined with castor oil. The final solution may then be filtrated through a 0,2 µm filter, optionally filled into, for instance, amber-glass bottles, before finally sterilised at 180°C for 3 hours.

30 [0054] It is submitted that the vehicle, wherein the testosterone ester is dissolved, may further comprise one or more excipients, such as preservatives, stabilising agents, other co-solvents and antioxidants. Suitable vehicles are sterile, pyrogen-free and free of particles.

[0055] As stated *supra*, the present inventors have provided a formulation of testosterone esters possessing superior pharmacokinetic profiles of testosterone in the blood upon

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- selecting a proper injection vehicle for the testosterone esters so as to ensure slowly diffusion of the testosterone esters from the site of injection and slowly disintegration of the testosterone ester into free testosterone in the blood and
 - selecting a simple and reliable administration scheme of such compositions for treating diseases and symptoms associated with deficient endogenous levels of testosterone in a man.

40 [0056] Thus, a further aspect of the invention relates to a method of treating diseases and symptoms associated with deficient endogenous levels of testosterone in a male, such as a mammalian male, such as a man, comprising administering by injection, such as by intramuscular injection, a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates, the method further comprises;

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I) an initial phase comprising 2 to 4 injections of a single dose of said testosterone ester with an interval of 4 to 10 weeks between each injections, each dose is in an amount therapeutically equivalent to a dose of testosterone undecanoate of between 500 mg and 2000 mg; followed by

50 II) a maintenance phase comprising subsequent injections of a single dose of said testosterone ester with an interval of at least 9 weeks between each subsequent injection, each dose is in an amount therapeutically equivalent to a dose of testosterone undecanoate of between 500 mg and 2000 mg.

55 [0057] The phrase "therapeutically equivalent" is meant to define the dose of any testosterone ester of the invention in terms of the therapeutically relevant dose of testosterone undecanoate. For example, if it has been shown that the therapeutically relevant dose of testosterone undecanoate for re-instating testosterone blood levels in the range of 12-35 nmol is about 1000 mg, the dose of any testosterone ester of the invention is the dose achieving the same effect as testosterone undecanoate.

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[0058] The term "administration by injection" is meant to encompass any form for injection into a muscle or subcutaneous injection. The preferred form of injection is by intramuscular injection.

[0059] Preferably, the initial phase comprises 2 or 3 injections of a dose of said testosterone ester, such as testosterone undecanoate, with an interval of 4 to 8 weeks between each injection. In a most interesting embodiment, the initial phase includes 2 injections of a single dose of said testosterone ester with an interval of 4 to 10 weeks between each injection.

In currently interesting embodiments, the interval between injections in the initial phase is 6 weeks.

[0060] In further aspects, the invention relates to the use of a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates for the preparation of a medicament for treating primary and secondary hypogonadism in a male, said medicament is in a form intended for injectable administration and further comprises a vehicle comprising castor oil and a co-solvent.

[0061] The present inventors provide herein evidence for that upon applying a first injection interval of 6 weeks (injection of a first dose followed by a second dose 6 weeks after the first injection), the time until steady-state conditions is shortened. Thus, a maintenance phase may start already after 6 weeks of therapy. As further shown herein, the subsequent injection of testosterone undecanoate can be conducted using intervals of 10 weeks or 12 weeks between injections so as to achieve serum testosterone levels remaining well within the normal range of 10 to 35 nmol/l throughout the entire period between injections. Thus, an injection scheme resulting in reliable serum testosterone levels ranging from 10-35 nmol/l has been found.

[0062] The pharmacokinetic profile of the composition of the invention allows for extended periods between injections when steady state conditions is first achieved. Thus, in preferred embodiments of the invention, the maintenance phase comprises that the subsequent injections are conducted with an interval of 10 weeks between subsequent injections, preferably with an interval of 11 weeks, such as intervals of 12, 13, 14, 15 and 16 weeks between subsequent injections of the compositions of the invention.

[0063] The actual dose of testosterone ester being injected will also modify the depot effect of the compositions of the invention. Therefore, in suitable embodiments of the invention, the injected single dose of said testosterone ester is in an amount therapeutically equivalent to a single dose of testosterone undecanoate of between 750 to 1500 mg. Preferably, 1000 mg of testosterone undecanoate is injected as a single dose or any therapeutically equivalent dose of another testosterone undecanoate of the invention.

