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RAISBECK, LARA, RODRÍGUEZ & RUEDA
MIEMBROS DE LA FIRMA
BAKER & MCKENZIE

CALLE 35 No. 7-25, Piso 4
TELÉFONO: (57-1) 332-2600
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SUPERINTENDENCIA Y COMERCIO
Radicación: C2074167 CCCCCC
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Creador: 2003 DIVISION DE NUEVAS CREACIONES

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: Expediente No. 00.074.167.

Solicitud de Patente de Invención titulada:

"REGIMENES DE DOSIFICACION PARA
LASOFOXIFENO".

Solicitante : PFIZER PRODUCTS INC.

RESPUESTA AL AUTO NOTIFICADO POR ESTADO No. 156
DE FECHA 19 DE OCTUBRE DE 2000, CONCEPTO TECNICO No. 1642

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma en mi carácter de apoderado de la sociedad en referencia, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del término legal:

1. En atención a la única observación del Examinador Jurídico, adjunto la sustitución del poder del Doctor Alvaro Correa Ordóñez a mi favor.

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2. Adicionalmente, presento la Copia Certificada de la Solicitud de Patente No. 60/156,652, de la cual se reclama prioridad en la presente solicitud, me permito aclarar que la traducción del documento anterior fue presentado junto con la solicitud.

3. Finalmente, con el objetivo de cumplir con los requisitos de patentabilidad dispuestos en el actual régimen para Patentes de Invención, solicito de manera atenta que el Capítulo Reivindicatorio Modificado que adjunto, sea aceptado como sustitutivo del anteriormente presentado. Este Capítulo Reivindicatorio Modificado contiene cinco (5) reivindicaciones nuevas dirigidas al uso del agonista/antagonista de estrógeno para la fabricación de un medicamento útil para mantener un nivel sanguíneo seguro y efectivo de un agonista/antagonista de estrógeno por un largo periodo de tiempo.

Para guardar concordancia con el Capítulo Reivindicatorio Modificado, presento un Extracto para Publicación Modificado y una Tarjeta de Archivo Temático Modificada. Señalo que el Capítulo Reivindicatorio Modificado adjunto no constituye una ampliación del material inicialmente presentado.

Atentamente,



CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Anexos: Sustitución.
Copia Certificada del Documento de Prioridad.
Capítulo Reivindicatorio Modificado.
Extracto para Publicación Modificado.
Tarjeta de Archivo Temático Modificada.

RAISBECK, LARA, RODRIGUEZ & RUEDA

MIEMBROS DE LA FIRMA

BAKER & MCKENZIE

CALLE 35 No. 7-25, Piso 4

TELÉFONO: (57-1) 285-1400 / 570-0010

SANTA FE DE BOGOTÁ, D.C.

COLOMBIA

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: Expediente No. 00'074.167
Solicitud de Patente de Invención
Titulada : "REGIMENES DE DOSIFICACION
PARA LASOFOXIFENO".
Solicitante : PFIZER PRODUCTS INC.

ALVARO CORREA ORDOÑEZ, mayor de edad y vecino de Santa fe de Bogotá D.C., identificado como aparece al pie de mi firma, actuando en mi carácter de apoderado de la sociedad en referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad en el doctor **CARLOS R. OLARTE**, identificado con la Cédula de Ciudadanía No. 79.782.747 de Bogotá y con la Tarjeta Profesional No. 74.295.

El apoderado sustituto queda con las mismas facultades del principal.

Atentamente,



ALVARO CORREA ORDOÑEZ

C.C. No. 79.143.366 de Usaquén

T.P.20.281

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**
Ante el Notario Once del Circulo de Santafé de Bogotá, compareció

Quién exhibió la C.G. No.
expedida en Usaquen T.P. 2025
y declaró que la firma y huella que aparecen en
el presente memorial son ayaes y que el conte-
nido del mismo es cierto.
Memorial dirigido a Intervento

Santafé de Bogotá, D.C. 20 NOV 2025

Firma del Declarante [Firma] **HUELLA**
Autorizó la anterior Diligencia

NOTA: UNCE DEL CIRCULO DE SANTAFÉ DE BOGOTÁ

REPUBLICA DE COLOMBIA
NOTARIO 11 DEL CIRCULO DE
SANTAFÉ DE BOGOTÁ, D.C.
[Firma]
MONTEZ. BRUTISTA II.
ESTADO CIVIL



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UNITED STATES PATENT AND TRADEMARK OFFICE

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

May 03, 2000

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

APPLICATION NUMBER: 60/156,652

FILING DATE: September 29, 1999



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. Lawrence

T. LAWRENCE
Certifying Officer

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[illegible]

002
CROSS V. M. P.
80/156652
D-289/96

☒ No.

