



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

21 EXPEDIENTE No.

04-117322

54 TITULO

Tratamiento de la hipertensión en mujeres que reciben terapia de reemplazo hormonal

51 CLASIFICACION INTERNACIONAL *A61K 31/485*

71 SOLICITANTE

Schering Aktiengesellschaft

DOMICILIO

Berlin, Alemania

74 APODERADO

Gustavo Hollmann Restrepo

22 BOGOTA, D.C.,

23 de noviembre de 2004

202099

SS

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

①

SOLICITUD DE



Patente de Invención



Patente de Modelo de Utilidad



Capítulo I



Capítulo II

②

SOLICITANTE
(71)

Nombre **SCHERING AKTIENGESELLSCHAFT**

Dirección **Müllerstrasse 178**
13353 Berlin, Alemania

Nacionalidad o Domicilio **Berlin, Alemania**
Lugar de Constitución **Alemania**

Teléfono
E-mail

Fax

IDENTIFICACION

CC



NIT



CE



Otro



Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre **GUSTAVO HOLLMANN RESTREPO**

Dirección **Cra 11ª No 94-76 - Of 308**

Teléfono **6161948**
E-mail

Fax **6163976**

IDENTIFICACION

CC



NIT



CE



Otro



Cual

Número **2.878.023** TP **5903**

④

INVENTOR (ES)
(72)

Nombre **KARARA Adél, H.**

Dirección **64 Yuma Trail,**

Nacionalidad o Domicilio **Branchburg, NJ 08876 Estados Unidos**

PCT (86)

Solicitud Internacional No **PCT/US03/12596** Fecha **Marzo 24 de 2003**

Publicación Internacional No **WO 03/090755 A1** Fecha **Noviembre 6 de 2003**

⑤

Título (54) TRATAMIENTO DE LA HIPERTENSION EN MUJERES QUE RECIBEN TERAPIA DE REEMPLAZO HORMONAL.

⑦

Clasificación Internacional (51) A61K 31/585

PRIORIDAD

SI ☒ NO ☐

(33) País de Origen

Estados Unidos

(32) Fecha

Abril 26, 2002

(31) Número de Solicitud

60/375.439

Comprobante de pago No. **04 - 89.927**

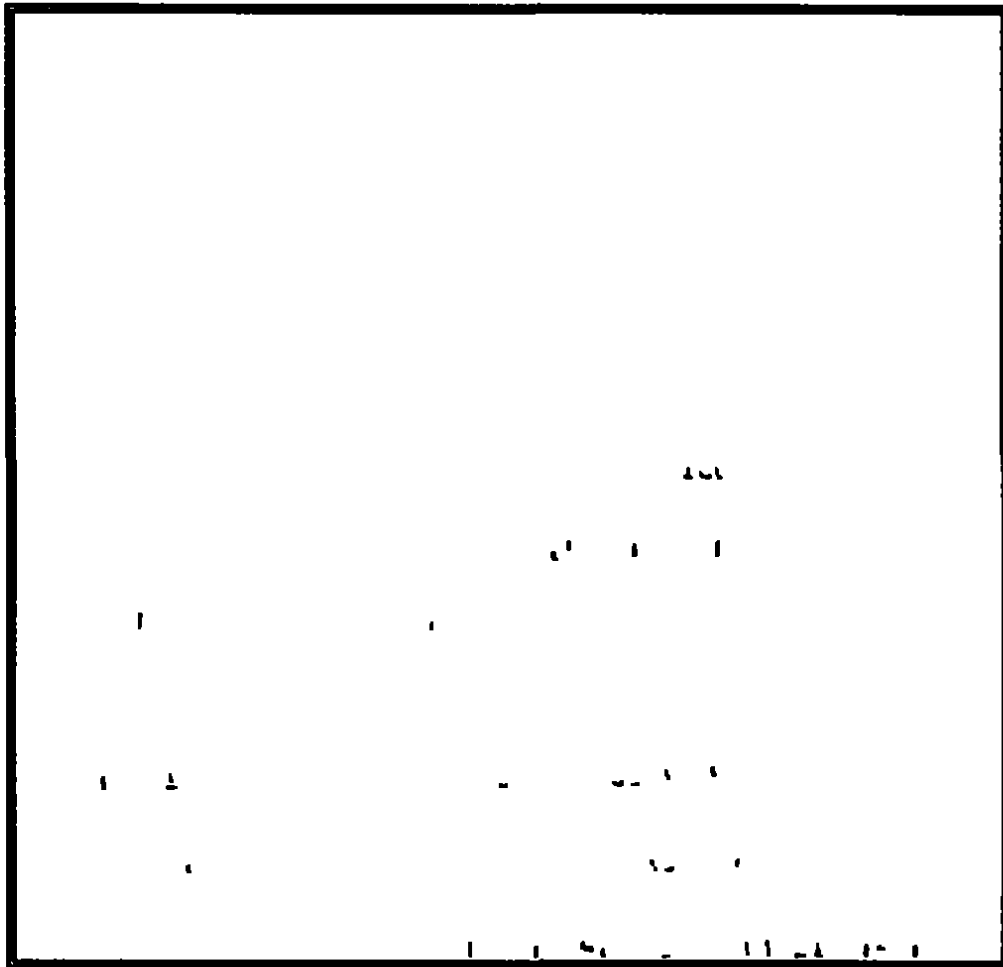
Fecha **Noviembre 9, 2004**

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

ANEXOS

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

(11) FIGURA CARACTERISTICA



(12) Solicito la concesión de la patente,

NOMBRE. GUSTAVO HOLLMANN RESTREPO

FIRMA. *Gustavo Hollmann Restrepo*

C.C. 2.878.023 Bogotá T.P. 5003

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

Otros anexos que se acompañan a la solicitud.

Forma PCT/RO/101 correspondiente a la presentación de la solicitud internacional

Forma PCT/IB/304 correspondiente a la notificación relativa al envío o transmisión del documento de prioridad

Forma PCT/IB301 correspondiente a notificación y recibo de la copia de archivo

 Forma PCTIB308 correspondiente a la notificación informando al solicitante de la comunicación de la solicitud internacional a las oficinas designadas

Copia de la respuesta a la opinión escrita en la solicitud internacional



SUPERINTENDENCIA Y COMERCIO
Radicación : 04117322 00000000 Folios: 106
Fecha (AMB) 2004-11-23 11:04:35
Trámite : 011 PCT-PATENT 379 PASE NACI 411 PRESENTA
Dependencia: 2009 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA 04 - 89,927
FECHA : NOVIEMBRE 19 DE 2004

***** CONSIGNACION *****

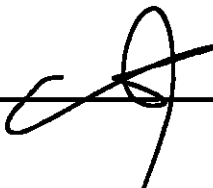
DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PAGO	Vr PAGO
 GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR	050-00110-6	33692687	18/11/2004	422,000 00

***** CONCEPTO *****

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRAMITES DE SOL DE PATENTE DE IN	422,000 00
		TOTAL	\$ 422,000 00

SUM: CUATROCIENTOS VEINTIDOS MIL PESOS

Ref. 58465

RESPONSABLE  _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

4

CONSULADO GENERAL DE COLOMBIA

Berlín, 23 de Agosto de 1999

No 05/99

El suscrito **ENCARGADO DE LAS FUNCIONES CONSULARES DEL CONSULADO GENERAL DE COLOMBIA EN BERLIN**, República Federal de Alemania

CERTIFICA

1 Que el señor **GETFERDT**, quien autoriza el documento anterior, ejercía legalmente en la fecha allí indicada, las funciones del Presidente Encargado del Tribunal Regional de Berlín, y que la firma y sello que en el documento aparecen como suyos son los que usa y acostumbra en sus actos oficiales

2 Que tuvo a la vista las pruebas de que la Compañía **SCHERING AG** domiciliada en Berlín, República Federal de Alemania, existe legalmente, y que actualmente ejerce su objeto social de acuerdo con las leyes del respectivo país

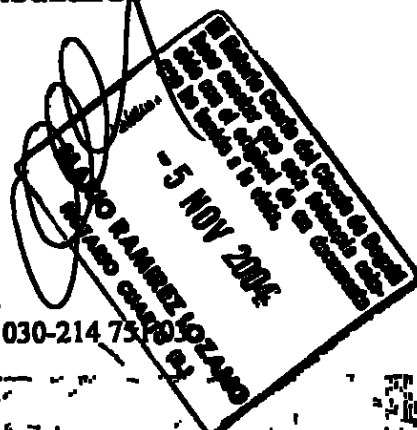
3 Que los señores **UWE HARTMANN** y **WALTER KLOSE** quienes firmaron el poder que precede, están autorizados para representarla en este acto y otorgar el certificado

El Encargado de las Funciones Consulares no asume responsabilidad alguna por el contenido del documento




GERMAN NEIRA
Encargado de las Funciones
Consulares

PAGADO IMPUESTO DE TIMBRE
Y DERECHOS CONSULARES
(107,00 U\$)



Taentzienstr 15, 10789 Berlin
TEL 030-214 751 63 - 030-214 751 64 - FAX 030-214 751 65

322052
German Neira
11/11/1941
11/11/1941
11/11/1941

U.S. DELEGATIONS
CHAFF OF HUNGARY

51542 Colombia

PARA PATENTES, MARCAS Y LICENCIAS FARMACEUTICAS
FOR PATENTS, TRADE MARKS AND PHARMACEUTICAL LICENSES

The undersigned

acting on behalf of and representing

Company's
Name

domiciled in

Company's
Domicile

heraby appoint/s

Leave blank

domicilled in Bogotá, Republic of Colombia.

as our true and legal attorneys with the necessary powers 1) to apply to the administrative judicial and police authorities of the Republic of Colombia, in any instance or appeal for obtaining letter patents, industrial designs and models, trademark registrations, registration of commercial names as well as their assignments, extensions, renewals and changes of name 2) to prepare apply for obtain execute and register contracts, licenses, authorizations and registrations of any kind 3) intervene as plaintiffs or defendants, in any instance or appeal before any judge court, tribunal corporation public offices or authority in any judicial administrative or police action such as actions dealing with commercial names oppositions against trademark registrations caducity and nullity actions recovery actions, actions arising from obtainment and exploitations of licenses actions dealing with unfair competition criminal actions actions claiming indemnity for damages claims or remarks on patent applications, industrial designs and models the performance of precautionary measures and in any other similar action measures or appeals related to industrial property matters.

To this effect, I (we) hereby authorize him (them) to file applications, make descriptions, amendments, protests, declarations, oppositions, cancellations appeals and claims to pay taxes, quotas and liens as provided by law to waive or abandon granted rights or rights in process of being granted to receive all kind of documents and securities to issue the respective releases and in general to take before said authorities, pertinent steps to the above mentioned purposes and take all measures he (they) may deem convenient to protect my (our) interests, with all other necessary legal faculties, and I (we) hereby declare as good and valid whatever the attorneys should do to my (our) benefit.

This power comprises the authority to ratify or confirm on my (our) behalf any actions, as well as the faculty of receiving desisting transacting compromising, substituting and revoking substitutions, taking notifications and appointing judicial or extrajudicial attorneys

Signed in

On this day of

19

SCHERING AKTIENGESELLSCHAFT

ppa

Signature(s)
Firma(s)

Yo(nosotros)

Dr. Uwe Hartmann y Dr. Walter Klose

obrando a nombre y representación de

SCHERING AKTIENGESELLSCHAFT

con domicilio en

Müllerstr 178

D-13353 Berlin / Germany

nombre(s) a

GUSTAVO HOLLMANN RESTREPO y/o

LUIS PATINO LEYVA

domiciliado(s) en Bogotá, República de Colombia, en

Cra. 11A No. 94-76 - Of. 308

apoderados verdaderos y legales con poder especial amplio y suficiente 1) Para recabar de las oficinas y autoridades colombianas, administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención de dibujos y modelos industriales, registro de marcas, depósito de nombres comerciales y casados, así como sus traslases, prórrogas, renovaciones y cambios de nombre 2) elaborar tramitar solicitar obtener realizar ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clases, 3) intervenir como demandante o como demandado en cualquier instancia y recurso y ante cualquier juez, entidad corporación funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas del nombre en material oposición al registro de marcas acciones de caducidad y nulidad acciones reivindicatorias acciones derivadas de la obtención o explotación de licencias acciones de competencia desleal demandas penales y civiles acciones de indemnización de perjuicios reclamos u observaciones a nulidades de patentes modelos y dibujos industriales en el ejercicio de medidas cautelares y en otras acciones, medidas o recursos similares relacionados con la propiedad industrial

A este efecto, lo(s) faculto(amos) para elevar solicitudes formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos pagar impuestos, cuotas y gravámenes prescritos por la ley renunciar o desistir a derechos concedidos o en curso de concesión recibir toda clase de documentos y valores dando el descargo respectivo, y en general para dar ante dichas autoridades todas las pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses, con todas las demás facultades necesarias, y por este documento desde ahora declaro(amos) válido y bueno todo cuanto los apoderados hicieren en mi (nuestro) beneficio.

Este poder comprende la facultad de ratificar o confirmar en mi(nuestro) nombre lo obrado, así como la facultad de desistir transigir comprometer sustituir y revocar sustituciones, recibir notificaciones, nombrar apoderados judiciales o extrajudiciales

Firmado en

en

5 NOV 2004
MARTIN RAMIREZ LOZANO
Firma(s)
ppa

CONSULAR CERTIFICATION

COMPANIES

The undersigned Consul certifies that the preceding signature(s) reading

is (are) authentic that the signer(s) at present fills (fill) the position of

Corporation
Company's

of

that he (they) is (are) empowered to grant this power and that said company exists and is organized in

in accordance with the laws of

All the foregoing facts are known to the Consul due to his having examined the respective documents to which he, the Consul, attests.

Signed in

On this day of

CERTIFICACION CONSULAR

SOCIEDADES

El infrascripto Consul certifica que la(s) firma(s) que antecede(n) y dice(n)

es(son) autentica(s) que el(los) signatario(s) desempeña(n) actualmente el(los) cargo(s) de

de

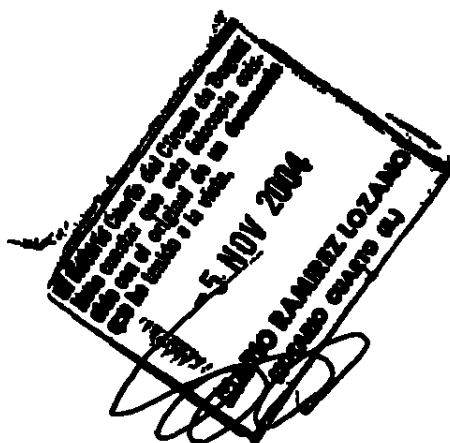
que tiene(n) facultad para otorgar este poder y que dicha compañía existe y está organizada en

conforme a las leyes de

Todos los hechos anteriores le constan por haber examinado los documentos respectivos y de todo ello da fe

Firmado en

El de de 19



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1
7

Die vorstehenden, heute vor mir gefertigten Unterschriften der mir persönlich bekannten Prokuristen,

- 1 Dr Uwe Hartmann,
- 2 Dr Walter Klose,

- beide geschäftsansässig in 13353 Berlin,
Müllerstraße 178 -,

beglaubige ich hiermit

Zugleich bescheinige ich aufgrund des mir vorliegenden beglaubigten Handelsregistrauszuges zum Aktenzeichen 93 HRB 283 des Amtsgerichts Berlin-Charlottenburg vom 17 Juni 1999, daß die vorgenannten Herren als Prokuristen gemeinsam zur Vertretung der Scherning Aktiengesellschaft, Berlin, berechtigt sind

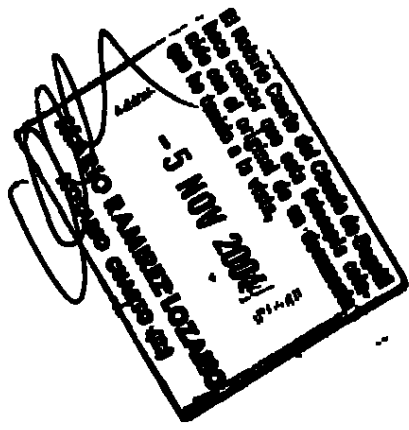
Ich habe den Beteiligten das Mitwirkungsverbot des § 3 Abs 1 Nr 7 BeurkG erläutert
Meine Frage, ob eine meine Mitwirkung an der Amtshandlung ausschließende Vorbefassung vorliege, wurde von den Beteiligten verneint

Berlin, den 11 August 1999
Urkundenrolle-Nr 656/1999

Handwritten signature
Notarin

Kostenrechnung		
<u>§§ 141, 154 KostO</u>		
<u>Geschäftswert 20 000,00 DM</u>		
Beglaubigungsgebühr	§ 45 I	25,00 DM
Wegegebühr	§ 58	25,00 DM
Gebühr für Vertretungsbescheinigung	§ 150	25,00 DM
16 % Mehrwertsteuer		<u>12,00 DM</u>
		<u>87,00 DM</u>

Handwritten signature
Notarin



Die Echtheit vorstehender Unterschrift der Notarin

Elisabeth Quack

in Berlin und die Echtheit des beigedrückten Dienstsiegels werden hiermit bestätigt. Zugleich wird bescheinigt, daß die Vorgenannte zur Vornahme der Amtshandlung gesetzlich befugt war

Berlin, den 17. August 1999

Der Präsident des Landgerichts
Im Auftrage



R. Getferdt
(Getferdt)

Richterin am Landgericht

9101 E-F. 2233/99

Gebühr: 25,00 DM
gezahlt

Berlin, den 17. August 1999

Justiz
Justizamt Berlin

CONSULADO GENERAL DE COLOMBIA
Berlin, 23 Agosto 1999 No. 357/99
El suscrito Cónsul General de Colombia CERTIFICA
Que R. Getferdt que autoriza el
presente documento ejerce legalmente en la fecha allí expresada
las funciones Encargada del Presidente
del Tribunal Regional de Berlín
y que la firma y sello que en el documento aparecen como suyos
son los que usa y acostumbra en sus actos oficiales
El Cónsul no asume responsabilidad alguna por el contenido
del documento



[Signature]
AVE. ADMINISTRATIVO 13-50
ENC. FUNCIONES CONSULARES

PAGADO IMPUESTO DE TIMBRE
Y DERECHOS CONSULARES
(Válidos dólares 22.00 (2%))

[Signature]
- 5 NOV 2000 -
ENC. ADMINISTRATIVO

MINISTERIO DE RELACIONES
EXTERIORES

322057
German Velazquez
CUBA FIDEL ALARCE FIDEL
DOCUMENTO DESMONTAJE
LAS FUNCIONES INDICADAS

5 NOV 2004
RAMIREZ LOZANO
COMANDO EN JEFE

Nº 57 ASU42
RESPONSABILIDAD GENERAL TEXTA

Y09 OCT 14 P2 17

JEFE DE LEGALIZACIONES
SANTOFF DE BARRIO

9

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Traducción oficial del alemán de la notarización (Registro Notarial No. 656/1999) y de la legalización de firmas correspondientes al poder de la compañía SCHERING AKTIENGESSELLSCHAFT domiciliada D-13353 Berlín, República Federal de Alemania.