[0064] As may be understood, the single doses referred to above, such as the doses injected during the initial phase and the doses injected during the maintenance phase may be similar or different. Therefore, in some embodiments of the invention, the doses injected during the initial phase comprise the same amount of testosterone ester. In other embodiments, the doses injected during the initial phase are different from one injection to another. Similarly, in some embodiments, the doses injected during the maintenance phase are similar throughout the period or they may vary. Obviously, the doses applied in the initial phase may differ from those applied in the maintenance phase. However, preferably the doses of the testosterone esters injected in the initial phase and maintenance phase comprise the same amount of testosterone ester.

[0065] As mentioned above, the invention relates to a method of treating diseases and symptoms associated with deficient endogenous levels of testosterone in a male, such as a mammalian male, such as a man. As used herein, deficient levels of testosterone in a man, such as a hypogonadal man, is meant to encompass levels testosterone in serum less than 10 or 9 nmol/l.

[0066] In one embodiment of the invention, the deficient endogenous levels of testosterone may be caused by therapy with progestins or gonadotropin suppressive agents. Thus, methods of treating deficient endogenous levels of testosterone in a male may imply methods for male contraception. Therefore, in some embodiments of the invention, methods of treatment and uses are directed to male contraception, optionally wherein a progestin or a further gonadotropin suppressive agent is included in the treatment.

[0067] Hence, in still further aspects, the invention relates to the use of a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates for the preparation of a medicament for treating diseases and symptoms associated with deficient levels of testosterone in a male in therapy with a progestin or a further gonadotropin suppressive agent, said medicament is in a form intended for being injected, such as in a form for intramuscular injection, and the testosterone ester, such as testosterone undecanoate is in a vehicle comprising castor oil and a co-solvent.

[0068] In general, the invention relates to the use of a composition as defined herein for male contraception or for treating diseases and symptoms associated with deficient endogenous levels of testosterone in a male.

[0069] Generally speaking, diseases and symptoms of deficient endogenous levels of testosterone in a male may imply sexual dysfunction, reduced muscle mass and muscle strength, depressed mood and/or osteoporosis.

[0070] Diseases of interest relate in general to primary and secondary hypogonadism and hypophyseal diseases. Thus, embodiments of the invention include treatment of diseases associated with primary and secondary hypogonadism and hypophyseal diseases. Primary hypogonadism may be derived from testicular failure such as resulting from cryp-

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torchidism, bilateral testicular torsion, orchitis, orchidectomy, Klinefelter syndrome, chemotherapy and toxic damage from alcohol or heavy metals. Secondary hypogonadism may be derived from idiopathic gonadotropin releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury associated with tumours, trauma or radiation.

5 [0071] Hence, in some embodiments of the invention, the treatment and uses of the invention is directed to a hypogonadal man, a man with hypophyseal diseases and/or a man in therapy with gonadotropin-suppressive agents or progestins.

10 [0072] Furthermore, as stated the single dose of a testosterone ester need to be justified so as to achieve reliable serum testosterone levels. Thus, in some embodiments, said use of a testosterone ester for the preparation of a medicament comprises that said testosterone ester is in a unit dose therapeutically equivalent to a dose of testosterone undecanoate, or that said testosterone ester is in a dose, corresponding to a 8-week dose of 500 mg to 2000 mg of testosterone undecanoate. In some embodiments, the dose corresponds to a 8-week dose of 500 mg to 2000 mg of testosterone undecanoate, a 10-week dose of 500 mg to 2000 mg, a 11-week dose of 500 mg to 2000 mg, a 12-week dose of 500 mg to 2000 mg, a 13-week dose of 500 mg to 2000 mg, a 14-week dose of 500 to 2000 mg, a 15-week dose of 500 to 2000 mg and a 16-week dose of 500 mg to 2000 mg. Preferably, such 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15- and 16-week doses of a testosterone ester are therapeutically equivalent to a dose of testosterone undecanoate of 750 mg to 1500 mg, preferably of 1000 mg.

15 [0073] As may be further understood, the method of treatments and uses as described herein include embodiments wherein the testosterone ester, such as testosterone undecanoate is provided in a composition as defined herein.