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

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

prover.dot

Dosing Regimens for Lasofoxifene

This invention relates to extended dosing regimens for the estrogen agonist/antagonist lasofoxifene, (-)-~~cis~~-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, D-tartrate.

Background of the Invention

Lasofoxifene and related estrogen agonists/antagonists are disclosed in U.S. Patent 5,552,421 (which is hereby incorporated by reference) as effective agents for treating or preventing diseases and conditions selected from obesity, breast cancer, osteoporosis, endometriosis and cardiovascular disease and hypercholesterolemia in male or female mammals and benign prostatic hypertrophy and prostatic carcinomas in male mammals.

This patent describes formulation and dosing procedures for the estrogen agonists/antagonists as follows:

"The pharmaceutically acceptable acid addition salts of the compounds of this invention may be formed of the compound itself, or of any of its esters, and include the pharmaceutically acceptable salts which are often used in pharmaceutical chemistry. For example, salts may be formed with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfonic acids including such agents as naphthalenesulfonic, methanesulfonic and toluenesulfonic acids, sulfuric acid, nitric acid, phosphoric acid, tartaric acid, pyrosulfuric acid, metaphosphoric acid, succinic acid, formic acid, phthalic acid, lactic acid and the like, most preferable with hydrochloric acid, citric acid, benzoic acid, maleic acid, acetic acid and propionic acid.

It is usually preferred to administer a compound of this invention in the form of an acid addition salt, as it is customary in the administration of pharmaceuticals bearing a basic group such as the pyrrolidino ring.

The compounds of this invention, as discussed above, are very often administered in the form of acid addition salts. The salts are conveniently formed, as is usual in organic chemistry, by reacting the compound of this invention with a suitable acid, such as have been described above. The salts are quickly formed in high yields at moderate temperatures, and often are prepared by merely isolating the compound from a suitable acidic wash as the final step of the synthesis. The salt-

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forming acid is dissolved in an appropriate organic solvent, or aqueous organic solvent, such as an alkanol, ketone or ester. On the other hand, if the compound of this invention is desired in the free base form, it is isolated from a basic final wash step, according to the usual practice. A preferred technique for preparing hydrochlorides is to dissolve the free base in a suitable solvent and dry the solution thoroughly, as over molecular sieves, before bubbling hydrogen chloride gas through it.

The dose of a compound of this invention to be administered to a human is rather widely variable and subject to the judgement of the attending physician. It should be noted that it may be necessary to adjust the dose of a compound when it is administered in the form of a salt, such as a laureate, the salt forming moiety of which has an appreciable molecular weight. The general range of effective administration rates of the compounds is from about 0.05 mg/day to about 50 mg/day. A preferred rate range is from about 0.25 mg/day to 25 mg/day. Of course, it is often practical to administer the daily dose of compound in portions, at various hours of the day. However, in any given case, the amount of compound administered will depend on such factors as the solubility of the active component, the formulation used and the route of administration.

The route of administration of the compounds of this invention is not critical. The compounds are known to be absorbed from the alimentary tract, and so it is usually preferred to administer a compound orally for reasons of convenience. However, the compounds may equally effectively be administered percutaneously, or as suppositories for absorption by the rectum, if desired in a given instance.

The compounds of this invention are usually administered as pharmaceutical compositions which are important and novel embodiments of the invention because of the presence of the compounds. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, troches, suppositories and suspensions. Compositions are formulated to contain a daily dose, or a convenient fraction of daily dose, in a dosage unit, which may be a single tablet or capsule or convenient volume of a liquid.

Any of the compounds may be readily formulated as tablets, capsules and the like; it is preferable to prepare solutions from water-soluble salts, such as the hydrochloride salt.

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In general, all of the compositions are prepared according to methods usual in pharmaceutical chemistry.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidone and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algin and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used as well as sodium lauryl sulfate.

Tablets are often coated with sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established in the art.

When it is desired to administer a compound as a suppository, the typical bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible

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suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use.