Por medio de este documento autentico oficialmente las firmas que aparecen anteriormente, ejecutadas en presencia mía el día de hoy por los Apoderados

1. Dr. Uwe Hartmann,

2. Dr. Walter Klose,

ambos con domicilio de negocios en Müllerstrasse 178, 13353 Berlín, y conocidos personalmente por la suscrita Notaria

Al mismo tiempo, con base en el extracto autenticado del Registro Comercial HRB 283 Acta 93 del Juzgado Municipal de Berlín- Charlottenburg fechado el 17 de Junio de 1999, certifico que los mencionados Señores en su calidad de Apoderados están autorizados para representar conjuntamente a la compañía Schering Aktiengesellschaft domiciliada en Berlín

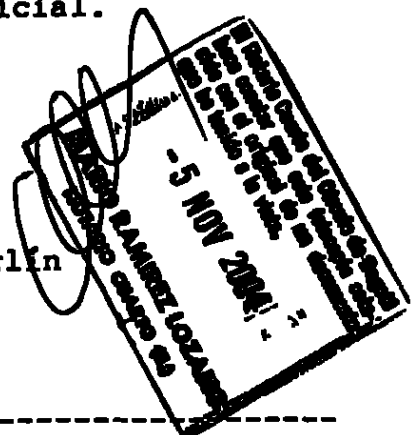
Yo les expliqué a los involucrados las prohibición de co-participación descrita en el Artículo 3 Inciso 1 Numeral 7 de la Ley de Certificaciones Notariales. Ellos contestaron negativamente mi pregunta acerca de si existía una prohibición que excluyera mi co-participación en este acto oficial.

Berlín, Agosto 11 de 1999

Registro Notarial No. 656/1999

Elisabeth Quack, Notaria en Berlín

(Firma y Sello Oficial)



------(continúa en la 2ª página)-----

N ta de gastos.

Artículos 141, 154 Disposición de Impuestos

Valor del negocio: 20.000,-- DM

Derechos por autenticación Artículo 45I	25,00 DM
Derechos por concepto de porte Artículo 58	25,00 DM
Derechos por Cert. de Representación Art. 150	25,00 DM
16% Impuesto sobre el Valor Agregado	12,00 DM
Total.	87,00 DM

Elisabeth Quack, Notaria (firma)

Se confirma la autenticidad de la firma que aparece anteriormente, la cual pertenece a la Notaria Elisabeth Quack en Berlín, y también la autenticidad del sello oficial que aparece al lado de dicha firma. Al mismo tiempo, se certifica que la persona mencionada se encontraba legalmente autorizada para la ejecución de ese acto oficial.

Berlín, 17 de Agosto de 1999

Getferdt, Representante del Presidente Tribunal Regional
(Firma y Sello Oficial)

910 E-F. 2233/99

Impuesto. 25,00 DM pagado

Berlín, 17 de Agosto de 1999

La inspectora de Impuestos (firma ilegible)

El documento traducido de alemán fue legalizado bajo el No. 322052 y bajo el No. 322053 el 10 de Octubre de 1999 en la Oficina de Legalizaciones del Ministerio de Relaciones Exteriores.

ADOLF WATZKE
Traductor Oficial
Reg. 2489 Mto/7-11-01

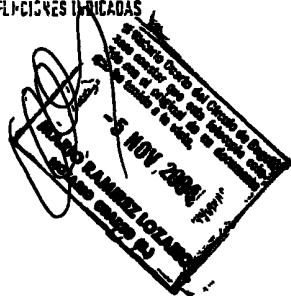
MINISTERIO DE RELACIONES
EXTERIORES

PO SE ASUME
RESPONSABILIDAD DEL TEXTO

323271
ADOLF WATZKE
Cuya firma aparece en el
documento de la página
5 flechas indicadas

1999 OCT 20 98

JEFE DE LEGALIZACIONES
SANTAFÉ DE BOGOTÁ



10

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 November 2003 (06.11 2003)

PCT

(10) International Publication Number
WO 03/090755 A1

(51) International Patent Classification⁷ A61K 31/585
31/565 31/567 31/401 38/55 31/675 A61P 9/12, 15/12

(21) International Application Number PCT/US03/12596

(22) International Filing Date 24 March 2003 (24.03.2003)

(25) Filing Language English

(26) Publication Language English

(30) Priority Data
60/375,439 26 April 2002 (26 04.2002) US

(71) Applicant (for all designated States except US) SCHERING AKTIENGESELLSCHAFT [DE/DE] Mullerstrasse 178 13353 Berlin (DE).

(72) Inventor; and

(75) Inventor/Applicant (for US only) KARARA, Adel, H [US/US] 64 Yuma Trail Branchburg NJ 08876 (US).

(74) Agents SHUBIN, Harry, B. et al., Millen, White, Zelano & Branigan, P.C. Suite 1400, Arlington Courthouse Plaza 1 2200 Clarendon Boulevard, Arlington, VA 22201 (US).

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

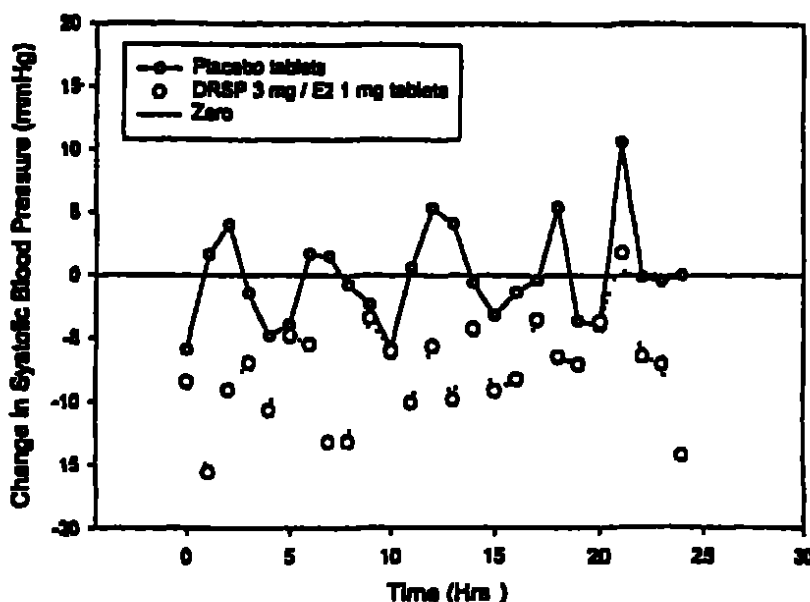
(84) Designated States (regional) ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published

— with international search report

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

(54) Title: TREATMENT OF HYPERTENSION IN WOMEN RECEIVING HORMONE REPLACEMENT THERAPY



(57) Abstract A method is described to lower blood pressure and effect hormone replacement therapy (HRT) in a hypertensive woman receiving HRT, comprising administering to the woman effective amounts of drospirenone and an estrogen. In one embodiment, the woman is already taking hypertensive medicine when the method is carried out.

WO 03/090755 A1

TREATMENT OF HYPERTENSION IN WOMEN RECEIVING HORMONE REPLACEMENT THERAPY

5 This application claims the benefit of US Provisional Application Serial No 60/375,439, filed April 26, 2002, which is incorporated herein in full by reference.

DESCRIPTION OF THE INVENTION

10 The present invention is directed *e.g.*, to a method to lower blood pressure and effect hormone replacement therapy (HRT) in a hypertensive human female (woman) receiving HRT, comprising administering to the woman an effective amount of drospirenone and an estrogen. In one embodiment, the woman simultaneously takes antihypertensive medicine.

15 Drospirenone (DRSP) is a 17- α -spiro lactone derivative progestin that, in combination with estrogens, is used for hormone replacement therapy (HRT), *e.g.*, in postmenopausal women. The present inventor has found, unexpectedly, that when hypertensive women in need of HRT, *e.g.*, women who are already taking antihypertensive medication, are administered a combination of DRSP and estrogen, their blood pressure is unexpectedly reduced compared to women taking the antihypertensive alone.

20 In one embodiment of the invention, the estrogen is ethinyl estradiol, 17 β -estradiol or an ester thereof, or a conjugated estrogen, the composition is administered orally, transdermally or by injection, preferably orally; the estrogen is 17 β -estradiol, at about 1-3 mg/day, and the drospirenone is at about 1-3 mg/day; the woman is postmenopausal, and/or the hypertension is mild hypertension or severe hypertension.

25 In one embodiment, a woman treated by the method of the invention is not taking hypertensive medication. See, *e.g.*, Example 3 herein.

30 In another embodiment, the woman to whom the inventive combination is administered also takes antihypertensive medication, beginning before or after the combination is administered, or beginning in conjunction with the administration of said combination. The antihypertensive medicine can be, *e.g.*, a diuretic, an α -adrenergic blocking agent, an adrenergic neuron blocking agent, a vasodilator, an angiotensin I converting enzyme (ACE) inhibitor, a calcium channel blocker, or a renin inhibitor, typically an ACE inhibitor.

 In another embodiment of the invention, the blood pressure of hypertensive women

administered the combination of drospirenone and estradiol without an antihypertensive medication was also unexpectedly reduced, see Example 3

A woman suitable for treatment by the method of the invention is hypertensive (suffering from hypertension, having elevated blood pressure) She may suffer from any degree of hypertension, e.g. borderline, mild (e.g., stage 1), or severe hypertension

The blood pressure that is lowered can be diastolic, systolic, mean and/or arterial blood pressure, or combinations thereof, and can be ambulatory blood pressure or office blood pressure (preferably ambulatory), measured at rest or during exercise, during the day and/or at night, and/or at any desirable time after administration of the combination of the invention. Typically, blood pressure is lowered within about 14 days after the combination is administered

Blood pressure can be measured by any of a variety of conventional procedures. See, for example, the Examples herein for some methods of monitoring blood pressure in human subjects

A woman suitable for treatment by the method of the invention is in need of hormone replacement therapy (HRT). Typically, the woman is menopausal or postmenopausal. As used herein, the terms "menopause" and "menopausal" include both the perimenopausal and postmenopausal states. Women in need of HRT include women who, as a result of the normal aging process, have entered or begun to enter menopause, or women who have ceased menstruation for non-age-related reasons, e.g., due to excessive exercise or as a result of surgery (e.g., hysterectomy, oophorectomy)

In one embodiment, a woman treated by the method of the invention is taking antihypertensive medication, e.g., she is already taking an antihypertensive medication before the combination of the invention is administered, or she begins taking an antihypertensive medication concomitantly with, or after, administration of the combination of the invention. The interval of time between the start of the antihypertensive medication treatment and the administration of the combination of the invention is not critical. In a preferred embodiment, the decrease in blood pressure in a woman receiving a combination of the invention is greater than the decrease achieved when the anti-hypertensive medication, alone, is administered.

Women treated by the method of the invention can be taking any of a variety of conventional antihypertensive medications (medications that are effective in reducing or alleviating hypertension), including, e.g., diuretics, α - and/or β -adrenergic blocking agents,

CNS-acting agents, adrenergic neuron blocking agents, vasodilators, angiotensin I converting enzyme (ACE) inhibitors, calcium channel blockers, renin inhibitors, or other antihypertensive agents, or combinations thereof

Diuretics include, *e.g.*, acetazolamide, amiloride, bendroflumethiazide, benzthiazide, bumetanide, chlorothiazide, chlorthalidone, cyclothiazide, ethacrynic acid, furosemide, hydrochlorothiazide, hydroflumethiazide, indacrinone (racemic mixture, or as either the (+) or (-) enantiomer alone, or a manipulated ratio, *e.g.*, 9:1 of said enantiomers, respectively), metolazone, methyclothiazide, mizolimine, polythiazide, quinethazone, sodium ethacrylate, sodium nitroprusside, ticrynafen, triamterene, and trichlormethiazide.

α -adrenergic blocking agents include, *e.g.*, dibenamine, phentolamine; phenoxybenzamine, prazosin, and tolazoline

β -adrenergic blocking agents include, *e.g.*, atenolol, metoprolol, nadolol, propranolol, timolol, and various other agents listed in USP 5,001,113

CNS-acting agents include, *e.g.*, clonidine and methyl dopa

Adrenergic neuron blocking agents include, *e.g.*, guanethidine, reserpine and other rauwolfia alkaloids such as rescinnamine.

Vasodilators include, *e.g.*, diazoxide, hydralazine, and minoxidil.

Calcium channel blockers include, *e.g.*, those listed in USP 5,001,113

Renin-inhibitors include, *e.g.*, pepstatin and the di- or tripeptide renin inhibitors disclosed in USP 5,001,113 and in references therein

Other antihypertensive agents include, *e.g.*, aminophylline, cryptenamine acetates and tannates, deserpidine, meremethoxyline procaine, pargyline, and trimethaphan camsylate

In a typical case, a woman being treated with the method of the invention is taking an ACE inhibitor, such as, *e.g.*, benazepril, captopril, enalapril, enalaprilat, fosinopril, lisinopril, pentopril, quinapril, quinaprilat, ramipril, transolapril, zofenopril, peptides such as those described in USP 6,232,438 and in references cited therein, compounds as described in USP 6,300,362, agents such as those listed in USP 5,001,113, and the like

Such antihypertensive agents are administered according to conventional procedures, using conventional dosages, lots, regimens of administration, and modes of administration

Any of a variety of estrogens, as is well known in the art, can be used in methods of hormone replacement therapy. Such estrogens include, *e.g.*, ethinyl estradiol, mestranol, estradiol (especially 17- β -estradiol, known as E2) and esters thereof (*e.g.*, valerate, acetate,

benzoate or undecylate), estriol, estriol succinate, polyestriol phosphate, estrone; estrone sulfate, natural or synthetic estrogens, and conjugated estrogens

DRSP can be obtained from commercial sources (e.g., from Schering Aktiengesellschaft) or can be synthesized by conventional methods, e.g., according to the methods disclosed in USP 6,121,465 and *Drugs of the Future 2000* 25 (12), 1247-1256

DRSP and an estrogen can be administered to a patient following conventional procedures, using conventional regimens of administration, kits, modes of administration, and dosages, all of which are well known to those of skill in the art.

Regimens are conventional and well known in the art for HRT purposes. The estrogen and DRSP can be administered concurrently, for any period of time, e.g., on a daily basis, 1-4 times a week, weekly, 2-3 weeks per month, etc. The two components can be administered separately (as disclosed, e.g., in USP 6,083,528), e.g., via a conventional kit, or as a combined preparation (e.g., a tablet or capsule)

The pharmaceutical compositions of the invention can be administered by any of a variety of conventional modes, including, e.g., oral (e.g., solutions, suspensions, tablets, dragees, capsules or pills), parenteral (including subcutaneous injection, or intravenous, intramuscular or intrasternal injection or infusion techniques), inhalation spray, transdermal, rectal, or vaginal (e.g., by vaginal rings or creams) administration. The two components can be administered by the same mode, or by different modes (e.g., transdermal estrogen and intravaginal DRSP)

A dosage that is "effective" to effect hormone replacement therapy is one that prevents or diminishes (alleviates) adverse physiological effects or symptoms resulting from reduced amounts of estrogen, such as, e.g., bone loss and resultant structural deformation, among many others. A dosage of a composition of the invention that is "effective" to reduce blood pressure is one that can achieve a measurable decrease in blood pressure. Any effective dosage can be administered in the methods of the invention, preferably a low dose formulation

Effective dosages of estrogens are conventional and well known in the art. Typical approximate dosages for oral administration are, e.g., ethinyl estradiol (0.001-0.030 mg/day), mestranol (5-25 mcg/day), estradiol (including 17- β estradiol), (0.5-6 mg/day), polyestriol phosphate (2-8 mg) and conjugated estrogens (0.3-1.2 mg/day). Dosages for other means of delivery will be evident to one of skill in the art. For example, transdermal dosages will vary

therefrom in accordance with the adsorption efficacy of the vehicle employed.

Effective dosages of drospirenone are also conventional and well known in the art. Typical dosages for oral administration are about 1.0-3.0 mg/day.

Preferred combinations of the invention include, for oral administration, 3 mg DRSP/1 mg E2 and 1 mg DRSP/1 mg E2.

It will be understood, of course, that the specific dose level and frequency of dosage for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Because the method of this invention involves effecting HRT, necessarily the individual doses of estrogen and DRSP are administered over a prolonged period of time, i.e., more than one month, usually at least several months and ordinarily for one or more years and often for one or more decades. During that period of time the size of the individual dose of either the estrogen or the DRSP or both can be changed at least once and often two or more times, usually stepwise increased in the case of the estrogen until the minimum effective therapeutic dosage is found. Often, it may be decreased again as the patient progresses from peri to post-menopause, because the estrogen dosage to prevent menopausal bone loss is usually higher than the dosage that is needed for effectively treating climacteric complaints.

Compositions of the invention can be formulated according to accepted pharmaceutical practice, with a conventional pharmaceutically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, and/or adjuvant, etc, for any given type of unit dosage form.