20 FIGURES

[0074]

25 Figure 1. Total levels of testosterone in serum following injection of testosterone undecanoate.

30 [0075] The figure shows the levels of testosterone (total amounts) following injecting a formulation of testosterone undecanoate in a vehicle containing 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume. See Example 3 for the injection scheme. The dotted lines shows the initial phase of two injections of 1000 mg of TU with an interval of 8 weeks, followed by 3 injections of TU with an interval of 10 weeks between injections. The filled lines show the continued injection of 1000-mg TU with an interval of 12 weeks between injections.

EXAMPLES

35 Example 1

[0076] Compositions according to the present invention are formulated for intramuscular injection and prepared according to techniques known by a person skilled in the art.

40 [0077] Compositions are in general prepared by incorporating a therapeutically effective amount of any of testosterone ester of the invention, such as the testosterone undecanoate, in an appropriate vehicle comprising castor oil and a co-solvent, such as benzyl benzoate. Further excipients may be added. Finally, the compositions are subjected to a sterilisation process. The vehicle wherein the active substance is dissolved may comprise excipients such as preservatives, stabilising agents, co-solvents and antioxidants. Suitable vehicles are sterile, pyrogen-free and free of particles.

[0078] The compositions may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers.

45 [0079] The preparation of compositions according to one embodiment of the invention may comprise the following steps:

I) Pre sterilisation of excipients and testosterone esters.

50 II) Preparation of a solution of testosterone esters

III) Addition of one or more excipients to the solution of testosterone esters

IV) Filtration of the composition

55 V) Preparation / filling of single or multi-dose containers

VI) Sterilisation.

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[0080] In one specific example of the invention the testosterone undecanoate is dissolved in benzyl benzoate, the testosterone undecanoate/co-solvent solution is then combined with the castor oil, which is then filtrated through a 0,2 µm filter, filled into amber-glass bottles, and finally sterilised at 180°C for 3 hours.

5 **Example 2**

[0081] The therapeutic efficacy and safety of a formulation containing testosterone undecanoate 1000 mg in a vehicle of 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume has been investigated in hypogonadal men. The formulation (4 mL, 1000 mg of testosterone undecanoate) was injected intramuscularly to the hypogonadal men according to the following scheme:

- Initial phase comprising 4 injections of the formulation with intervals of 8 weeks between the injections.
- maintenance phase comprising injecting the formulation in intervals of 10 or 12 weeks between injections.

15 [0082] The present study relates to a one-arm study examining the efficacy and safety of long-term intramuscular injection of testosterone undecanoate for the treatment of symptoms of hypogonadism in men. The patients received 4 testosterone undecanoate injections of 1000 mg the first three times of injections with an interval of 8 weeks, the 4th injection and subsequent injections with 12-week intervals.

20 [0083] Protocol:

25	Name of active ingredient:	Testosterone Undecanoate (TU)
	Objectives:	To obtain further information on efficacy and safety of the TU preparation after long-term administration over a period of more than 18 months at prolonged (12-week) intervals between the injections of 1000 mg TU in 4 ml oily solution
	Methodology:	Open, one-arm, multiple-dose study
	Total number of subjects:	planned: 38
30	Diagnosis and main criteria for inclusion:	Hypogonadal men aged 18 to 85 years and with serum T (testosterone) levels without androgen treatment lower than 5 nmol/L, who orderly completed the main study with a final examination, did not exhibit any relevant pathological findings, and gave their written informed consent to either extend the TU treatment from the main study or switch over from TE (testosterone enanthate) to TU
35	Test product:	Testosterone Undecanoate (TU)
	dose:	In patients on TU : 8 x 1000 mg at 12-week intervals
	mode of administration:	Intramuscular injections (<i>gluteus medius</i> muscle)
40	Duration of treatment:	80 weeks 84 weeks
	Efficacy end points: -	Primary variables: erythropoiesis (hemoglobin, hematocrit), grip strength; Secondary variables: serum levels of testosterone (T), dihydrotestosterone (DHT), estradiol (E2), lutealizing hormone (LH), follicle stimulating hormone (FSH), leptin and sex hormone-binding globulin (SHBG); bone density; parameters of bone metabolism; body composition; lipids (total cholesterol, triglycerides, low-density, high-density and very low-density lipoproteins, apolipoprotein A1 and B, lipoprotein (a))
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50	Safety end points:	Adverse events (AEs); serum level of prostate-specific antigen (PSA); ultrasonographic findings in prostate; hematological and liver (ASAT, ALAT, gamma-GT, total bilirubin) parameters, ferritin, iron;

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[0084] The results of this study allow for the following conclusion:
Treatment with only 4 TU doses of 1000 mg i.m. per year was sufficient to restore physiological serum T levels in all 38

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patients over most of the measurement times. This demonstrates that an injection interval of 12 weeks is adequate for most of the patients.