5 The effect of the compounds may be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the compound may be prepared and incorporated in a tablet or capsule. The technique may be improved by making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules may be coated with a film which resists dissolution for a predictable period of time. Even the parenteral preparations may be made long-acting, by dissolving or suspending the compound in oily or emulsified vehicles which
10 allow it to disperse only slowly in the serum.

The active ingredient may be usually administered once to four times a day with a unit dosage of 0.1 mg to 50 mg in human patients, but the above dosage may be properly varied depending on the age, body weight and medical condition of the patient and the type of administration. A preferred dose is 0.25 mg in human
15 patients. One dose per day is preferred."

Summary of the Invention

20 We have now found unexpectedly that because of a long biological half-life, high potency and favorable safety factors it is possible to dose lasofodfene only once per a period of 7-30 days by oral delivery and achieve equivalent effect as if the drug were administered on a daily basis as described above.

This invention provides a method of maintaining a safe, effective blood level of an estrogen agonist/antagonist for an extended period of time which comprises
25 administering an oral dose which is of sufficient quantity to maintain said effective blood level for said extended period of time.

This invention also provides a method of maintaining a safe, effective blood level of an estrogen agonist/antagonist for an extended period of time which comprises administering an oral dose which is of sufficient quantity to maintain said
30 effective blood level for said extended period of time wherein said estrogen agonist/antagonist is lasofodfene.

* emphasis added

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5 This invention also provides a method of maintaining a safe, effective blood level of an estrogen agonist/antagonist for an extended period of time which comprises administering an oral dose which is of sufficient quantity to maintain said effective blood level for said extended period of time wherein said extended period of time is 7 days.

10 This invention also provides a method of maintaining a safe, effective blood level of an estrogen agonist/antagonist for an extended period of time which comprises administering an oral dose which is of sufficient quantity to maintain said effective blood level for said extended period of time wherein said sufficient quantity is 0.8 to 10.0 mg per dose.

Detailed Description of the Invention

15 The prior art, for example U.S. Patent 5,552,421, teaches that lasofoxifene and related compounds should be administered frequently in small doses. Doses as low as 0.1 mg four times per day are suggested for human patients.

20 We have now unexpectedly found that a single dose of 0.8 mg of lasofoxifene administered to healthy women resulted in an initial blood level of 0.7 ng/ml within a few hours. Levels declined slowly thereafter to a concentration of about 0.3 ng/ml after 168 hours (1 week). 0.3 ng/ml is considered to be a therapeutic effective concentration.

Doses from 10 to 20 mg of lasofoxifene are acceptable. Such a dose would provide a therapeutically effective dose for up to 30 days. See Table 2.

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Example 1

5 A dose of 0.8 mg of lasofoxifene was administered to 12 healthy, postmenopausal women and blood samples were analyzed periodically as shown in Table 1.

10 A 1.0 ml sample of human plasma was analyzed for lasofoxifene according to CEDRA's Procedure TM-234 (CEDRA's Corp., 8609 Cross Park Dr., Austin, TX 78754). Internal standard used for this procedure was a pentadeuterated lasofoxifene. The plasma sample containing lasofoxifene and the internal standard
15 was extracted with MTBE. Following centrifugation, the organic layer was transferred to another tube and evaporated. An aliquot of the reconstituted sample extract was then injected onto a SCIEX API^{III} LC-MS-MS instrument equipped with a short ion exchange HPLC column. Peak areas of the m/z 414→97.9 daughter ion of lasofoxifene were measured against the peak areas of the m/z 419→97.9 daughter
of the internal standard. Quantitation was performed using a 1/x weighted least squares regression line generated from spiked plasma calibration samples.

Plasma levels of lasofoxifene for 168 hours are shown in Table 1 below.

Example 2

20 The procedure of Example 1 was repeated with a dose of 10 mg lasofoxifene administered to 8 healthy postmenopausal women. Plasma levels for lasofoxifene are shown for 672 hours in Table 2.