Formulations for oral administration are conventional in the art. For example, tablets generally contain a pharmaceutically acceptable carrier, e.g., a binder such as gum tragacanth, acacia, corn starch or gelatin, an excipient such as dicalcium phosphate or cellulose, a disintegrating agent such as corn starch or alginate acid, a lubricant, such as magnesium stearate, and/or a sweetening agent or flavoring agent. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac,

sugar or both. A syrup or elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilized, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange. When administered orally as a suspension, these compositions may contain microcrystalline cellulose for
 5 imparting bulk, alginate acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, disintegrants, diluents and lubricants known in the art.

10 Formulations suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The solutions are stable and preserved against the contaminating action of microorganisms such as bacteria and fungi. The injectable solutions or suspensions
 15 may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3 butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be
 20 prepared by mixing the drug with a suitable non irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Methods of formulating HRT compositions for local application (e.g., as extrudable viscous liquids, semi-solid preparations such as gels, ointments or creams, or a spreadable
 25 solid such as a stick deodorant), and of applying them to a patient, e.g., to a surface such as skin or mucosa, are disclosed in USP 6,083,528.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius, and, unless otherwise indicated, all parts and percentages are by weight.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 - shows the mean change from baseline (pretreatment day 1) for 24 hour systolic blood pressure on treatment day 14

Figure 2 - shows the mean change from baseline (pretreatment day 1) for 24 hour diastolic blood pressure on treatment day 14

Figure 3 - shows changes in systolic 24 hour ambulatory blood pressure from baseline (pretreatment day 1) at steady state (day 14) in subjects (mildly hypertensive postmenopausal women maintained on enalapril maleate 20 mg/day for the duration of treatment) receiving DRSP/E2 or placebo. Horizontal lines represent means

Figure 4 - shows changes in diastolic 24 hour ambulatory blood pressure from baseline (pretreatment day 1) at steady state (day 14) in subjects (mildly hypertensive postmenopausal women maintained on enalapril maleate 20 mg/day for the duration of treatment) receiving DRSP/E2 or placebo. Horizontal lines represent means

Figure 5 - shows daytime and nighttime change in systolic 24 hour ambulatory blood pressure from baseline (pretreatment day 1) at steady state (day 14) in subjects (mildly hypertensive postmenopausal women maintained on enalapril maleate 20 mg/day for the duration of treatment) receiving DRSP/E2 or placebo. Horizontal lines represent means

Figure 6 - shows daytime and nighttime change in diastolic 24 hour ambulatory blood pressure from baseline (pretreatment day 1) at steady state (day 14) in subjects (mildly hypertensive postmenopausal women maintained on enalapril maleate 20 mg/day for the duration of treatment) receiving DRSP/E2 or placebo. Horizontal lines represent means

Figure 7 - shows mean systolic blood pressure across study days (office blood pressure, except days 1 and 14 are mean 24 ambulatory blood pressure). Study day 1 refers to pretreatment day 1

Figure 8 - shows mean diastolic blood pressure across study days (office blood pressure, except days 1 and 14 are mean 24 ambulatory blood pressure). Study day 1 refers to pretreatment day 1

EXAMPLES

Example I Administration of DRSP /E2 to mildly hypertensive postmenopausal women being treated with an ACE inhibitor - methods

This study was a double-blind, randomized, 2-parallel group study to compare the effects of DRSP 3 mg/E2 1 mg versus placebo on 24-hour ambulatory blood pressure in postmenopausal mildly hypertensive subjects treated with (e.g., maintained on) enalapril maleate 10 mg twice daily

5 Subjects

To be included in the study each subject had to meet the following criteria. healthy, postmenopausal (natural or surgical), 45-75 years of age who were under treatment with ACE inhibitor enalapril maleate (10 mg bid daily dose for a minimum of 7 days) for mild hypertension and who weighed not less than 100 pounds and who were within $\pm 15\%$ of normal according to subject's height and frame size. Subjects had systolic blood pressure equal to or less than 150 mm Hg and diastolic blood pressure equal to or less than 90 mm Hg. Subjects must have had at screening a serum potassium between 3.5 and 4.5 mEq/L and screening creatinine clearance greater than 60 mL/min. Subjects were excluded from the study if, during screening evaluations, any of the following criteria applied: clinically significant abnormal laboratory values and electrocardiogram (ECG) abnormalities, significant history of disease, history of drug or alcohol abuse in the past 10 years, positive tests of hepatitis B or C and HIV, previous diagnosis of cancer of any type, smokers in the previous one year, subjects who donated a pint or more of blood within 3 months of the study or a known sensitivity to estrogen therapy, DRSP or enalapril.

20 Study Design

This was a randomized, double-blind, 2-parallel groups study. The treatments were

Test	Enalapril maleate 10 mg oral tablet twice daily (bid) + DRSP (3 mg)/E2 (1 mg) oral tablet daily for 14 days
Placebo	Enalapril maleate 10 mg oral tablet bid + DRSP/E2 look-alike placebo oral tablet daily for 14 days

The subjects began to take enalapril at least 7 days prior to the treatment period and continued throughout the treatment period (14 days). Accordingly, 24 postmenopausal women were

randomly assigned to 1 of the above treatments. The study was conducted primarily on an out patient basis. On Pretreatment Day 1, subjects entered the clinic for 24-hour ambulatory blood pressure and laboratory assessments. On Treatment Day 1 subjects were discharged from the clinic after dosing, which began the 14-day treatment phase consisting of active or placebo treatment, while continuing on enalapril therapy. Subjects reported back to the clinic on Treatment Day 2 and every 2 days after (up to Treatment Day 12) for safety laboratory assessments and plasma concentrations of DRSP. On Treatment Day 14, subjects reported back to the clinic for approximately a 24-hour period during which the last dose of study drug was administered and 24-hour ambulatory blood pressure and laboratory assessments.

10 Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) was performed using a Spacelabs Inc Model 90207 (Spacelabs Inc, Redmond Washington) on study Pretreatment Day 1 and Treatment Day 14 according to a standard protocol. The monitor was initialized for each patient and the blood pressure cuff placed on the non-dominant arm. Five correlation readings using a mercury sphygmomanometer (Baumanometer, W A. Baum Co, Inc, Copiague, New York) were obtained to verify the calibration of the monitor. Readings were recorded every 20 minutes during the period 7 AM to 11 PM and then every 30 minutes from 11 PM to 7 AM. After 24-hours the blood pressure monitoring was terminated and the monitor removed. The ABPM data was then transmitted to Biomedical Systems for analysis via a modem connected to a dedicated phone line. Subjects were instructed to keep their arm immobile during the recording of the blood pressure. Showering and strenuous exercise were not allowed.

Laboratory Assessments

Plasma Renin Activity (PRA) was measured by measuring the generation of Angiotensin I from angiotensinogen by a commercially available RIA. Blood was collected 24 hours prior to dosing (time zero, Pretreatment Day 1) at least 1 hour after rising in the morning at approximately the same time on Pretreatment Day 1 and Treatment Day 14 under fasting conditions. In addition, subjects were to be ambulatory for 30 minutes prior to specimen

collection. Subjects were to refrain from taking medications, preferably 3 weeks prior to blood collection.

Serum aldosterone was measured by a commercially available RIA. Blood was collected 24 hours prior to dosing (time zero, Pretreatment Day 1). Subjects were in the ambulatory position for 2 hours before and during blood and refrained from taking medications, preferably 3 weeks prior to blood collection.

Statistical Methods

The 24-hour mean systolic and diastolic blood pressure data were analyzed with an ANCOVA using baseline values (Pretreatment Day 1) as covariates. It was assumed that the blood pressure data were normally distributed with common variances. The sources of variation were the treatments (fixed factor with the levels test and placebo), and the baseline value (covariate). The goodness of fit was checked using a residual plot. The hypothesis tested was $H_0: \mu_T = \mu_P$ versus the alternate $H_1: \mu_T \neq \mu_P$ at the significance level of 5%. The individual change from baseline of both systolic and diastolic 24-hour, daytime and nighttime blood pressure data were analyzed using paired-t-test.

Example II Administration of DRSP/E2 to mildly hypertensive postmenopausal women being treated with an ACE inhibitor - results

Demographic Data

A total of 24 mildly hypertensive but otherwise healthy postmenopausal women were randomized for this double-blind, two-parallel groups study. The subjects were postmenopausal women with a mean ($\pm$ standard deviation [SD]) age of 57 ± 5 , 62 ± 6 years, and weight of 77 ± 11 , 70 ± 7 kg, for the placebo and DRSP/E2 treatments, respectively. The study population comprised Caucasian (4%), African American (4%) and Hispanic (92%). All twenty-four subjects completed the study.

24-hour ambulatory blood pressure and heart rate

Table 1 presents a summary of 24-hour ambulatory blood pressure data for both the placebo and DRSP/E2 groups

Table 1 24-Hour Ambulatory Blood Pressure Assessment (mm Hg). Data is Mean (SD).

5		Pretreatment Day 1				Treatment Day 14			
		Placebo +		DRSP/E2 +		Placebo +		DRSP/E2 +	
		ACE Inhibitor (n=12)		ACE Inhibitor (n=12)		ACE Inhibitor (n=12)		ACE Inhibitor (n=12)	
		Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
		139 (12)	83 (8)	139 (19)	80 (7)	139 (11)	83 (9)	130* (16)	75** (5)

ACE = angiotensin converting enzyme; DRSP = drospirenone; E2 = estradiol

*p=0.006 Treatment Day 14 baseline corrected mean DRSP/E2 versus placebo

**p=0.003 Treatment Day 14 baseline corrected mean DRSP/E2 versus placebo

Both systolic and diastolic blood pressures were significantly lower in the DRSP/E2 group relative to those of the placebo group. The baseline adjusted declines were 9 mm Hg (p=0.006) for systolic and 6 mm Hg (p=0.003) for the diastolic. See Figures 1 and 2. The changes in systolic and diastolic blood pressure from baseline for the individual subjects are presented in Figures 3 and 4. There was no significant change in either systolic or diastolic blood pressure observed in the placebo group from Pretreatment Day 1 (baseline) to Treatment Day 14. For the DRSP/E2 group, the mean systolic/diastolic blood pressure declined from 139/80 mm Hg at baseline to 130/75 mm Hg on Treatment Day 14. A statistically significant difference between DRSP/E2 and placebo treatment groups was observed with respect to the change from baseline in regard to both systolic (p=0.014) and diastolic (p=0.007) blood pressures.

Changes from baseline in daytime and nighttime systolic and diastolic blood pressure for the placebo and DRSP/E2 groups are presented in Figures 5 and 6. There was no significant change from baseline in either systolic or diastolic blood pressure for the placebo group during both daytime and nighttime blood pressure monitoring. However, in the DRSP/E2 group, there was a significant decrease in daytime systolic (p=0.007) and diastolic (p=0.006) blood pressures from baseline. The nighttime blood pressure did not have a significant change.

Mean changes in hourly blood pressure from baseline on Day 14 for 24-hour ambulatory systolic and diastolic pressures are presented in Figures 7 and 8. The mean change from

baseline for subjects in the placebo treatment group fluctuated about the zero line suggesting no trend during the 24-hour monitoring period. On the other hand, for subjects in the DRSP/E2 group, the mean change from baseline was generally below the zero line suggesting a sustained and consistent blood pressure lowering effect.

5 Twenty-four hour, daytime and nighttime heart rate changes from Pretreatment Day 1 to Treatment Day 14 did not differ between the placebo and DRSP/E2 treatment groups

Serum and plasma pharmacodynamic variables

The changes in PRA and serum aldosterone from Pretreatment Day 1 to Treatment
10 Day 14 demonstrated considerable variability among the subjects. The change in PRA (mean (SD)) was 1.13 (2.12) ng/mL/h for the DRSP/E2 group and did not differ from that of the placebo group 2.3 (5.1) ng/mL/h, $p=0.50$. On the other hand, the serum aldosterone increased by 2.6 (4.5) ng/dL in the DRSP/E2 group, and fell by 0.3 (5.5) ng/dL in the placebo group, a difference which approached significance ($p=0.08$). In DRSP/E2 treated subjects, the
15 observed increases in serum aldosterone relative to baseline are consistent with a mild antimineralocorticoid effect due to DRSP. DRSP pharmacokinetic data and safety serum assessments of potassium are reported in Karara *et al.* (2001), *J. Clin. Pharmacol.* 41, 1014-1033.

20 Example III Administration of DRSP/E2 to hypertensive postmenopausal women not being treated with an ACE inhibitor.

In a multicenter, double-blind randomized study examining the effect on the endometrium of 1142 postmenopausal women treated for 1 year with 1 of 4 doses of DRSP (0.5, 1, 2, and 3 mg) compared with E2 alone, mean systolic and diastolic blood pressure
25 decreased from baseline for all treatment groups. In a *post hoc* analysis of a subset of women (E2 1 mg N=15, E2 1mg + 0.5 mg DRSP N=20, E2 1 mg + 1 mg DRSP N=27, E2 1 mg + 2mg DRSP N=15, E2 1 mg + 3 mg DRSP N=25) with elevated BP at baseline (systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg, mean systolic and diastolic blood pressures decreased in all groups after 11 weeks although a greater mean decrease was
30 observed in systolic values. The mean decrease in systolic blood pressure was greater for the

DRSP + E2 groups (-8.9 mm Hg to -12.7) compared with the E2 alone group (-3.7 mm Hg). This mean decrease was statistically significant ($p < 0.05$) in all DRSP + E2 groups.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make changes and modifications of the invention to adapt it to various usage and conditions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The preceding preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The entire disclosure of all applications, patents and publications, cited above and in the figures are hereby incorporated in their entirety by reference.

Aspects of the invention include a method to lower blood pressure and effect hormone replacement therapy (HRT) in a hypertensive human female mammal (woman) receiving HRT, comprising administering to said woman effective amounts of drospirenone (DRSP) and an estrogen, wherein said combination is administered orally, transdermally or by injection, wherein said estrogen is ethinyl estradiol, 17 β -estradiol, or a conjugated estrogen, wherein the estrogen is 17 β -estradiol at 1-3 mg/day, and the drospirenone is at 1-3 mg/day; and/or wherein the woman is post-menopausal.

Another aspect is a method to lower blood pressure and effect hormone replacement therapy (HRT) in a hypertensive human female (woman) receiving HRT, wherein said woman is taking antihypertensive medication, comprising administering to said woman effective amounts of drospirenone (DRSP) and an estrogen, wherein the woman begins taking the hypertensive medication before, or after, said combination is administered, wherein the woman begins taking the hypertensive medication in conjunction with the administration of said combination, wherein said antihypertensive medication is a diuretic, an α -adrenergic blocking agent, an adrenergic neuron blocking agent, a vasodilator, an angiotensin I converting enzyme (ACE) inhibitor, a calcium channel blocker, or a renin inhibitor; wherein said antihypertensive medication is an ACE inhibitor; wherein said combination is administered orally, transdermally or by injection, wherein said estrogen is ethinyl estradiol, 17 β -estradiol, or a conjugated estrogen, wherein the estrogen is 17 β -estradiol at 1-3 mg/day,

and the drospirenone is at 1-3 mg/day, and/or wherein the woman is post-menopausal.

In another aspect, the blood pressure of hypertensive woman administered the combination of drospirenone and estradiol without an antihypertensive medication was also unexpectedly reduced, see Example 3

What is claimed is

1 A method to lower blood pressure and effect hormone replacement therapy
(HRT) in a hypertensive human female patient, comprising administering to said patient
5 effective amounts of drospirenone (DRSP) and at least one estrogen

2 The method of claim 1, further comprising administering antihypertensive
medication to said patient

10 3 The method of claim 2, wherein said patient began taking the antihypertensive
medication before initiation of the administration of said DRSP and estrogen.

15 4 The method of claim 2, wherein said antihypertensive medication is
administered in conjunction with the administration of said DRSP and estrogen.

5 The method of claim 2, wherein administration of said antihypertensive
medication is initiated after initiation of administration of said DRSP and estrogen.

20 6 The method of claim 2, wherein said antihypertensive medication is a diuretic,
an α -adrenergic blocking agent, a β -adrenergic blocking agent, a CNS-acting agent, an
adrenergic neuron blocking agent, a vasodilator, an angiotensin I converting enzyme (ACE)
inhibitor, a calcium channel blocker, a renin inhibitor or a combination thereof

25 7 The method of claim 6, wherein said antihypertensive medication is an ACE
inhibitor

8 The method of claim 7, wherein said ACE inhibitor is benazepril, captopril,
enalapril, enalaprilat, fosinopril, lisinopril, pentopril, quinapril, quinaprilat, ramipril,
transolapril, or zofenopril.

30

9 The method of claim 1, wherein said DRSP and estrogen are administered orally, transdermally or by injection.

5 10 The method of claim 9, wherein said DRSP and estrogen are administered orally

11 The method of claim 1, wherein said estrogen is ethinyl estradiol, mestranol, 17 β -estradiol, an ester of estradiol, estrol, estrol succinate, polyestril phosphate, estrone, 10 estrone sulfate, natural or synthetic estrogens or a conjugated estrogen.

12 The method of claim 1, wherein the estrogen is 17 β -estradiol.

13 The method of claim 12, wherein said 17 β -estradiol is administered in an amount ranging from 1 to 3 mg/day and the drospirenone is administered in an amount ranging from 1 to 3 mg/day

14 The method of claim 2, wherein the estrogen is 17 β -estradiol and said antihypertensive medication is enalapril maleate.