Example 3

Pharmacokinetic profile of compositions of the invention:

[0085] The pharmacokinetic profile of a formulation containing testosterone undecanoate (TU) 1000 mg in a vehicle of 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume was tested in hypogonadal men (having testosterone levels in serum of less than 10 nmol/l). An initial phase of two first intramuscularly injections of 1000 mg TU with 8-weeks interval between the two injections, followed by a maintenance phase of subsequent 3 intramuscularly injections of 1000 mg TU separated by an interval of 10 weeks between each of the injections. Then 1000 mg of testosterone undecanoate (TU) was intramuscularly injected every 12 weeks. 5 treatment periods were provided with an interval of 12 weeks between each injection.

[0086] The result from this study shows (see figure 1) that the treatment scheme resulted in testosterone levels (total levels) wherein the maximal and minimal levels are within the physiological acceptable range and no accumulation of testosterone is seen over time. Furthermore, the minimum testosterone levels (total levels) after 12 weeks do not fall below the lowest acceptable concentration of testosterone of about 10 nmol. The same was shown to apply for a treatment period of 14 weeks upon extrapolating the serum levels of testosterone. The study also demonstrated that injection of 1000 mg of TU in the above-mentioned formulation in intervals of 12 weeks between injections was efficient over a period of 14 weeks.

Example 4

[0087] Comparison of initial phases with 8 weeks between injections and 10 weeks between injections.

[0088] The pharmacokinetic profile of a formulation containing testosterone undecanoate (TU) 1000 mg in a vehicle of 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume was tested using two different regimens in hypogonadal men.

[0089] In regimen A, an initial phase of two first intramuscularly injections of 1000 mg TU with mean of 9.2-weeks (64.4 days) interval between the two injections, followed by a maintenance phase of subsequent intramuscularly injections of 1000 mg TU separated by an interval of a mean of 10.2 weeks (78.2 days) after second injection.

[0090] In regimen B, an initial phase of two first intramuscularly injections of 1000 mg TU with mean of 8.1-weeks (42.5 days) interval between the first two injections, followed by a maintenance phase of subsequent intramuscularly injections of 1000 mg TU separated by an interval of mean of 10.1 weeks (70.5 days) after second injections.

[0091] The concentration of testosterone (total) was determined in serum before each additional injection of TU.

Results.

[0092] The table below shows the mean serum levels of testosterone (total) for regimen A versus regimen A based on data for 8 men.

Mean Testosterone levels (total) in serum according to the number of weeks between injections.

Regime	Base value; mean testosterone level (nmol/l) before 1 st injection	↓ 1 st injection		↓ 2 nd injection	
		Mean weeks after 1 st injection	Mean testosterone level (nmol/l) after weeks	Mean weeks after 2 nd injection	Mean testosterone level (nmol/l) after weeks
A	7.9	9.2	7.0	10.8	8.8
B	6.8	8.1	12.2	10.1	12.5

[0093] It appears that regimens including long-term intervals between injections, both with respect to the initial phase and maintenance phase, do not result in the sufficient levels of testosterone above 10 nmol over the entire period and up to the following injection (Regimen A). However, upon decreasing the interval between injections in the initial phase

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to 8 weeks, a reliable regimen is achieved, wherein sufficient testosterone levels are reinstated very fast and remains at levels above 10 nmol/l.