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Table 1			
Mean plasma concentrations of lasofoxfene following oral administration of a single dose of 0.8 mg to twelve healthy, postmenopausal women			
Hours after dosing	ng Lasofoxfene per ml plasma	Standard Deviation	Coefficient of variation
0	—	—	—
.5	0.13	0.10	77
1	0.32	0.09	28
2	0.37	0.08	15
4	0.46	0.10	23
8	0.72	0.13	19
12	0.73	0.14	19
24	0.64	0.11	18
48	0.56	0.10	17
72	0.49	0.08	16
120	0.40	0.07	18
168	0.34	0.10	29

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Table 2

Mean plasma concentrations of lasofoxfene following oral administration of a single 10 mg dose to eight healthy, postmenopausal women

Hours after dosing	ng Lasofoxfene per ml plasma	Standard Deviation	Coefficient of variation
0	0		
.5	2.33	1.19	51
1	4.42	0.86	19
2	5.64	1.38	24
4	8.46	2.25	27
8	10.45	1.38	13
12	10.25	1.96	19
24	8.35	1.29	15
48	7.16	0.87	12
72	5.97	1.28	21
120	4.56	0.72	16
168	3.74	0.62	17
216	2.88	0.49	17
264	2.27	0.41	18
336	1.60	0.45	28
408	1.05	0.30	29
480	0.75	0.24	32
576	0.50	0.21	41
672	0.31	0.15	47

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Claims

1. A method of maintaining a safe, effective blood level of an estrogen agonist/antagonist for an extended period of time which comprises administering an
5 oral dose which is of sufficient quantity to maintain said effective blood level for said extended period of time.
2. The method of claim 1 wherein said estrogen agonist/antagonist is lasofoxfene.
3. The method of claim 2 wherein said extended period of time is one week.
- 10 4. The method of claim 3 wherein said sufficient quantity is 0.8 mg per dose.
5. The method of claim 2 wherein said extended period of time is one to four weeks and said sufficient quantity is 0.8 mg to 20 mg. .

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Abstract

Based on lasofloxfene's half life and potency, the drug may be doeed once per week and achieve a similar effect as if given daily.

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REIVINDICACIONES

1. El uso de un agonista/antagonista de estrógeno para la manufactura de un medicamento para ser administrado oralmente y en suficiente cantidad con el objetivo de mantener un nivel sanguíneo seguro y efectivo de un agonista/antagonista de estrógeno por un largo periodo de tiempo.
2. El uso de la Reivindicación 1, en donde dicho agonista/antagonista es lasofoxifeno.
3. El uso de la Reivindicación 2, en donde dicho largo periodo de tiempo es una semana.
4. El uso de la Reivindicación 3, en donde dicha cantidad suficiente es de 0.8 mg por dosis.
5. El uso de la Reivindicación 2, en donde dicho largo periodo de tiempo oscila entre una y cuatro semanas y dicha cantidad suficiente oscila entre 0.8 mg y 20 mg.
6. Un método para mantener un nivel sanguíneo seguro y efectivo de un agonista/antagonista del estrógeno por un largo periodo de tiempo el cual comprende administrar una dosis oral de suficiente cantidad para mantener dicho nivel sanguíneo efectivo por dicho largo periodo de tiempo.
7. El método de la de la Reivindicación 1, en donde dicho agonista/antagonista es lasofoxifeno.
8. El método de la Reivindicación 2, en donde dicho largo periodo de tiempo es una semana.
9. El método de la Reivindicación 3, en donde dicha cantidad suficiente es de 0.8 mg por dosis.
10. El método de la Reivindicación 2, en donde dicho largo periodo de tiempo oscila entre una y cuatro semanas y dicha cantidad suficiente oscila entre 0.8 mg y 20 mg.

Nota: Se retiraron los folios 83 = Tarjeta de
Archivo temático
Folio 84 = Extracto para publicación.

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 83

Radicación no 00-74167

Concepto Técnico no 900

Clasificación Internacional de Patentes A61K 31/40

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

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

OBSERVACIONES Y OTROS: SI ☐ NO ☒ ver hoja(s) anexa(s)

EXAMINADOR TÉCNICO
202039

Bogotá D. C., Abril 25/02



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Industria y Comercio

SUPERINTENDENCIA

Folio 84

2020
Bogotá DC

Doctor(a)
CARLOS R. OLARTE
Apoderado(a)

REFERENCIA:	Radicación No.	00-74167
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	1158
	Folios	001

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

Cúmplase
Dado en Bogotá DC, a los 11 JUN. 2002


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

Bogotá, DC,
Gaceta de Propiedad Industrial, de fecha
expiró el

El extracto de esta solicitud fue publicado en el número 520 de la
. El término hábil señalado por la ley
y SI ___ NO ___ se presentaron oposiciones por parte de terceros.

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
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Bogotá, D.C., Colombia