15 The method of claim 1, wherein the patient is perimenopausal, menopausal or post-menopausal

16 The method of claim 1, wherein said hypertension is mild or severe

17 The method of claim 1, wherein said estrogen is ethinyl estradiol administered in an amount ranging from 0.001-0.030 mg/day, mestranol administered in an amount ranging from 5 to 25 mcg/day, estradiol administered in an amount ranging from 0.5 to 6 mg/day, polyestril phosphate administered in an amount ranging from 2 to 8 mg/day or a conjugated 30 estrogen administered in an amount ranging from 0.3 to 1.2 mg/day

18 The method of claim 1, wherein said DRSP is administered in an amount ranging from 1 to 3 mg/day

19 The method of claim 17, wherein said DRSP is administered in an amount
5 ranging from 1 to 3 mg/day

20 The method of claim 13, wherein said amount of DRSP is 3 mg and said amount of 17 β -estradiol is 1 mg

10 21 The method of claim 13, wherein said amount of DRSP is 1 mg and said amount of 17 β -estradiol is 1 mg

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25

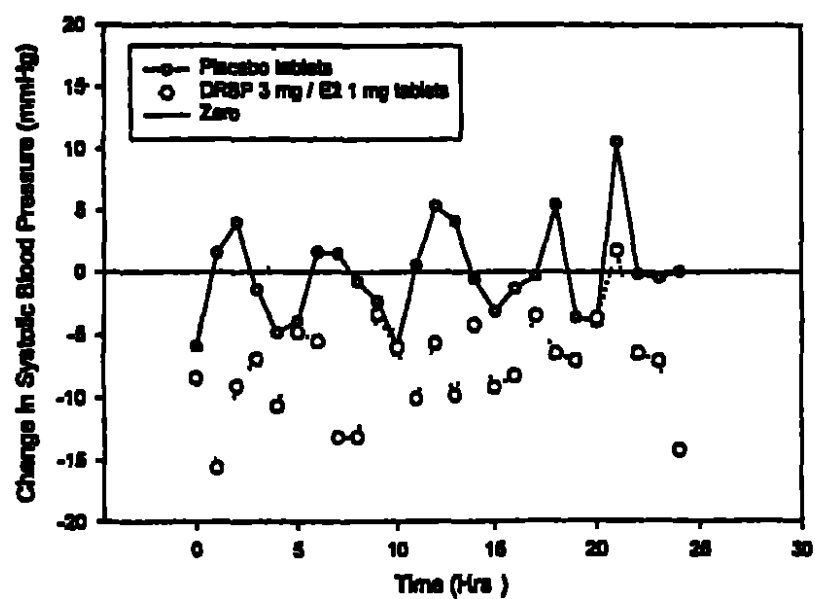


Fig. 1

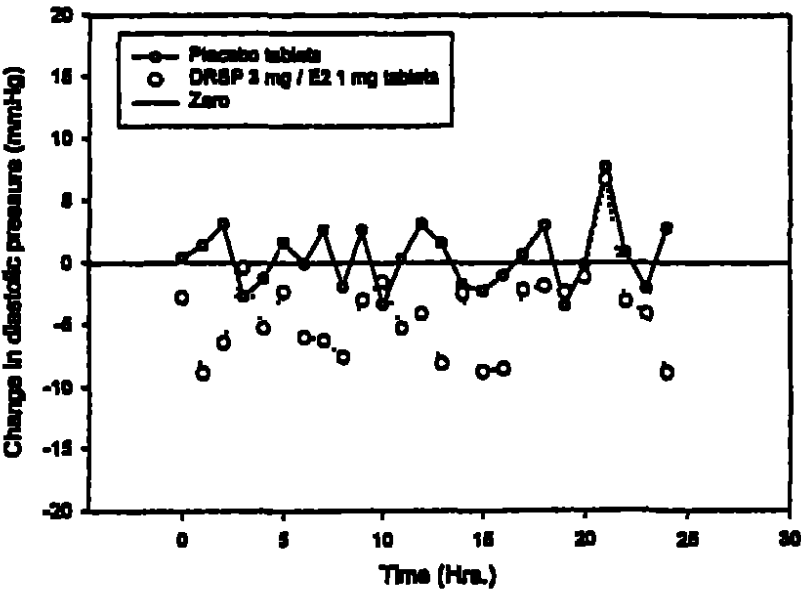


Fig. 2

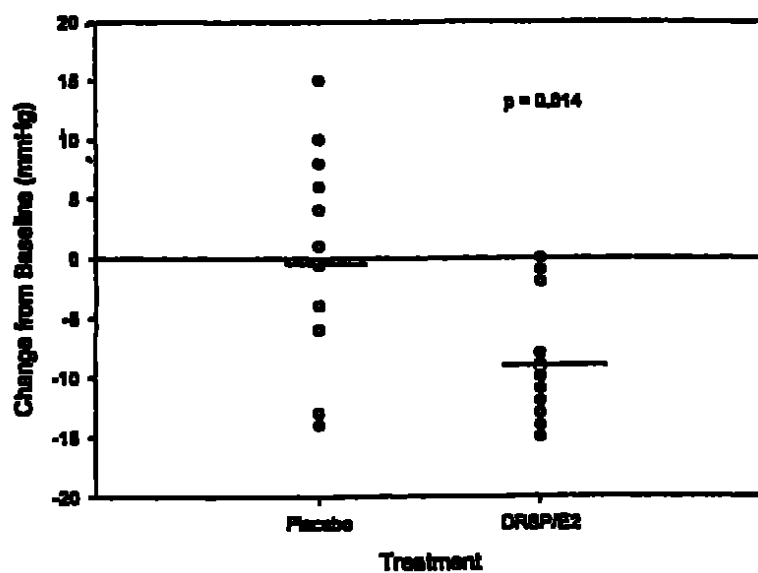


Fig. 3

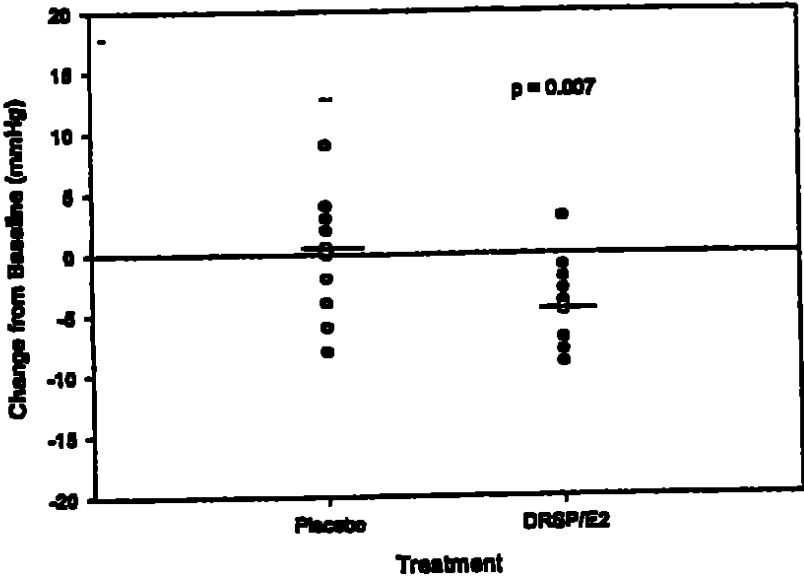


Fig. 4

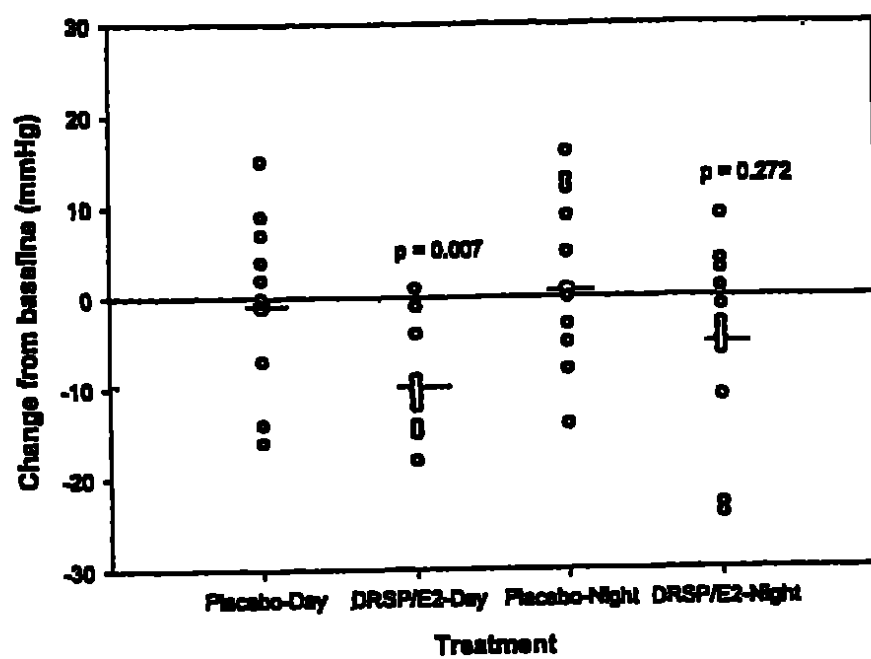


Fig. 5

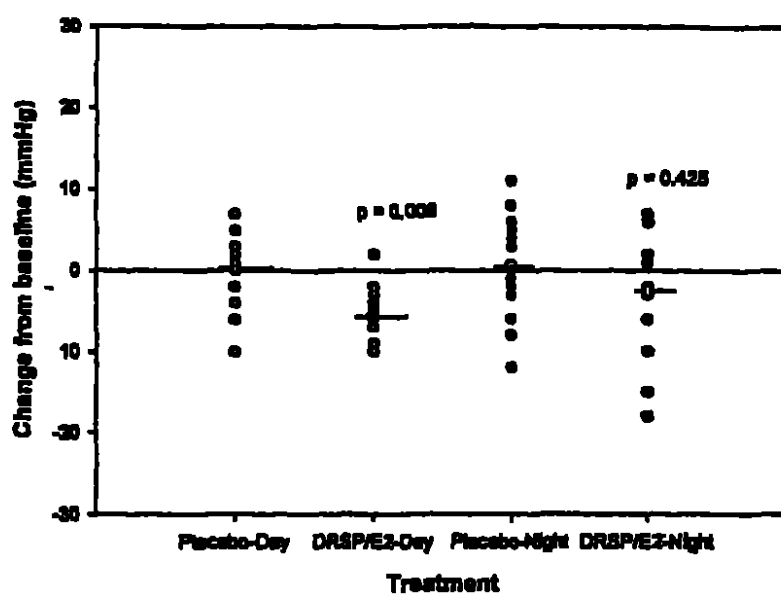


Fig. 6

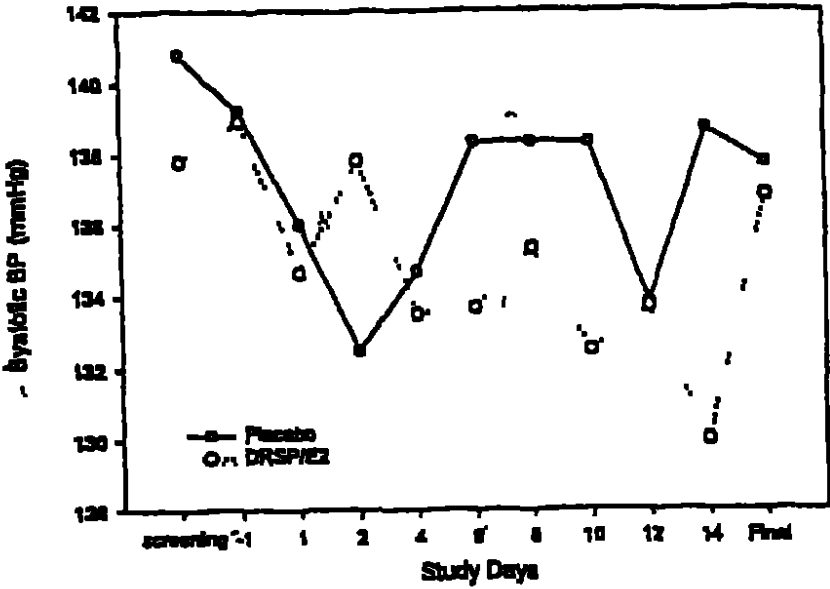


Fig 7

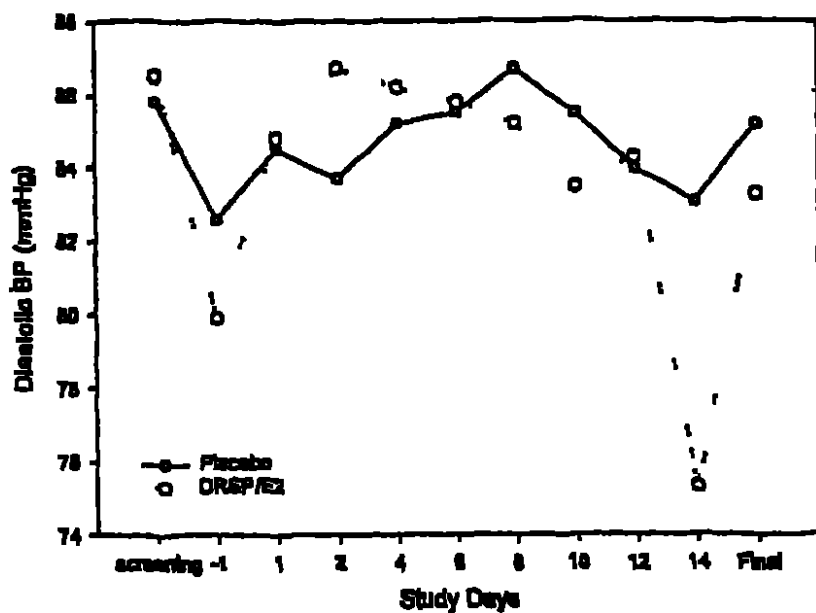


Fig 8

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/585 A61K31/565 A61K31/567 A61K31/401 A61K38/55
A61K31/675 A61P9/12 A61P15/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document with indication, where appropriate of the relevant passages	Relevant to claim No.
X	PRESTON RICHARD A ET AL "Additive effect of drospirenone/17-beta estradiol (DRSP/E2) on 24-hour ambulatory blood pressure in hypertensive postmenopausal women receiving enalapril maleate " AMERICAN JOURNAL OF HYPERTENSION, vol 15, no 4 Part 2, April 2002 (2002-04), page 235A XP001154391 Seventeenth Annual Scientific Meeting of the American Society of Hypertension, New York, N Y , USA, May 14-18, 2002, April, 2002 ISSN 0895-7061 the whole document — —/—	1-21

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents

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

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

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

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

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

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& document member of the same patent family

Date of the actual completion of the international search

14 August 2003

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Name and mailing address of the ISA

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 52857 A (HEIL WOLFGANG, SCHERING AG (DE), HILMANN JUERGEN (DE), LIPP RALPH) 26 July 2001 (2001-07-26) the whole document	1-21
A	DELKERS W "Drospirenone—a new progestogen with antimineralocorticoid activity, resembling natural progesterone" THE EUROPEAN JOURNAL OF CONTRACEPTION & REPRODUCTIVE HEALTH CARE THE OFFICIAL JOURNAL OF THE EUROPEAN SOCIETY OF CONTRACEPTION ENGLAND DEC 2000, vol 5 Suppl 3, December 2000 (2000-12), pages 17-24, XP009015507 ISSN 1362-5187	
A	NORMAN P ET AL "Drospirenone Contraceptive, hormone replacement therapy, aldosterone antagonist, progestogen 1,2-dihydrospirorenone, SH-470, ZK-30595" DRUGS OF THE FUTURE, vol 25, no 12, December 2000 (2000-12), pages 1247-1256, XP000993474 ISSN 0377-8282	
A	WO 01 15701 A (HEITHECKER RENATE, HEIL WOLFGANG (DE), SCHERING AG (DE), HILMAN JU) 8 March 2001 (2001-03-08)	

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 03/12596

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

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

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Although claims 1-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
- 2 ☐ Claims Nos. because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
- 3 ☐ Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

- 1 ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
- 2 ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
- 3 ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
- 4 ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0152857	A	26-07-2001	AU	2541301 A		31-07-2001
			BG	106915 A		30-04-2003
			BR	0107683 A		12-11-2002
			CA	2394165 A1		26-07-2001
			CN	1395488 T		05-02-2003
			CZ	20022411 A3		12-02-2003
			EP	1257280 A1		20-11-2002
			HU	0204291 A2		28-04-2003
			WO	0152857 A1		26-07-2001
			JP	2003520239 T		02-07-2003
			NO	20022966 A		18-09-2002
WO 0115701	A	08-03-2001	AU	6589500 A		26-03-2001
			BG	106533 A		31-10-2002
			BR	0014159 A		07-05-2002
			CA	2382426 A1		08-03-2001
			CN	1407895 T		02-04-2003
			CZ	20020615 A3		14-08-2002
			EE	200200110 A		16-06-2003
			EP	1214076 A1		19-06-2002
			HU	0202500 A2		28-10-2002
			WO	0115701 A1		08-03-2001
			JP	2003508441 T		04-03-2003
			NO	20020801 A		26-04-2002
			SK	2572002 A3		06-11-2002

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	NORMAN P ET AL "Drospirenone Contraceptive, hormone replacement therapy, aldosterone antagonist, progestogen 1,2-dihydrospirorenone, SH-470, ZK-30595 " DRUGS OF THE FUTURE, vol 25, no 12, December 2000 (2000-12), pages 1247-1256, XP000993474 ISSN 0377-8282	
A	WO 01 15701 A (HEITHECKER RENATE ,HEIL WOLFGANG (DE), SCHERING AG (DE), HILMAN JU) 8 March 2001 (2001-03-08)	

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 03/12596

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Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0152857	A	26-07-2001	AU 2541301 A	31-07-2001
			BG 106915 A	30-04-2003
			BR 0107683 A	12-11-2002
			CA 2394165 A1	26-07-2001
			CN 1395488 T	05-02-2003
			CZ 20022411 A3	12-02-2003
			EP 1257280 A1	20-11-2002
			HU 0204291 A2	28-04-2003
			WO 0152857 A1	26-07-2001
			JP 2003520239 T	02-07-2003
			NO 20022966 A	18-09-2002
WO 0115701	A	08-03-2001	AU 6589500 A	26-03-2001
			BG 106533 A	31-10-2002
			BR 0014159 A	07-05-2002
			CA 2382426 A1	08-03-2001
			CN 1407895 T	02-04-2003
			CZ 20020615 A3	14-08-2002
			EE 200200110 A	16-06-2003
			EP 1214076 A1	19-06-2002
			HU 0202500 A2	28-10-2002
			WO 0115701 A1	08-03-2001
			JP 2003508441 T	04-03-2003
			NO 20020801 A	26-04-2002
			SK 2572002 A3	06-11-2002