5 Claims

1. A composition formulated for intramuscular injection comprising a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates; and a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent.
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2. The composition according to claim 1, wherein the testosterone ester is testosterone undecanoate.
3. The composition according to claim 2, wherein the testosterone undecanoate is in a dose of 150 to 500 mg per mL.
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4. The composition according to any of the preceding claims, wherein the vehicle comprises the castor oil in a concentration of 25-40 vol%.
5. The composition according to any of claims 1-3, wherein the co-solvent is in an amount ranging from 55 to 65 vol% of the vehicle.
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6. The composition according to any one of the preceding claims, wherein the co-solvent is benzyl benzoate.
7. A pharmaceutical formulation containing 1.000 mg testosterone undecanoate in a vehicle of 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume.
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8. Use of a composition as defined in any one of claims 1-6 or a pharmaceutical formulation as defined in claim 7 in male contraception.
9. Use of a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates for the preparation of a medicament for treating primary and secondary hypogonadism in a man, said medicament is in a form for intramuscular injection and comprises a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent.
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10. The use according to claim 9, wherein said primary hypogonadism is derived from testicular failure selected from the group consisting of cryptorchidism, bilateral testicular torsion, orchitis, orchidectomy, Klinefelter syndrome, chemotherapy and toxic damage from alcohol or heavy metals.
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11. The use according to claim 9, wherein said secondary hypogonadism is derived from idiopathic gonadotropin releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury caused by tumours, trauma or radiation.
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12. Use of a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates for the preparation of a medicament for treating diseases and symptoms associated with deficient levels of testosterone in a man who is in therapy with a progestin or a gonadotropin suppressive agent, said medicament is in a form for intramuscular injection and comprises a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent.
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13. The use according to claim 10, wherein said deficient levels of testosterone in a man is such that the concentration of testosterone in serum is less than 10 nmol/l.
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14. The use according to claims 8-13, wherein the testosterone ester is testosterone undecanoate.
15. The use according to any of claims 8 to 14, wherein said medicament comprises said testosterone ester in a 6-week dose of 500 mg to 2000 mg, a 8-week dose of 500 mg to 2000 mg, a 10-week dose of 500 mg to 2000 mg, a 11-week dose of 500 mg to 2000 mg, a 12-week dose of 500 mg to 2000 mg, a 13-week dose of 500 mg to 2000 mg, a 14-week dose of 500 to 2000 mg, a 15-week dose of 500 to 2000 mg or a 16-week dose of 500 mg to 2000 mg.
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16. The use according to claim 15, wherein said 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15- and 16-week dose is of 750 mg to 1500 mg.

17. The use according to any of claims 8 to 16, wherein the co-solvent is benzyl benzoate.

Patentansprüche

1. Zusammensetzung, die für das intramuskuläre Einspritzen formuliert ist, umfassend einen Testosteronester ausgewählt aus der Gruppe von Estern bestehend aus linearen und verzweigten Nonanoaten, Decanoaten, Undecanoaten, Dodecanoaten, Tridecanoaten, Tetradecanoaten und Pentadecanoaten; und ein Vehikel umfassend Rizinusöl in einer Konzentration von 25 - 45 Vol.-% und ein Hilfölungsmittel.

2. Zusammensetzung nach Anspruch 1, wobei der Testosteronester Testosteronundecanoat ist.

3. Zusammensetzung nach Anspruch 2, wobei das Testosteronundecanoat in einer Dosis von 150 bis 500 mg pro ml vorliegt.

4. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei das Vehikel das Rizinusöl in einer Konzentration von 25 - 40 Vol.-% umfasst.

5. Zusammensetzung nach einem der Ansprüche 1 - 3, wobei das Hilfölungsmittel in einer Menge im Bereich von 55 bis 65 Vol.-%, auf das Vehikel bezogen, vorliegt.

6. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei das Hilfölungsmittel Benzylbenzoat ist.

7. Pharmazeutische Rezeptur enthaltend 1000 mg Testosteronundecanoat in einem Vehikel von 4 ml einer Mischung von Rizinusöl und Benzylbenzoat in einem Verhältnis von 1:1,7, auf das Volumen bezogen.

8. Verwendung einer Zusammensetzung wie in einem der Ansprüche 1 - 8 definiert, oder einer pharmazeutischen Rezeptur, wie in Anspruch 7 definiert, in einem empfängnisverhütenden Mittel für Männer.

9. Verwendung eines Testosteronesters ausgewählt aus der Gruppe von Estern bestehend aus linearen und verzweigten Nonanoaten, Decanoaten, Undecanoaten, Dodecanoaten, Tridecanoaten, Tetradecanoaten und Pentadecanoaten für die Zubereitung eines Medikaments für die Behandlung von primärem und sekundärem Hypogonadismus beim Mann, wobei das Medikament in Form einer intramuskulären Einspritzung vorliegt und ein Vehikel umfasst, das Rizinusöl in einer Konzentration von 25 - 45 Vol.-% und ein Hilfölungsmittel umfasst.

10. Verwendung nach Anspruch 9, wobei der primäre Hypogonadismus aus dem Versagen der Hoden herrührt ausgewählt aus der Gruppe bestehend aus Hodenretention, beidseitiger Hodenatrophie, Hodenentzündung, Hodenentfernung, Klinefelter-Syndrom, Chemotherapie und toxischem Schaden durch Alkohol oder Schwermetalle.

11. Verwendung nach Anspruch 9, wobei der sekundäre Hypogonadismus von einem Mangel an Idiopathisches Gonadotropin freisetzendem Hormon (GnRH) oder durch Tumore, Trauma oder Strahlungsbehandlung hervorgerufener Verletzung der Hirnanhangdrüse/des Hypothalamus herrührt.

12. Verwendung eines Testosteronesters ausgewählt aus der Gruppe von Estern bestehend aus linearen und verzweigten Nonanoaten, Decanoaten, Undecanoaten, Dodecanoaten, Tridecanoaten, Tetradecanoaten und Pentadecanoaten für die Zubereitung eines Medikaments für die Behandlung von Krankheiten und Symptomen, die mit mangelhaften Testosteronspiegeln bei einem Mann assoziiert sind, der eine Therapie mit einem Progestin oder Gonadotropin unterdrückenden Mittel durchmacht, wobei das Medikament in Form einer intramuskulären Einspritzung vorliegt und ein Vehikel umfasst, das Rizinusöl in einer Konzentration von 25 - 45 Vol.-% und ein Hilfölungsmittel umfasst.

13. Verwendung nach Anspruch 10, wobei die mangelhaften Testosteronspiegel bei einem Mann derart sind, dass die Testosteronkonzentration im Serum weniger als 10 nmol/l beträgt.

14. Verwendung nach Ansprüchen 8 - 13, wobei der Testosteronester Testosteronundecanoat ist.

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15. Verwendung nach einem der Ansprüche 8 bis 14, wobei das Medikament den Testosteronester in einer 6-Wochendosis von 500 mg bis 2000 mg, einer 9-Wochendosis von 500 bis 2000 mg, einer 10-Wochendosis von 500 mg bis 2000 mg, einer 11-Wochendosis von 500 bis 2000 mg, einer 12-Wochendosis von 500 bis 2000 mg, einer 13-Wochendosis von 500 bis 2000 mg, einer 14-Wochendosis von 500 bis 2000 mg, einer 15-Wochendosis von 500 bis 2000 mg oder einer 16-Wochendosis von 500 bis 2000 mg umfasst.
16. Verwendung nach Anspruch 15, wobei die 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15- und 16-Wochendosis 750 mg bis 1500 mg beträgt.
17. Verwendung nach einem der Ansprüche 8 bis 16, wobei das Hilfsmittel Benzylbenzoat ist.

Revendications

1. Composition formulée pour des injections intramusculaires, qui comprend un ester de testostérone sélectionné dans le groupe d'esters constitué de nonanoates, de décanoates, d'undécanoates, de dodécanoates, de tridécanoates, de tétradécanoates et de pentadécanoates linéaires ou ramifiés, ainsi qu'un excipient comprenant de l'huile de ricin en une concentration de 25 à 45 % en volume et un co-solvant.
2. Composition selon la revendication 1, dans laquelle l'ester de testostérone est l'undécanoate de testostérone.
3. Composition selon la revendication 2, dans laquelle l'undécanoate de testostérone est sous forme d'une dose de 150 à 500 mg par ml.
4. Composition selon l'une quelconque des revendications précédentes, dans laquelle l'excipient comprend de l'huile de ricin en une concentration de 25 à 40 % en volume.
5. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle le co-solvant est présent en une quantité allant de 55 à 65 % en volume de l'excipient.
6. Composition selon l'une quelconque des revendications précédentes, dans laquelle le co-solvant est du benzoate de benzyle.
7. Formulation pharmaceutique comprenant 1000 mg d'undécanoate de testostérone dans un excipient de 4 ml d'un mélange d'huile de ricin et de benzoate de benzyle dans un rapport de 1:1,7 en volume.
8. Utilisation d'une composition telle que définie dans l'une quelconque des revendications 1 à 6 ou d'une formulation pharmaceutique telle que définie dans la revendication 7 pour la contraception masculine.
9. Utilisation d'un ester de testostérone sélectionné dans le groupe d'esters constitué de nonanoates, de décanoates, d'undécanoates, de dodécanoates, de tridécanoates, de tétradécanoates et de pentadécanoates linéaires ou ramifiés pour la préparation d'un médicament pour le traitement de l'hypogonadisme primaire ou secondaire chez l'homme, ledit médicament étant utilisé sous forme d'une injection intramusculaire et comprenant un excipient comprenant de l'huile de ricin en une concentration de 25 à 45 en volume ainsi qu'un co-solvant.
10. Utilisation selon la revendication 9, dans laquelle ledit hypogonadisme primaire provient d'une insuffisance testiculaire sélectionnée dans le groupe constitué de la cryptorchidie, la torsion testiculaire bilatérale, l'orchite, l'orchidectomie, le syndrome de Klinefelter, la chimiothérapie et les lésions toxiques causées par l'alcool ou des métaux lourds.
11. Utilisation selon la revendication 9, dans laquelle ledit hypogonadisme secondaire provient d'une déficience en gonadolibérine (GnRH) idiopathique ou d'une lésion pituitaire hypothalamique causée par des tumeurs, des traumatismes ou des radiations.
12. Utilisation d'un ester de testostérone sélectionné dans le groupe d'esters constitué de nonanoates, de décanoates, d'undécanoates, de dodécanoates, de tridécanoates, de tétradécanoates et de pentadécanoates linéaires ou ramifiés pour la préparation d'un médicament pour le traitement de maladies ou symptômes associés à des niveaux déficients de testostérone chez un homme qui suit une thérapie à la progestérone ou avec un agent supprimeur de la gonadotrophine, ledit médicament étant utilisé sous forme d'une injection intramusculaire et comprenant un