**(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL
TRATADO DE COOPERACIÓN DE PATENTES (PCT)**

- (19) Organización Mundial de la Propiedad Intelectual
Oficina Internacional
OMPI
- (43) Fecha de Publicación Internacional
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- (10) Número de Publicación Internacional
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- (21) Número de Solicitud Internacional PCT/US03/12596
- (22) Fecha de Presentación Internacional 24 Marzo 2003 (24 03 2003)
- (25) Idioma de Presentación Inglés
- (26) Idioma de Publicación Inglés
- (30) Datos de Prioridad
60375,439 30 Abril 2002 (30 04 2002) US
- (71) Solicitante (para todos los estados designados excepto US) SCHERING AG
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- (72) Inventores , e
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- (74) Agentes SHUBIN, Harry, B Y otros, Millen, White, Zelano & Branigan, P
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Arlington, VA 22201 (US)
- (81) Estados Designados (nacional) AE, AG, AL, AM, AT, AU, AZ, BA, BB,
BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN,
TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW
- (84) Estados Designados (regional) ARIPO patente (GH, GM, KE, LS, MW, MZ,
SD, SL, SZ, TZ, UG, ZM, ZW), Patente Euroasiática (AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), patente OAPI (BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Publicada

- con reporte de búsqueda internacional

Para códigos de dos letras y otras abreviaturas, referirse a la "Notas de Guía sobre
Códigos y Abreviaturas" que aparece al comienzo de cada número regular de la
Gaceta del PCT

**(54) Título TRATAMIENTO DE HIPERTENSIÓN EN MUJERES QUE RECIBEN
TERAPIA DE REEMPLAZO HORMONAL**

(57) Extracto Se describe un método para bajar la presión sanguínea y efectuar
terapia de reemplazo hormonal (HRT) en una mujer hipertensa que recibe HRT, que
comprende administrar a la mujer cantidades efectivas de drospirenona y un
estrógeno En una modalidad, la mujer ya está tomando medicina hipertensa cuando
el método se lleva a cabo

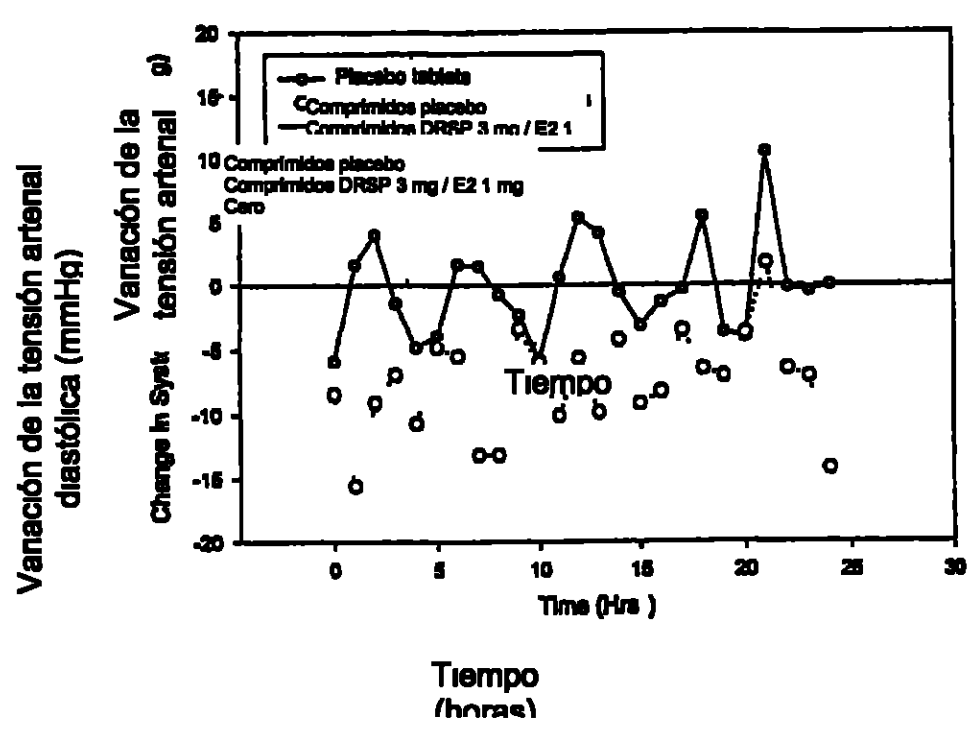


Fig. 2

TRATAMIENTO DE LA HIPERTENSIÓN EN MUJERES QUE RECIBEN TERAPIA DE REEMPLAZO HORMONAL

Esta solicitud reivindica y tiene derecho al beneficio de prioridad de la Solicitud de Patente Provisoria de los Estados Unidos Serie N° 60/375 439, presentada el 26 de abril de 2002, que queda incorporada en su totalidad a la presente mediante referencia

DESCRIPCIÓN DE LA INVENCION

La presente invención está dirigida, por ejemplo, a un metodo para reducir la tensión arterial y lograr el efecto de una terapia de reemplazo hormonal (TRH) en una hembra hipertensa humana (mujer) que recibe TRH, que comprende la administración a la mujer de una dosis efectiva de drospirenona y un estrógeno. En una realizacion, la mujer toma simultáneamente medicación antihipertensiva.

La drospirenona (DRSP) es un derivado progestágeno de la 17- α -espirolactona que, en combinación con estrógenos, se utiliza para la terapia de reemplazo hormonal (TRH), por ejemplo, en mujeres posmenopáusicas. El inventor de la presente descubrió en forma inesperada que cuando a las mujeres hipertensas que necesitan TRH, por ejemplo, mujeres que ya están tomando medicación antihipertensiva, se les administra una combinación de DRSP y estrógeno, su tensión arterial se reduce inesperadamente, en comparación con las mujeres que toman solamente un antihipertensivo.

En una realización de la invención, el estrógeno es etinil estradiol, 17 β -estradiol o un éster del mismo, o un estrógeno conjugado, la composición se administra por via oral, transdérmica o inyectable, de preferencia por via oral, el estrógeno es el 17 β -estradiol, en dosis

aproximadamente de 1-3 mg/día, y la drospirenona en dosis de aproximadamente 1-3 mg/día, la mujer es posmenopáusica, y/o la hipertensión es una hipertensión leve o una hipertensión severa.

En una realización, una mujer tratada con el método de la invención no está tomando medicación antihipertensiva. Ver, por ejemplo, el Ejemplo 3 de la presente

En otra realización, la mujer a la que se administra la combinación de la invención también toma medicación antihipertensiva, comenzada antes o después de administrársele la combinación, o comenzada simultáneamente con la administración de dicha combinación. La medicación antihipertensiva puede ser, por ejemplo, un diurético, un bloqueante α -adrenérgico, un bloqueante neuronal adrenérgico, un vasodilatador, un inhibidor de la enzima convertidora de la angiotensina I (ECA), un bloqueante del canal del calcio o un inhibidor de la renina, típicamente es un inhibidor de la ECA

En otra realización de la invención, la tensión arterial de la mujer hipertensa a la que se administró la combinación de drospirenona y estradiol sin una medicación antihipertensiva, también se redujo en forma inesperada, ver Ejemplo 3

Una mujer apta para ser tratada con el método de la invención es hipertensa (sufre de hipertensión, tiene elevada la tensión arterial). Puede sufrir de cualquier grado de hipertensión, por ejemplo, en el límite (*'borderline'*), leve (por ejemplo, estadio 1) o hipertensión severa.

La tensión arterial que se reduce puede ser únicamente la diastólica, la sistólica o la media, y/o la tensión arterial, o combinaciones de las mismas, y puede ser tensión arterial medida con monitoreo ambulatorio o en el consultorio médico (preferentemente, con monitoreo ambulatorio), medida en reposo o durante el esfuerzo, durante el día y/o por la noche, y/o en cualquier momento deseable después de la

administración de la combinación de la invención. Típicamente, la tensión arterial se reduce dentro del lapso aproximado de los 14 días posteriores a la administración de la combinación.

La tensión arterial se puede medir con una variedad de procedimientos convencionales. Algunos de los métodos para monitorear la tensión arterial en sujetos humanos se pueden ver en los Ejemplos de la presente.

⑤

Una mujer apta para el tratamiento con el método de la invención necesita terapia de reemplazo hormonal (TRH). Típicamente, la mujer es menopáusica o posmenopáusica. En la presente, los términos "menopausia" y "menopáusica/o" incluyen tanto los estados perimenopáusicos como posmenopáusicos. Las mujeres que necesitan TRH incluyen aquellas mujeres que, como consecuencia del proceso normal de envejecimiento, han entrado o comienzan a entrar en la menopausia, o bien mujeres que han cesado de menstruar por causas no relacionadas con la edad, por ejemplo, debido a esfuerzos excesivos o como consecuencia de una intervención quirúrgica (por ejemplo, histerectomía, o ooforectomía).

⑥

En una realización, una mujer tratada con el método de la invención está tomando medicación antihipertensiva, por ejemplo, ya está tomando una medicación antihipertensiva antes de que se le administre la combinación de la invención, o comienza a tomar una medicación antihipertensiva concomitantemente con la administración de la invención o con posterioridad al comienzo de dicha administración. El intervalo entre el comienzo del tratamiento con medicación antihipertensiva y la administración de la combinación de la invención no es un factor crítico. En una realización de preferencia, la disminución de la tensión arterial en una mujer que recibe una combinación de la invención es superior a la disminución que se logra cuando se administra

unicamente la medicación antihipertensiva Las mujeres tratadas con el método de la invención pueden estar tomando cualquiera de una serie de medicaciones antihipertensivas convencionales (medicaciones que son efectivas para reducir o atenuar la hipertensión) incluyendo, por ejemplo, diuréticos, bloqueantes α - y/o β -adrenérgicos, agentes que actúan sobre el SNC, bloqueantes neuronales adrenérgicos, vasodilatadores, inhibidores de la enzima convertidora de angiotensina I (ECA), bloqueantes del canal del calcio, inhibidores de la renina u otros agentes antihipertensivos o combinaciones de los mismos

⊖

Los diuréticos incluyen, por ejemplo, acetazolamida, amilorida, bendroflumetiazida, benzotiazida, bumetanida, clorotiazida, clortalidona, ciclotiazida, ácido etacrínico, furosemida, hidroclorotiazida, hidroflumetiazida, indacrinona (mezcla racémica o únicamente el enantiómero (+) o el (-), o una relación manipulada, por ejemplo, de 9 1 de dichos enantiómeros, respectivamente), metolazona, meticlotiazida, muzolimina, politiazida, quinetazona, etacrinato sódico, nitroprusiato sódico, ticrinafeno, triamtereno, y triclormetiazida.

⊕

Los agentes bloqueantes α -adrenérgicos incluyen, por ejemplo, dibenammina, fentolamina, fenoxibenzamina, prazosina, y tolazolina

Los agentes bloqueantes β -adrenérgicos incluyen, por ejemplo, atenolol, metoprolol, nadolol, propranolol, timolol, y diversos otros agentes que figuran listados en la USP 5 001 113

Los agentes que actúan sobre el SNC incluyen, por ejemplo, clonidina y metildopa

Los agentes bloqueantes neuronales adrenérgicos incluyen, por ejemplo, guanetidina, reserpina y otros alcaloides de la rauwolfia, como la rescinamina

Los vasodilatadores incluyen, por ejemplo, diazoxida, hidralazina, y minoxidil

Los bloqueantes del canal del calcio incluyen, por ejemplo, los que figuran listados en la USP 5 001 113

Los inhibidores de la renina incluyen, por ejemplo, pepstatina y los inhibidores de la renina di o tripeptídicos que figuran listados en la USP 5 001 113 y sus respectivas referencias

Otros agentes antihipertensivos incluyen, por ejemplo, aminofilina, criptenamina acetatos y tanatos, deserpidina, meremetoxilina procaína, pargilina, y tirmetafan camsilato

En un caso típico, una mujer que está siendo tratada con el método de la invención está tomando un inhibidor de la ECA, como, por ejemplo, benazepril, captopril, enalapril, enalaprilato, fosinopril, lisinopril, pentopril, quinapril, quinaprilato, ramipril, transolapril, zofenopril, péptidos como los descritos en la USP 6 232 438 y en las referencias allí citadas, compuestos como los descritos en la USP 6 300 362, agentes como los listados en la USP 5 001 113, y similares

Estos agentes antihipertensivos se administran de acuerdo con los métodos convencionales, utilizando dosis, equipos, regimenes y vías de administración convencionales. En los métodos de terapia de reemplazo hormonal se puede usar cualquiera de una variedad de estrógenos, como es bien conocido en el arte. Dichos estrógenos incluyen, por ejemplo, etinil estradiol, mestranol, estradiol (especialmente el 17- β -estradiol, conocido como E2) y ésteres de los mismos (por ejemplo, valerato, acetato, benzoato o undecilato), estriol, estriol succinato, poliestriol fosfato, estrona, estrona sulfato, estrógenos naturales o sintéticos y estrógenos conjugados

La DRSP se puede obtener comercialmente (por ejemplo, de Schering Aktiengesellschaft) o se la puede sintetizar con métodos convencionales, por ejemplo, de acuerdo con los métodos revelados en la USP 6 121 465 y en *Drugs of the Future* 2000 25 (12), 1247-1256

La DRSP y un estrógeno se pueden administrar a una paciente siguiendo los métodos convencionales, utilizando regímenes de administración, equipos, vías de administración y dosis convencionales, todos los cuales son bien conocidos por los expertos en el arte

Los regímenes son los convencionales y son bien conocidos en el arte para efectuar la TRH. El estrógeno y la DRSP se pueden administrar simultáneamente durante cualquier periodo de tiempo, por ejemplo, diariamente, de 1 a 4 veces por semana, semanalmente, de 2 a 3 semanas por mes, etc. Los dos componentes se pueden administrar por separado (como se revela, por ejemplo, en la USP 6 083 528), por ejemplo, por medio de un equipo convencional o como preparado combinado (por ejemplo, un comprimido o cápsula)

Las composiciones farmacéuticas de la invención se pueden administrar mediante alguna de una variedad de vías de administración, incluyendo, por ejemplo, la oral (por ejemplo, soluciones, suspensiones, comprimidos, grageas o píldoras), la parenteral (incluyendo inyecciones subcutáneas, intravenosas, intramusculares o intraesternales, o por medio de infusiones), pulverizador para inhalación, la vía transdérmica, rectal o la administración vaginal (por ejemplo, óvulos o cremas vaginales). Los dos componentes pueden administrarse por la misma vía o por vías diferentes (por ejemplo, estrógeno por vía transdérmica y DRSP por vía intravaginal)

La dosis "efectiva" para lograr el efecto de una terapia de reemplazo hormonal es aquella que previene o disminuye (atenúa) los efectos o síntomas fisiológicos adversos que resultan de la reducción de la cantidad de estrógenos, tales como, p. ej. y entre muchos otros, la descalcificación ósea y la consiguiente deformación estructural. La dosis de la composición de la invención que es "efectiva" para reducir la tensión arterial es la que permite obtener una disminución medible de la

tensión arterial Con los métodos de la invención se puede administrar cualquier dosis efectiva, preferiblemente una formulación con dosis bajas

Las dosis efectivas de los estrógenos son convencionales y bien conocidas en el arte Las dosis típicas aproximadas para la administración oral son, por ejemplo, etinil estradiol (0,001-0,030 mg/día), mestranol (5-25 mcg/día), estradiol (incluido el 17- β estradiol), (0,5-6 mg/día), poliestriol fosfato (2-8 mg) y estrógenos conjugados (0,3-1,2 mg/día) Las dosis para otras vías de administración serán evidentes para un experto en el arte Por ejemplo, las dosis transdérmicas varían de acuerdo con la eficacia de la absorción del vehículo empleado

Las dosis efectivas de drospirenona son también convencionales y bien conocidas en el arte Las dosis típicas para la administración oral varían aproximadamente entre 1,0 y 3,0 mg/día.

Las combinaciones de preferencia de la invención incluyen, para la administración oral, 3 mg DRSP / 1 mg E2 y 1 mg DRSP / 1 mg E2

Queda entendido, desde ya, que la dosis específica y la frecuencia de administración para una paciente en particular dependerá de una variedad de factores, incluyendo la actividad del compuesto químico específicamente utilizado, la estabilidad metabólica y la duración de la acción de dicho compuesto, la edad, el peso, el estado general, el sexo, la dieta, la vía y el horario de administración, la velocidad de excreción, la combinación de drogas, la severidad del cuadro y la terapia que esté recibiendo ya la paciente

Como el método de la presente invención involucra el logro de la TRH, necesariamente las dosis individuales de estrógeno y DRSP se administran durante períodos prolongados, es decir, más de un mes, usualmente por lo menos varios meses, comunmente durante uno o más años y a menudo durante una o más décadas Durante dicho período, la

dosis individual del estrógeno o de la DRSP, o la de ambas drogas, puede ser modificada por lo menos una vez, a menudo dos o más veces y, usualmente, los incrementos se hacen en forma escalonada hasta encontrar la dosis mínima terapéutica efectiva. Con frecuencia, se la puede volver a disminuir, a medida que la paciente pasa de la perimenopausia a la posmenopausia, porque la dosis de estrógeno para prevenir la descalcificación ósea menopáusica usualmente es superior a la dosis que se necesita para tratar las molestias del climaterio.

Las composiciones de la invención se pueden formular siguiendo las prácticas farmacéuticas aceptadas, con vehículo, transportador, excipiente, aglutinante, conservante, estabilizador, saborizante y/o adyuvante, etc. convencionales y farmacéuticamente aceptables para cada tipo de forma farmacéutica.