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excipient comprenant de l'huile de ricin en une concentration de 25 à 45 % en volume ainsi qu'un co-solvant.

13. Utilisation selon la revendication 10, dans laquelle lesdits niveaux déficients de testostérone chez un homme sont tels que la concentration sérique de testostérone est inférieure à 10 nmole/l.
14. Utilisation selon les revendications 8 à 13, dans laquelle l'ester de testostérone est l'undécanoate de testostérone.
15. Utilisation selon l'une quelconque des revendications 8 à 14, dans laquelle ledit médicament comprend ledit ester de testostérone dans une dose de 6 semaines de 500 mg à 2000 mg, une dose de 9 semaines de 500 mg à 2000 mg, une dose de 10 semaines de 500 mg à 2000 mg, une dose de 11 semaines de 500 mg à 2000 mg, une dose de 12 semaines de 500 mg à 2000 mg, une dose de 13 semaines de 500 mg à 2000 mg, une dose de 14 semaines de 500 mg à 2000 mg, une dose de 15 semaines de 500 mg à 2000 mg ou une dose de 16 semaines de 500 mg à 2000 mg.
16. Utilisation selon la revendication 15, dans laquelle lesdites doses de 6, 9, 10, 11, 12, 13, 14, 15 et 16 semaines sont de 750 mg à 1500 mg.
17. Utilisation selon l'une quelconque des revendications 8 à 16, dans laquelle le cosolvant est du benzoate de benzyle.

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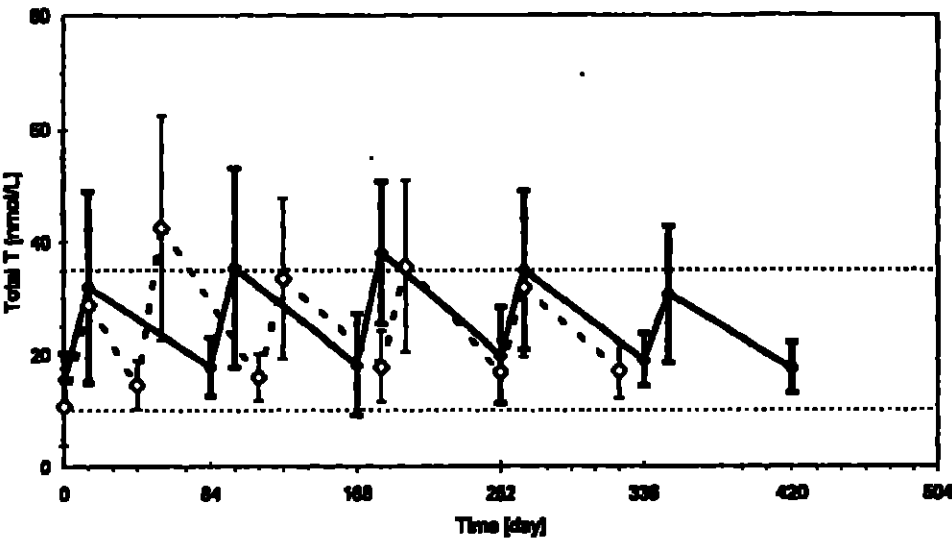