Las formulaciones para la administración oral son las convencionales en el arte. Por ejemplo, los comprimidos generalmente contienen un transportador farmacéuticamente aceptable, por ejemplo, un aglutinante como goma tragacanto, acacia, almidón de maíz o gelatina, un excipiente como fosfato dicálcico o celulosa, un agente desintegrador como almidón de maíz o ácido algínico, un lubricante, como el estearato de magnesio, y/o un edulcorante o saborizante. Cuando la forma farmacéutica es una cápsula, puede contener, además de los materiales del tipo antes mencionado, un transportador líquido, como un aceite graso. Pueden estar presentes diversos otros materiales, como recubrimientos u otros elementos para modificar de otro modo la forma física farmacéutica. Por ejemplo, los comprimidos o cápsulas pueden estar recubiertos con shellac, azúcar o ambos. Un jarabe o elixir puede contener el compuesto activo, agua, alcohol o similares como transportador, glicerol como solubilizante, sacarosa como edulcorante, metil y propil parabens como conservantes y un colorante y saborizante.

como el de cereza o naranja. Cuando se las administra oralmente como suspensión, estas composiciones pueden contener celulosa microcristalina para aumentar el volumen, ácido algínico o alginato sódico como agente de suspensión, metilcelulosa para aumentar la viscosidad y edulcorantes/saborizantes conocidos en el arte. Como comprimidos de liberación inmediata, estas composiciones pueden contener celulosa microcristalina, fosfato dicálcico, almidón, estearato de magnesio y lactosa y/u otros excipientes, aglutinantes, desintegradores, diluyentes y lubricantes conocidos en el arte.

Las formulaciones aptas para uso inyectable incluyen soluciones o dispersiones acuosas estériles y polvos estériles para la preparación extemporánea de soluciones o dispersiones inyectables estériles. Las soluciones son estables y están preservadas contra la acción contaminante de microorganismos tales como las bacterias y los hongos. Las soluciones o suspensiones inyectables se pueden formular con los métodos conocidos en el arte, utilizando diluyentes o solventes aptos, no tóxicos, parenteralmente aceptables, tales como manitol, 1,3 butanediol, agua, solución Ringer o solución isotónica de cloruro de sodio, o agentes dispersantes o humidificantes aptos, como aceites fijados, blandos, estériles, incluyendo los mono o diglicéridos sintéticos, y ácidos grasos, incluyendo el ácido oleico.

Para la administración por vía rectal en forma de supositorios, estas composiciones se pueden preparar mezclando la droga con un excipiente apto no irritante, como manteca de cacao, ésteres glicéridos sintéticos o polietilenglicoles, que son sólidos a temperaturas ordinarias pero se licúan y/o disuelven en la cavidad rectal, liberando la droga.

Métodos para formular composiciones para TRH para aplicación local (por ejemplo, como líquidos viscosos extruibles, preparados semisólidos como geles, ungentos y cremas, o sólidos untables, como

una barra desodorante) y para aplicarlas a una paciente, por ejemplo, a una superficie como la piel o mucosas, figuran revelados en la USP 6 083 528

En los ejemplos precedentes y en los que siguen, todas las temperaturas se consignan sin corregir en grados Celsius y, excepto indicación en contrario, todas las partes y porcentajes son por peso

BREVE DESCRIPCIÓN DE LAS FIGURAS

La Figura 1 muestra la variación respecto de la línea de base (día 1 pretratamiento) de la tensión arterial sistólica de 24 horas en el día de tratamiento 14

La Figura 2 muestra la variación media respecto de la línea de base (día 1 pretratamiento) de la tensión arterial diastólica de 24 horas en el día de tratamiento 14

La Figura 3 muestra las variaciones de la tensión arterial sistólica de 24 horas, medida con monitoreo ambulatorio, respecto de la línea de base (día 1 pretratamiento) en estado estable (día 14) en pacientes (mujeres posmenopáusicas con hipertensión leve mantenidas con enalapril maleato 20 mg/día durante el período de tratamiento) que recibían DRSP/E2 o placebo Las líneas horizontales representan las medias

La Figura 4 muestra las variaciones de la tensión arterial diastólica de 24 horas, medida con monitoreo ambulatorio, respecto de la línea de base (día 1 pretratamiento) en estado estable (día 14) en pacientes (mujeres posmenopáusicas con hipertensión leve mantenidas con enalapril maleato 20 mg/día durante el período de tratamiento) que recibían DRSP/E2 o placebo Las líneas horizontales representan las medias

La Figura 5 muestra las variaciones diurnas y nocturnas de la tensión arterial sistólica de 24 horas medida con monitoreo ambulatorio respecto de la línea de base (día 1 pretratamiento) en estado estable (día 14) en pacientes (mujeres posmenopáusicas con hipertensión leve mantenidas con enalapril maleato 20 mg/día durante el período de tratamiento) que recibían DRSP/E2 o placebo. Las líneas horizontales representan las medias.

La Figura 6 muestra las variaciones diurnas y nocturnas de la tensión arterial diastólica de 24 horas medida con monitoreo ambulatorio respecto de la línea de base (día 1 pretratamiento) en estado estable (día 14) en pacientes (mujeres posmenopáusicas con hipertensión leve mantenidas con enalapril maleato 20 mg/día durante el período de tratamiento) que recibían DRSP/E2 o placebo. Las líneas horizontales representan las medias.

La Figura 7 muestra la tensión arterial sistólica media a lo largo de los días del estudio (medida en consultorio, excepto en los días 1 y 14, que corresponden a la tensión arterial media de 24 horas medida en forma ambulatoria). El día 1 del estudio corresponde al día 1 pretratamiento.

La Figura 8 muestra la tensión arterial diastólica media a lo largo de los días del estudio (medida en consultorio, excepto en los días 1 y 14, que corresponden a la tensión arterial media de 24 horas medida en forma ambulatoria). El día 1 del estudio corresponde al día 1 pretratamiento.

EJEMPLOS

Ejemplo I Administración de DRSP / E2 a mujeres posmenopáusicas con hipertensión leve tratadas con un inhibidor de la ECA - Métodos

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Este estudio fue doble ciego, randomizado, con 2 grupos paralelos, para comparar los efectos de DRSP 3 mg / E2 1 mg versus placebo sobre la tensión arterial de 24 horas medida con monitoreo ambulatorio en mujeres posmenopáusicas con hipertensión leve tratadas con (por ejemplo, mantenidas con) enalapril maleato 10 mg dos veces diarias

Pacientes

Para ser incluida en el estudio, cada paciente debía cumplir los siguientes criterios: ausencia de otras enfermedades concomitantes, posmenopausia (natural o quirúrgica), 45-75 años de edad, en tratamiento con el inhibidor de la ECA enalapril maleato (dosis diaria de 10 mg 2 veces al día durante un mínimo de 7 días) por hipertensión leve, peso no inferior a 100 libras y dentro $\pm 15\%$ de lo normal de acuerdo con su altura y contextura. Las pacientes tenían una tensión arterial sistólica igual o inferior a 150 mm Hg y una tensión arterial diastólica igual o inferior a 90 mm Hg. Las pacientes debían tener en la etapa de análisis ('screening') un potasio sérico entre 3,5 y 4,5 mEq/l y una depuración de creatinina superior a 60 ml/min. Se excluyeron del estudio a las pacientes que, durante las evaluaciones en el período de análisis, presentaban cualquiera de los siguientes criterios: valores de laboratorio anormales clínicamente significativos y anomalías electrocardiográficas (ECG), antecedentes de enfermedades significativas, antecedentes de abuso de drogas o alcohol durante los 10 últimos años, pruebas positivas para la hepatitis B o C o para el VIH, diagnóstico previo de cáncer de cualquier tipo, fumadoras durante el año anterior, que hubieran donado una pinta o más de sangre durante los 3 meses previos al estudio o que tuvieran sensibilidad conocida a la terapia estrogénica, a la DRSP o al enalapril.

Diseño del estudio

Fue un estudio randomizado, doble ciego con 2 grupos paralelos

Los tratamientos fueron

Droga del ensayo	Enalapril maleato, un comprimido de 10 mg por via oral, dos veces diarias + DRSP (3 mg) / E2 (1 mg) en un comprimido oral diario durante 14 días
Placebo	Enalapril maleato un comprimido de 10 mg por vía oral, dos veces diarias + un comprimido oral diario de placebo con apariencia igual al de DRSP / E2 durante 14 días

Las pacientes comenzaron a tomar enalapril por lo menos 7 días antes del período de tratamiento y lo continuaron a lo largo de toda la duración del mismo (14 días) De conformidad con los criterios mencionados, 24 mujeres posmenopáusicas fueron randomizadas a uno de los tratamientos descritos más arriba El estudio se realizó principalmente en pacientes ambulatorias En el Día 1 de Pretratamiento, las pacientes ingresaron a la clínica para las evaluaciones de 24 horas de la tensión arterial con monitoreo ambulatorio y las pruebas de laboratorio El Día 1 de Tratamiento, las pacientes fueron dadas de alta de la clínica, después de recibir sus respectivas dosis, con lo que se inició la fase de tratamiento de 14 días que consistió en tratamiento activo o con placebo, continuando en todos los casos la terapia con enalapril Las pacientes volvieron a la clínica el Día 2 de Tratamiento y posteriormente cada 2 días (hasta el Día 12 de Tratamiento) para las evaluaciones de seguridad de laboratorio y la dosificación de las concentraciones plasmáticas de DRSP El Día 14 de Tratamiento, las pacientes volvieron a la clínica durante un período de aproximadamente 24 horas, durante el cual se les administró la última dosis de la droga del estudio y se hicieron las mediciones de la tensión arterial con monitoreo ambulatorio de 24 horas y las evaluaciones de laboratorio

Monitoreo ambulatorio de la tensión arterial

El monitoreo ambulatorio de la tensión arterial ('ABPM') se realizó usando un Spacelabs Inc Modelo 90207 (Spacelabs Inc, Redmond Washington) en el Día 1 Pretratamiento y en el Día 14 de Tratamiento del estudio, siguiendo un protocolo estándar. Se inicializó el monitor de cada paciente y el manguito para la tensión arterial se colocó en el brazo no predominante. Se hicieron cinco lecturas para correlación utilizando un esfigmomanómetro de mercurio (Baumanometer, W A Baum Co, Inc, Copiague, Nueva York) a fin de verificar la calibración del monitor. Las lecturas se registraron cada 20 minutos durante el período entre las 7 a.m. y las 11 p.m. y posteriormente cada 30 minutos entre las 11 p.m. y las 7 a.m. Al cabo de 24 horas se concluyó el monitoreo de la tensión arterial y se retiró el monitor. Los datos del ABPM se transmitieron luego a Biomedical Systems para su análisis, utilizando un módem conectado a una línea telefónica dedicada. Las pacientes fueron instruidas para que mantuvieran inmóvil el brazo durante el registro de la tensión arterial. No se autorizaron las duchas ni los esfuerzos extremos.

Evaluaciones de laboratorio

La Actividad de la Renina Plasmática ('PRA') se midió dosando la generación de Angiotensina I a partir del angiotensinógeno utilizando un radio inmunoensayo ('RIA') comercial. Las muestras de sangre se tomaron en ayunas 24 horas antes de la administración (hora cero, Día 1 Pretratamiento), por lo menos 1 hora después de levantarse a la mañana y aproximadamente a la misma hora en el Día 1 Pretratamiento y en el Día 14 de Tratamiento. Además, las pacientes tenían que estar levantadas 30 minutos antes de la extracción de la muestra. Las pacientes debían

abstenerse de tomar medicaciones, preferiblemente durante las 3 semanas anteriores a la extracción de la muestra de sangre

La aldosterona sérica se dosó con un RIA comercial. La sangre se extrajo 24 horas antes de la administración (hora cero, Día 1 Pretratamiento). Las pacientes estuvieron levantadas durante 2 horas antes y durante la extracción de sangre y se abstuvieron de tomar medicaciones, preferiblemente durante las 3 semanas anteriores a la extracción de la muestra de sangre.

Métodos estadísticos

Los datos de 24 horas de la tensión arterial media sistólica y diastólica se analizaron con un ANCOVA usando los valores de línea de base (Día 1 Pretratamiento) como covariables. Se asumió que los datos de tensión arterial tenían una distribución normal con variancias comunes. Las fuentes de variación fueron los tratamientos (factor fijo con los niveles de drogas del ensayo y el placebo), y el valor de línea de base (covariable). La bondad del ajuste se verificó usando un trazado residual. La hipótesis sometida a ensayo fue $H_0: \mu_T = \mu_P$ versus la alternativa $H_1: \mu_T \neq \mu_P$ a un nivel de significación del 5%. La variación individual respecto de la línea de base de la tensión sistólica y diastólica de 24 horas, los datos de tensión arterial diurna y nocturna se analizaron usando una prueba de t apareada.

Ejemplo II

Administración de DRSP/E2 a mujeres posmenopáusicas con hipertensión leve tratadas con un inhibidor de la ECA - resultados

Datos demográficos

Un total de 24 mujeres posmenopáusicas con hipertensión leve pero sin otras enfermedades concomitantes fueron randomizadas en este

estudio doble ciego con dos grupos paralelos Las pacientes eran mujeres posmenopáusicas con una media de edad ($\pm$ desviación estándar [DE]) de 57 ± 5 , 62 ± 6 años, y un peso de 77 ± 11 , 70 ± 7 kg, en el grupo placebo y el grupo de tratamiento DRSP/E2, respectivamente La población del estudio incluyó caucásicas (4%), afroamericanas (4%) e hispanicas (92%) Las veinticuatro pacientes completaron el estudio

Tensión arterial y frecuencia cardiaca con monitoreo ambulatorio de 24 horas

La Tabla 1 presenta un resumen de los datos de tensión arterial medida con monitoreo ambulatorio de 24 horas en el grupo placebo y el grupo de tratamiento con DRSP/E2

Tabla 1 Medición de la tensión arterial con monitoreo ambulatorio de 24 horas (mm Hg) Los datos están expresados como media (DE)

Día 1 Pretratamiento				Día 14 Tratamiento			
Placebo +		DRSP/E2 +		Placebo +		DRSP/E2 +	
Inhibidor de la ECA		Inhibidor de la ECA		Inhibidor de la ECA		Inhibidor de la ECA	
(n = 12)		(n = 12)		(n = 12)			
Sistólica	Diastólica	Sistólica	Diastólica	Sistólica	Diastólica	Sistólica	Diastólica
139 (12)	83 (8)	139 (19)	80 (7)	139 (11)	83 (9)	130* (16)	75** (5)

ECA = enzima convertidora de la angiotensina, DRSP = drospirenona, E2 = estradiol

*p=0,006 Media corregida Día 14 Tratamiento línea de base DRSP/E2 versus placebo

**p=0,003 Media corregida Día 14 Tratamiento línea de base DRSP/E2 versus placebo

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Tanto la tensión arterial sistólica como la diastólica fueron significativamente menores en el grupo DRSP/E2 en comparación con el grupo placebo. Las declinaciones reajustadas respecto de la línea de base fueron de 9 mm Hg ($p = 0,006$) para la sistólica y de 6 mm Hg ($p = 0,003$) para la diastólica. Ver Figuras 1 y 2. Las variaciones respecto de la línea de base de la tensión arterial sistólica y diastólica para cada paciente se presentan en las Figuras 3 y 4. No se registró variación significativa en la tensión arterial sistólica ni diastólica en el grupo placebo entre el Día 1 Pretratamiento (línea de base) y el Día 14 de Tratamiento. En el grupo DRSP/E2, la tensión arterial sistólica/diastólica media declinó de 139/80 mm Hg en la línea de base a 130/75 mm Hg el Día 14 de Tratamiento. Se observó una diferencia estadísticamente significativa entre los grupos de tratamiento DRSP/E2 y placebo en la variación respecto de la línea de base tanto en la tensión arterial sistólica ($p = 0,014$) como en la diastólica ($p = 0,007$).

Las variaciones respecto de la línea de base en la tensión arterial sistólica y diastólica diurna y nocturna en los grupos placebo y DRSP/E2 se presentan en las Figuras 5 y 6. No hubo variación significativa respecto de la línea de base en la tensión arterial sistólica ni diastólica en el grupo placebo, tanto durante el monitoreo diurno como en el nocturno. En cambio, en el grupo DRSP/E2 hubo una disminución significativa en la tensión arterial diurna sistólica ($p = 0,007$) y diastólica ($p = 0,006$) en comparación con la línea de base. La tensión arterial nocturna no presentó variaciones significativas.

Las variaciones medias de la tensión arterial horaria sistólica y diastólica medidas con monitoreo ambulatorio de 24 horas en la línea de base y el Día 14 se presentan en las Figuras 7 y 8. La variación media respecto de la línea de base en las pacientes del grupo placebo fluctuó alrededor de la línea cero, indicando la ausencia de una tendencia

durante el periodo de monitoreo de 24 horas. En cambio, en las pacientes del grupo DRSP/E2, la variación media respecto de la línea de base estuvo generalmente por debajo de la línea cero, indicando un efecto hipotensor sostenido consistente.

Las variaciones de la frecuencia cardíaca diurna y nocturna medida con monitoreo de 24 horas en el Día 1 Pretratamiento y el Día 14 de Tratamiento no presentaron diferencias entre los grupos placebo y DRSP/E2.

Parámetros farmacodinámicos séricos y plasmáticos

Las variaciones de la PRA y la aldosterona sérica entre el Día 1 Pretratamiento y el Día 14 de Tratamiento exhibieron una considerable variabilidad individual. La variación de la PRA (media (DE)) fue de 1,13 (2,12) ng/ml/h en el grupo DRSP/E2 y no difirió de la del grupo placebo, que fue de 2,3 (5,1) ng/ml/h, $p = 0,50$. En cambio, la aldosterona sérica aumentó en 2,6 (4,5) ng/dl en el grupo DRSP/E2, y cayó en 0,3 (5,5) ng/dl en el grupo placebo, diferencia que estuvo próxima a la significativa ($p = 0,08$). En las pacientes tratadas con DRSP/E2, los aumentos observados de la aldosterona sérica en comparación con la línea de base son compatibles con un leve efecto anti-mineralocorticoide debido a la DRSP. Los datos farmacocinéticos y las evaluaciones séricas de seguridad del potasio se informan en Karara *et al* (2001), J Clin Pharmacol 41, 1014-1033.

Ejemplo III

Administración de DRSP/E2 a mujeres posmenopáusicas hipertensas que no están tratadas con un inhibidor de la ECA.