Fig. 1

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Solubilidad de undecanoato de testosterona (UT) en diferentes aceites

Objetivo

Diferentes mezclas de benzoato de bencilo/aceite que contienen 250 mg de UT por ml fueron estudiadas por su cristalizabilidad en refrigerador a 2-8 °C. Determinar qué aceite particular y relación de concentraciones de benzoato de bencilo/aceite tienen la mayor capacidad de disolver UT.

Materiales

Aceite de ricino refinado para uso parenteral: DAB [Farmacopea Aleman]

Aceite de maní para uso parenteral: Ph. Eur.

Migliol 812: Ph Eur.

Benzoato de bencilo: Ph. Eur., USP

Undecanoato de testosterona: Monografía interna

Preparación

Para preparar cada solución, se disolvieron 25 g de UT a 50°C en la cantidad respectiva de benzoato de bencilo, con lo cual la cantidad de aceite respectivo fue adicionada. La mezcla resultante entonces fue agitada. Una solución clara fue formada. Fueron llenadas ampollas con 4 ml de parte de la solución y entonces fueron cerradas. 8 ampollas fueron guardadas en refrigerados (a 2-8°C) y 4 ampollas fueron mantenidas a 25°C. Las ampollas fueron chequeadas a tiempos específicos en busca de presencia de precipitados (cristales).

Relaciones

25 g UT en una mezcla de 40% de benzoato de bencilo + 60% de aceite de ricino refinado

25 g UT en una mezcla de 50% de benzoato de bencilo + 50% de aceite de ricino refinado

25 g UT en una mezcla de 63% de benzoato de bencilo + 37% de aceite de ricino refinado

25 g UT en una mezcla de 40% de benzoato de bencilo + 60% de aceite de maní

25 g UT en una mezcla de 50% de benzoato de bencilo + 50% de aceite de maní

25 g UT en una mezcla de 63% de benzoato de bencilo + 37% de aceite de maní

25 g UT en una mezcla de 40% de benzoato de bencilo + 60% de aceite de migliol 812

25 g UT en una mezcla de 50% de benzoato de bencilo + 50% de aceite de migliol 812

25 g UT en una mezcla de 63% de benzoato de bencilo + 37% de aceite de migliol 812

Resultados

Estabilidad de las soluciones oleosas a temperatura ambiente (25°C)

No aparecieron precipitados en ningún ampolla después de 34°C

Estabilidad de soluciones oleosas durante almacenamiento en refrigerador (a 2-8°C)

Formulaciones que comprenden aceite de ncino refinado para uso parenteral	Numero de ampollas con precipitación (cristales)								
	0 d	1 d	2 d	3 d	6 d	8 d	10 d	21 d	34 d
40% de benzoato de bencilo	0	5	6	6	6	6	6	6	6
50% de benzoato de bencilo	0	0	1	3	3	3	3	4	5
63% de benzoato de bencilo	0	0	0	0	0	0	0	0	0

Formulaciones que comprenden aceite de mani para uso parenteral	Numero de ampollas con precipitación (cristales)						
	0 d	1 d	4 d	6 d	8 d	19 d	32 d
40% de benzoato de bencilo	0	5	6	6	7	8	8
50% de benzoato de bencilo	0	2	5	5	5	7	8
63% de benzoato de bencilo	0	0	5	5	5	7	8

Formulaciones que comprenden miglitol 812 para uso parenteral	Numero de ampollas con precipitación (cristales)							
	0 d	1 d	2 d	5 d	7 d	9 d	20 d	33 d
40% de benzoato de bencilo	0	4	4	7	8	8	8	8
50% de benzoato de bencilo	0	1	1	8	8	8	8	8
63% de benzoato de bencilo	0	0	1	1	1	1	5	6

Se puede decir en conclusión que la formulación que contiene aceite de ncino refinado para uso parenteral con un porcentaje de 63% de benzoato de bencilo (= composición de la formulación original Nebido ®) es la única formulación en la cual UT no precipita durante el almacenamiento por más de 34 días en refrigerador a 2-8°C. Todos los otros aceites y respectivas relaciones dieron un producto inestable.

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