En un estudio multicéntrico, doble ciego, randomizado para estudiar el efecto sobre el endometrio de 1142 mujeres posmenopáusicas

tratadas durante un año con una de cuatro dosis de DRSP (0,5, 1, 2 y 3 mg) en comparación con E2 solamente, la tensión arterial sistólica y diastólica media disminuyó respecto de la línea de base en todos los grupos de tratamiento. En un análisis *post hoc* de un subgrupo de mujeres (E2 1 mg N = 15, E2 1 mg + 0,5 mg DRSP N = 20, E2 1 mg + 1 mg DRSP N = 27, E2 1 mg + 2 mg DRSP N = 15, E2 1 mg + 3 mg DRSP N = 25) con TA elevada en la línea de base (TA sistólica ≥ 140 mm Hg y o TA diastólica ≥ 90 mm Hg, la tensión arterial sistólica y diastólica media disminuyó en todos los grupos al cabo de 11 semanas, si bien se observó una mayor disminución media en los valores sistólicos. La disminución media de la tensión arterial sistólica fue mayor en los grupos DRSP + E2 (-8,9 mm Hg a -12,7), en comparación con el grupo tratado con E2 solamente (-3,7 mm Hg). Esta disminución media resultó estadísticamente significativa ($p < 0,05$) en todos los grupos DRSP + E2.

A partir de la descripción precedente, un experto en el arte puede ponderar fácilmente las características esenciales de esta invención y, sin apartarse del espíritu ni de los alcances de la misma, podrá introducir cambios y modificaciones a la invención para adaptarla a diversos usos y cuadros.

Se considera que un experto en el arte, sin necesidad de elaboración ulterior, puede utilizar la descripción precedente en toda su magnitud. Por lo tanto, las realizaciones específicas de preferencia mencionadas deben interpretarse a título meramente de ejemplo y de ningún modo con carácter limitativo del resto de la revelación.

La revelación completa de todas las aplicaciones, patentes y publicaciones citadas anteriormente y en las figuras quedan incorporadas en su totalidad a la presente mediante referencia.

Entre los aspectos de la invención se incluye un método para reducir la tensión arterial y lograr el efecto de una terapia de reemplazo

hormonal (TRH) en un mamífero hembra humano (mujer) con hipertensión que recibe TRH, y que comprende la administración a dicha mujer de cantidades efectivas de drospirenona (DRSP) y un estrógeno, en el cual dicha combinación se administra por vía oral, transdérmica o inyectable, en el cual dicho estrógeno es el etinil estradiol, el 17β -estradiol, o un estrógeno conjugado, en el cual el estrógeno es el 17β -estradiol en dosis de 1-3 mg/día, y la drospirenona en dosis de 1-3 mg/día, y/o en el cual las mujeres son posmenopáusicas

Otro aspecto es un método para reducir la tensión arterial y lograr el efecto de una terapia de reemplazo hormonal (TRH) en una hembra humana (mujer) hipertensa que recibe TRH, en el cual dicha mujer está tomando medicación antihipertensiva, que comprende la administración a dicha mujer de cantidades efectivas de drospirenona (DRSP) y de un estrógeno, en el cual la mujer comienza a tomar la medicación antihipertensiva antes o después de que se le administre dicha combinación, en el cual la mujer comienza a tomar la medicación antihipertensiva conjuntamente con la administración de dicha combinación, en el cual dicha medicación antihipertensiva es un diurético, un bloqueante α -adrenérgico, un bloqueante neuronal adrenérgico, un vasodilatador, un inhibidor de la enzima convertidora de angiotensina I (ECA), un bloqueante del canal del calcio o un inhibidor de la renina, en el cual dicha combinación se administra por vía oral, transdérmica o inyectable, en el cual dicho estrógeno es el etinil estradiol, el 17β -estradiol, o un estrógeno conjugado, en el cual el estrógeno es el 17β -estradiol en dosis de 1-3 mg/día, y la drospirenona en dosis de 1-3 mg/día, y/o en el cual la mujer es posmenopáusica.

En otro aspecto, la tensión arterial de la mujer hipertensa que recibió la combinación de drospirenona y estradiol sin una medicación antihipertensiva también se redujo en forma inesperada, ver Ejemplo 3

Se reivindica lo siguiente

- 1 Un método para reducir la tensión arterial y lograr el efecto de terapia de reemplazo hormonal (TRH) en una paciente hembra humana hipertensa, que comprende administrar a dicha paciente drospirenona (DRSP) en dosis de 0,5-3 mg/día y 17β -estradiol en dosis de 1-3 mg/día
- 2 El método de la reivindicación 1, que comprende además la administración de medicación antihipertensiva a dicha paciente
- 3 El método de la reivindicación 2, en el cual dicha paciente comenzó a tomar la medicación antihipertensiva antes de iniciarse la administración de dicha DRSP y dicho 17β -estradiol
- 4 El método de la reivindicación 2, en el cual dicha medicación antihipertensiva se administra conjuntamente con la administración de dicha DRSP y dicho 17β -estradiol
- 5 El método de la reivindicación 2, en el cual la administración de dicha medicación antihipertensiva se inicia después de iniciarse la administración de dicha DRSP y dicho 17β -estradiol
- 6 El método de la reivindicación 2, en el cual dicha medicación antihipertensiva es un diurético, un bloqueante α -adrenérgico, un bloqueante β -adrenérgico, un agente que actúa sobre el SNC, un bloqueante neuronal adrenérgico, un vasodilatador, un inhibidor de la enzima convertidora de la angiotensina I (ECA), un bloqueante del canal del calcio, un inhibidor de la renina o una combinación de los mismos

7 El método de la reivindicación 6, en el cual dicha medicación antihipertensiva es un inhibidor de la ECA

8 El método de la reivindicación 7, en el cual dicho inhibidor de la ECA es benazepril, captopril, enalapril, enalaprilato, fosinopril, lisinopril, pentopril, quinapril, quinaprilat, ramipril, transolapril, o zofenopril

9 El método de la reivindicación 1, en el cual dicha DRSP y dicho 17β -estradiol se administran por vía oral, transdérmica o inyectable

10 El método de la reivindicación 9, en el cual dicha DRSP y dicho 17β -estradiol se administran por vía oral

11 El método de la reivindicación 2, en el cual dicha medicación antihipertensiva es enalapril maleato

12 El método de la reivindicación 1, en el cual la paciente es perimenopáusica, menopáusica o posmenopáusica.

13 El método de la reivindicación 1, en el cual dicha hipertensión es leve o severa

14 El método de la reivindicación 1, en el cual dicha dosis de DRSP es de 3 mg y dicha dosis de 17β -estradiol es de 1 mg

15 El método de la reivindicación 1, en el cual dicha dosis de DRSP es de 2 mg y dicha dosis de 17β -estradiol es de 1 mg

16 El método de la reivindicación 1, en el cual dicha dosis de DRSP es de 1 mg y dicha dosis de 17β -estradiol es de 1 mg

17 El método de la reivindicación 1, en el cual dicha dosis de DRSP es de 0,5 mg y dicha dosis de 17β -estradiol es de 1 mg

RESUMEN

Se describe un método para reducir la tensión arterial y lograr el efecto de una terapia de reemplazo hormonal (TRH) en una mujer hipertensa que recibe TRH, y que comprende administrar a la mujer dosis efectivas de drospirenona y un estrógeno. En una realización, la mujer ya está tomando medicación antihipertensiva cuando se inicia el método.

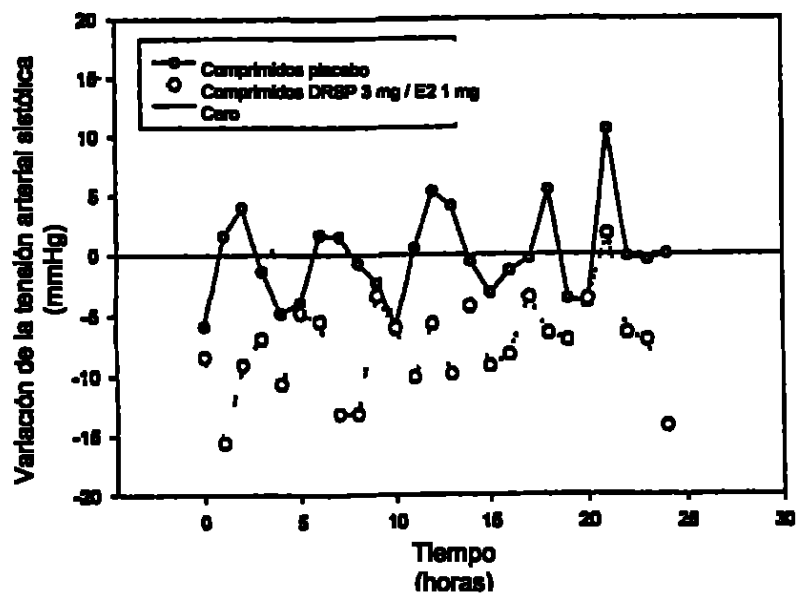


Fig. 1

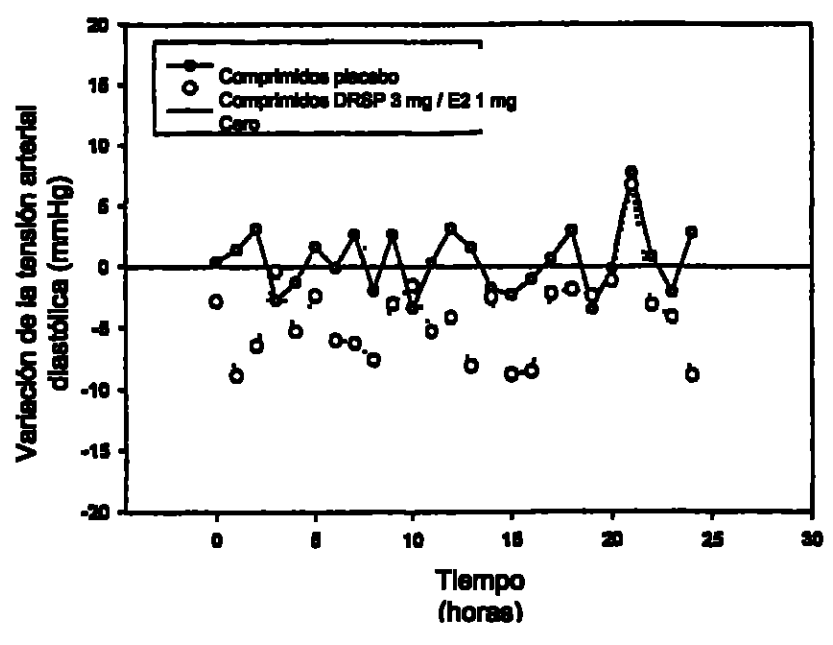


Fig. 2

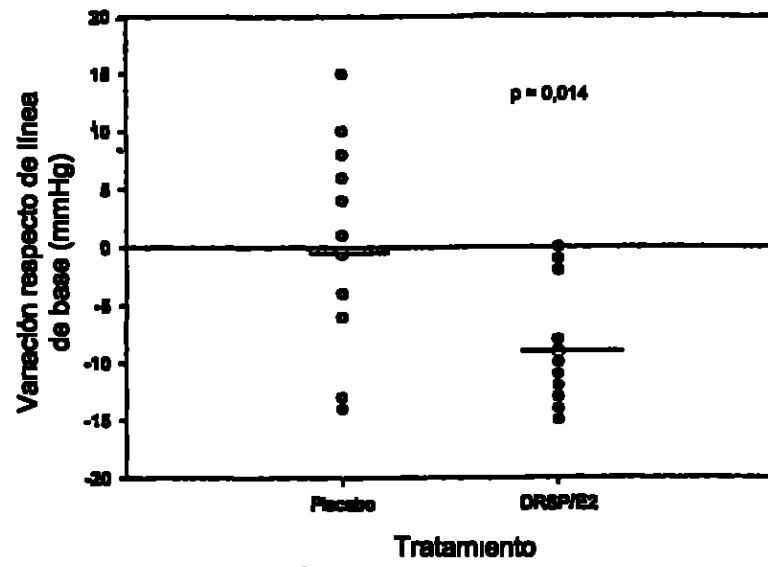


Fig. 3

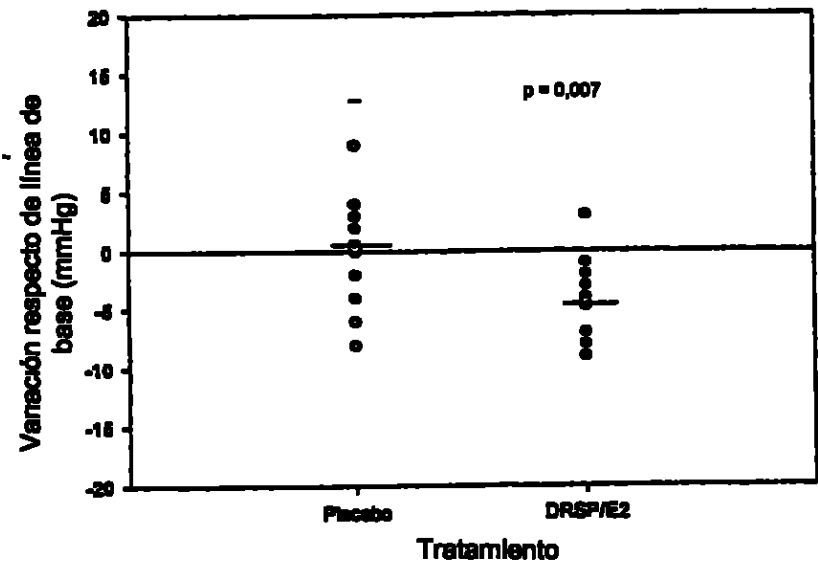


Fig. 4

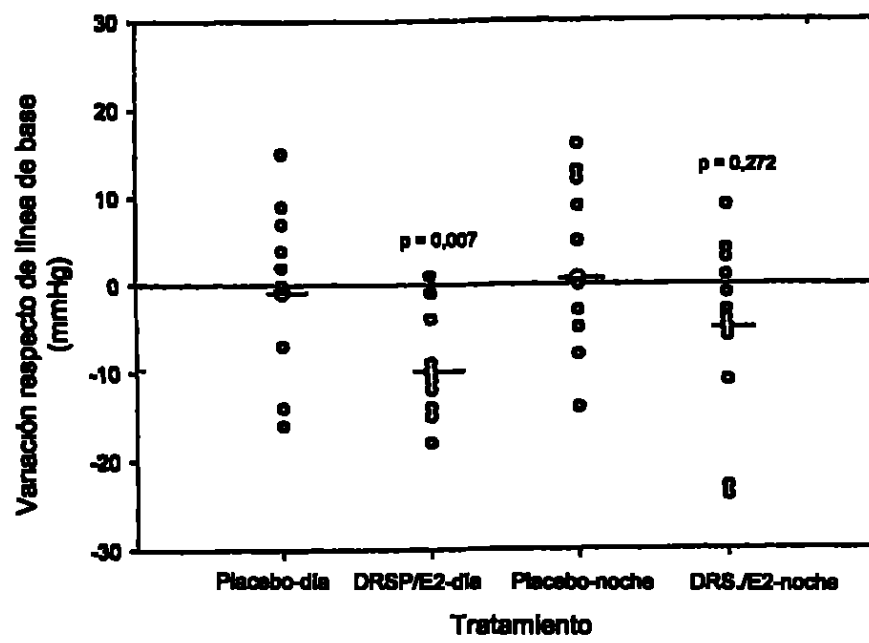


Fig. 5

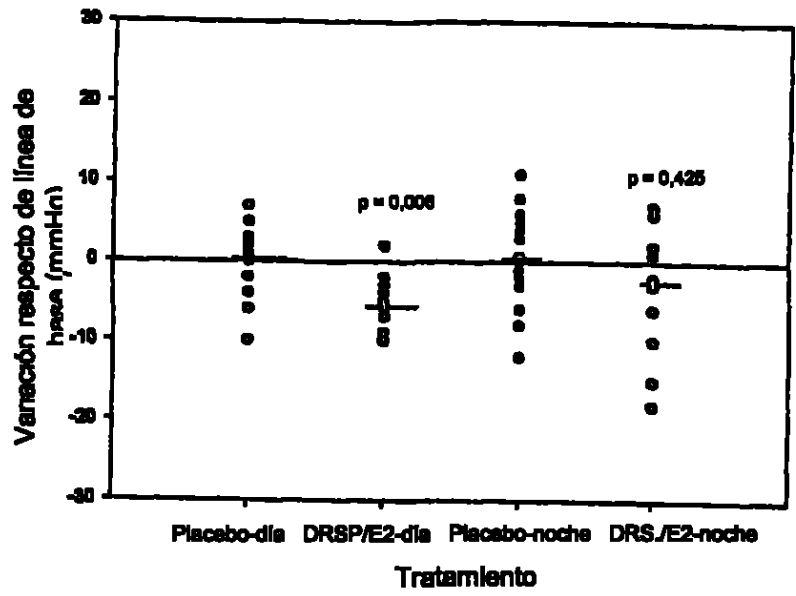


Fig. 6

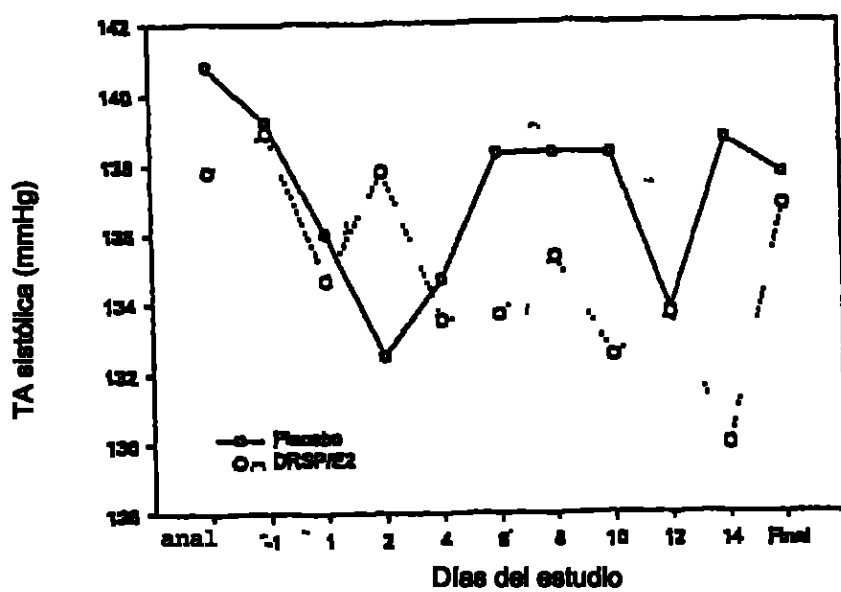


Fig 7

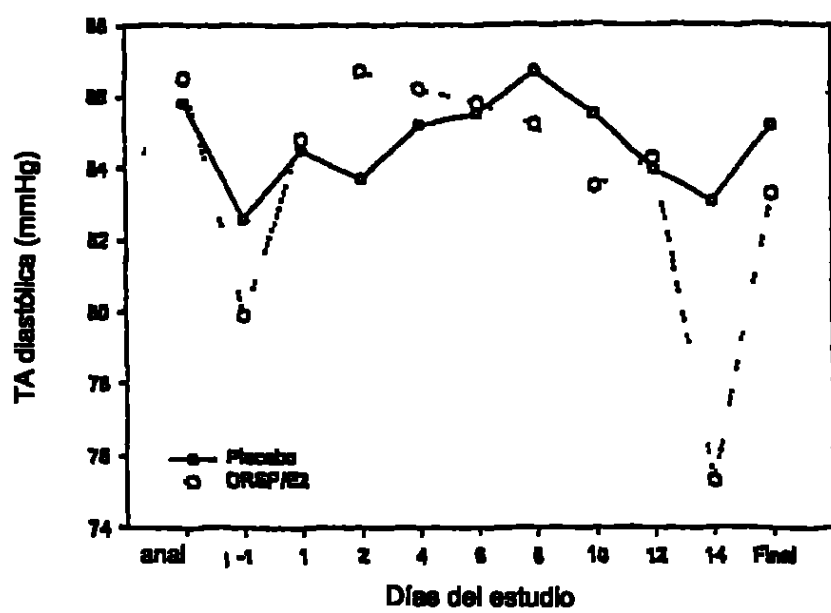


Fig 8

TRANSMITTAL LETTER TO THE
UNITED STATES RECEIVING OFFICE

Date	24 April 2003
International Application No.	To Be Assigned
Attorney Docket No.	BERLX 298 WO

I Certification under 37 CFR 1.10 (if applicable)

Express Mail mailing number

Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231

Signature of person mailing correspondence
--

Typed or printed name of person mailing correspondence
--

II. [X] New International Application

TITLE	TREATMENT OF HYPERTENSION IN WOMEN RECEIVING HORMONE REPLACEMENT THERAPY
-------	--

Earliest priority date (Day/Month/Year)
26 APRIL 2002

SCREENING DISCLOSURE INFORMATION In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. [] The invention disclosed was not made in the United States.
 B. [] There is no prior U.S. application relating to this invention.
 C. [X] The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority)

application no.	60/375,439	filed on	26 APRIL 2002
application no.		filed on	

- D. [] The present international application [] is identical to [] contains less subject matter than that found in the prior U.S. application(s) identified in paragraph C above.
 E. [X] The present international application [X] contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C above. The additional subject matter [X] DOES NOT ALTER [] MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 3.1 See 37 CFR 3.13.

III [] A Response to an Invitation from the RO/US. The following document(s) is(are) enclosed

- A. [] A Request for An Extension of Time to File a Response
 B. [] A Power of Attorney (General or Regular)
 C. [] Replacement pages

pages	of the request (PCT/RO/101)	pages	of the figures
pages	of the description	pages	of the abstract
pages	of the claims		

- D. [] Submission of Priority Documents
 E. [] Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV [] A Request for Rectification under PCT Rule 91 [] A Petition [] A Sequence Listing Diskette

V [] Other (please identify)-

The person signing this form is the: ☐ Applicant ☐ Attorney/Agent (Reg. No. 32,804) ☐ Common Representative

Typed name of signer	Harry B. [Signature]	Signature	
----------------------	----------------------	-----------	--

PCT

REQUEST

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

International Application No.

International Filing Date

Name of receiving Office and "PCT" International Application

Applicant's or agent's file reference
(if desired) (12 characters maximum) BERLX 298 WO

Box No. I TITLE OF INVENTION
TREATMENT OF HYPERTENSION IN WOMEN RECEIVING HORMONE REPLACEMENT THERAPY

Box No. II APPLICANT

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SCHERING AKTIENGESSELLSCHAFT
Mullenstrasse 178
D-13353 Berlin
DE

☐ This person is also inventor

Telephone No.

Facsimile No.

Teleprinter No

N/A

State (that is, country) of nationality DE

State (that is, country) of residence DE

This person is applicant ☐ all designated States ☒ all designated States except the United States of America
for the purposes of ☐ the United States of America only ☐ the States indicated in the Supplemental Box

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

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KARARA, Adel H,
64 Yuma Trail
Branchburg, NJ 08876
US

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (if this check-box is marked, do not fill in below.)

State (that is, country) of nationality US

State (that is, country) of residence US

This person is applicant ☐ all designated States ☐ all designated States except the United States of America
for the purposes of ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE, OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf ☒ agent ☐ common representative
of the applicant(s) before the competent International Authorities as:

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)

SHUBIN, Harry B
MILLEN WHITE, ZBLANO & BRANIGAN, P C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201

Telephone No.

(703) 243-6333

Facsimile No

(703) 243-6410

Teleprinter No

N/A

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes at least one must be marked)
Regional Patent

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

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

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

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet
[X] Any countries available at time of filing but not included on this sheet

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

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

1. If, in any of the Boxes, the space is insufficient to furnish all the information. In such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the caption of the Box in which the space was insufficient, in particular:

(i) If more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available. In such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below:

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

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

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

(v) If, in Box No. V the name of a State (or OAPI) is accompanied by the indication "parent of addition," or "certificate of addition," or if, in Box No. V the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part" in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application.

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

(vii) If, in Box No. VI, the earlier application is an ARIPO application. In such case, write "Continuation of Box No. VI" specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.

2. If, with regard to the procedural designation statement contained in Box No. V the applicant wishes to exclude any State(s) from the scope of that statement. In such case, write "Designation(s) excluded from procedural designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty. In such case write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box No. IV.

BRANIGAN, Alan E. J
BRANIGAN, Jennifer J
HEANEY, Brian P
MILLEN, I William
MOSES, John R.
RULAND, James E.
SHUBIN, Harry B
SOFF, John A.
TRAVERSO, Richard J
WHITE, John L.
ZELANO, Anthony J
McCARTHY, Robert E.
HENTON, Cinda
KINSEY, Nicole

All members of the firm of MILLEN, WHITE, ZELANO & BRANIGAN P C. at the address telephone and facsimile numbers as indicated in Box No. IV

Sheet No. 4

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is		
		national application country	regional application* regional Office	international application receiving Office
item (1) 26 APRIL 2002	60/375,439	US		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s) _____ (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen, the two-letter code may be used): ISA/EP	Request to use results of earlier search, reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority) Date (day/month/year) Number Country (or regional Office)
---	--

Box No. VIII CHECK LIST: LANGUAGE OF FILING

The international application contains the following number of sheets: request 4 sheets description (excluding sequence listing part) 14 sheets claims 3 sheets abstract 1 sheet drawings 3 sheets sequence listing part of description - sheets Total number of sheets 30 sheets	This international application is accompanied by the item(s) marked below 1 ☒ the calculation sheet (duplicate) 2 ☐ separate signed power of attorney 3 ☐ copy of general power of attorney reference number if any 4 ☐ statement explaining lack of signature 5 ☐ priority document(s) identified in Box No. VI as item(s). 6 ☐ translation of international application into (language): 7 ☐ separate indications concerning deposited microorganism or other biological material 8 ☐ nucleotide and/or amino acid sequence listing in computer readable form 9 ☒ other (specify): Transmittal
Figure of the drawings which should accompany the abstract: FIG 1	Language of filing of the international application ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Must be each signature indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).



Harry B. SHUBIN
Agent for the Applicant(s)

For receiving Office use only

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

For International Bureau use only

Date of receipt of the record copy by the International Bureau.

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

For receiving Office use only

PCT

FEE CALCULATION SHEET
Annex to the Request

International application No.

Applicant's or agent's
file reference BERLX 298 WODate stamp of the receiving
Office

Applicant SCHERING AKTIENGESELLSCHAFT et al

CALCULATION OF PRESCRIBED FEES

1 TRANSMITTAL FEE - -

240 | T

2 SEARCH FEE

936 | S

International search to be carried out by ISA/EP

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3 INTERNATIONAL FEE

Basic Fee

The international application contains 30 sheets.

first 30 sheets - - - -

b1 | 476

 X 12.00

remaining sheets X additional amount =

b2 |

Add amounts entered at b1 and b2 and enter total at B

476 | B

Designation Fees

The international application contains ALL designations5 X 104.00
payable (maximum 5)

520 | D

Add amounts entered at B and D and enter total at I

996 | I

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

4. FEE FOR PRIORITY DOCUMENT (if applicable)

20 | P

5 TOTAL FEES PAYABLE

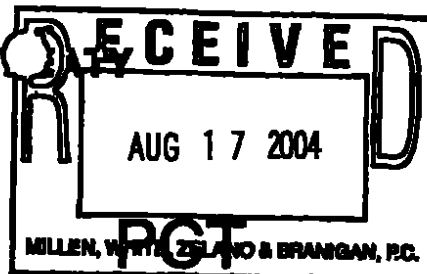
Add amounts entered at T, S, I and P, and enter total in the
TOTAL boxUSD \$ 2192.00
TOTAL☐ The designation fee is not paid at this time.

MODE OF PAYMENT

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

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/US ☐ is hereby authorized to charge the total fees indicated above to my deposit account.☒ (this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.☒ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.13-3482
Deposit Account Number24 April 2003
Date (day/month/year)Signature: H. B. SHUBIN Registration No. 32,004



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To

Shubin, Harry B
MILLEN, WHITE, ZELANO
& BRANIGAN P C
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NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71 1)

Date of mailing
(day/month/year) 13 08.2004

Applicant's or agent's file reference
BERLX 298 WO

IMPORTANT NOTIFICATION

International application No. PCT/US 03/12596	International filing date (day/month/year) 24 03.2003	Priority date (day/month/year) 26 04.2002
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Applicant
SCHERING AKTIENGESELLSCHAFT et al

- 1 The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application
- 2 A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices
- 3 Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices
- 4 REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301)

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims

Name and mailing address of the international preliminary examining authority  European Patent Office D-80298 Munich Tel +49 89 2399 0 Tx: 523656 epmu d Fax +49 89 2399 4465	Authorized Officer Hutterer, G Tel +49 89 2399-8088 <i>DKT P 2/17/04</i>
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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BERLX 298 WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/18)	
International application No. PCT/US 03/12596	International filing date (day/month/year) 24 03 2003	Priority date (day/month/year) 28 04 2002	
International Patent Classification (IPC) or both national classification and IPC A61K31/585			
Applicant SCHERING AKTIENGESELLSCHAFT et al			
1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36 2 This REPORT consists of a total of 6 sheets, including this cover sheet. ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT) These annexes consist of a total of 1 sheets.			
3 This report contains indications relating to the following items. I ☒ Basis of the opinion II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application			
Date of submission of the demand 19 11 2003		Date of completion of this report 13 08 2004	
Name and mailing address of the international preliminary examining authority  European Patent Office D-80298 Munich Tel. +49 89 2369 0 Tx. 523656 epmu d Fax +49 89 2369 4465		Authorized Officer Hornich, E Telephone No. +49 89 2369-6721 	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No PCT/US 03/12596

I Basis of the report

- 1 With regard to the elements of the International application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-14 as originally filed

Claims, Numbers

1-15 filed with telefax on 16 07 2004

Drawings, Sheets

1-8 as originally filed

- 2 With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the International application was filed, unless otherwise indicated under this item

These elements were available or furnished to this Authority in the following language , which is

- ☐ the language of a translation furnished for the purposes of the International search (under Rule 23.1(b))
- ☐ the language of publication of the International application (under Rule 48.3(b))
- ☐ the language of a translation furnished for the purposes of International preliminary examination (under Rule 55.2 and/or 55.3)

- 3 With regard to any nucleotide and/or amino acid sequence disclosed in the International application, the International preliminary examination was carried out on the basis of the sequence listing

- ☐ contained in the International application in written form
- ☐ filed together with the International application in computer readable form
- ☐ furnished subsequently to this Authority in written form
- ☐ furnished subsequently to this Authority in computer readable form
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

- 4 The amendments have resulted in the cancellation of

- ☐ the description, pages
- ☐ the claims, Nos
- ☐ the drawings, sheets

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No **PCT/US 03/2596**

5 ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c))
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report)

6 Additional observations, if necessary

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

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

- ☐ the entire international application,
- ☒ claims Nos 1-15 (with regard to industrial applicability)

because

- ☒ the said international application, or the said claims Nos 1-15 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify)

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos are so unclear that no meaningful opinion could be formed (*specify*)
- ☐ the claims, or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed
- ☐ no international search report has been established for the said claims Nos

2 A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions.

- ☐ the written form has not been furnished or does not comply with the Standard
- ☐ the computer readable form has not been furnished or does not comply with the Standard

V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Statement

Novelty (N)	Yes	Claims	2-8, 11
	No	Claims	1, 9, 10, 12-15
Inventive step (IS)	Yes	Claims	
	No	Claims	1-15
Industrial applicability (IA)	Yes	Claims	-
	No	Claims	

2 Citations and explanations

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No

PCT/US 03/12596**see separate sheet**

SECTION III

- 1 Claims 1-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67 1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT)

SECTION V**2 References**

- D1 PRESTON RICHARD A ET AL 'Additive effect of drospirenone/17-beta estradiol (DRSP/E2) on 24-hour ambulatory blood pressure in hypertensive postmenopausal women receiving enalapril maleate' AMERICAN JOURNAL OF HYPERTENSION, vol 15, no 4 Part 2, April 2002 (2002-04-16), page 235A Seventeenth Annual Scientific Meeting of the American Society of Hypertension, New York, N Y, USA, May 14-18, 2002, April, 2002 ISSN 0895-7061
- D2 WO 01 52857 A
- D3 OELKERS W 'Drospirenone--a new progestogen with antimineralocorticoid activity, resembling natural progesterone' THE EUROPEAN JOURNAL OF CONTRACEPTION & REPRODUCTIVE HEALTH CARE THE OFFICIAL JOURNAL OF THE EUROPEAN SOCIETY OF CONTRACEPTION ENGLAND DEC 2000, vol 5 Suppl 3, December 2000 (2000-12), pages 17-24, ISSN 1362-5187
- D4 NORMAN P ET AL 'Drospirenone Contraceptive, hormone replacement therapy, aldosterone antagonist, progestogen 1,2-dihydrospirorenone, SH-470, ZK-30595' DRUGS OF THE FUTURE, vol 25, no 12, December 2000 (2000-12), pages 1247-1256, ISSN 0377-8282
- D5 WO 01 15701 A

3 Novelty (Art. 33(2) PCT)

D2 discloses the use of a composition comprising an estrogen (estradiol) and drospirenone for hormone replacement therapy. The dosages of the compounds correspond to the dosages defined in the present application. The use of the

composition for hormone replacement therapy is especially useful 'where the woman suffers from other disorders not compatible with the use of an exogenous source of estrogen (such as hypertension,) ' very low amounts of estrogen may be in the composition In such embodiments, the dose of drospirenone may be such that the disorder, disease or symptom is alleviated' (p 9, second paragraph)

The passage cited above is in clear context with the compositions disclosed in D2 and therefore as well with the dosages disclosed in D2

D2 is thus considered *anticipating* the subject-matter of claims 1, 9, 10 and 12-15.

4 Inventive Step (Art. 33(3) PCT)

D1 discloses the antihypertensive effect of a composition comprising drospirenone and 17beta-estradiol in hypertensive postmenopausal women receiving enalapril maleate

The difference between D1 and the claims of the present application which would appear to be novel is the *dosage* of the compounds However, the dosages defined in the present claims are common for HRT (see e g D2)

An *inventive step* could therefore *not* be *acknowledged* for the subject-matter of claims 2-8 and 11.

5 Industrial Applicability (Art. 33(4) PCT)

For the assessment of the present claims 1-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States The patentability can also be dependent upon the formulation of the claims The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment

NEW CLAIMS 1-15 - PCT/US03/12596

1 A method to lower blood pressure and effect hormone replacement therapy (HRT) in a hypertensive human female patient, comprising administering to said patient drospirenone (DRSP) in an amount of 1-3 mg/day and 17 β -estradiol in an amount of 1-3 mg/day

2 The method of claim 1, further comprising administering antihypertensive medication to said patient.

3 The method of claim 2, wherein said patient began taking the antihypertensive medication before initiation of the administration of said DRSP and 17 β -estradiol

4 The method of claim 2, wherein said antihypertensive medication is administered in conjunction with the administration of said DRSP and 17 β -estradiol.

5 The method of claim 2, wherein administration of said antihypertensive medication is initiated after initiation of administration of said DRSP and 17 β -estradiol.

6 The method of claim 2, wherein said antihypertensive medication is a diuretic, an α -adrenergic blocking agent, a β -adrenergic blocking agent, a CNS-acting agent, an adrenergic neuron blocking agent, a vasodilator, an angiotensin I converting enzyme (ACE) inhibitor, a calcium channel blocker, a renin inhibitor or a combination thereof

7 The method of claim 6, wherein said antihypertensive medication is an ACE inhibitor

8 The method of claim 7, wherein said ACE inhibitor is benazepril, captopril, enalapril, enalaprilat, fosinopril, lisinopril, perindopril, quinopril, quinoprilat, ramipril, transolapril, or zofenopril

9 The method of claim 1, wherein said DRSP and 17 β -estradiol are administered orally, transdermally or by injection.

10 The method of claim 9, wherein said DRSP and 17 β -estradiol are administered orally

11 The method of claim 2, wherein said antihypertensive medication is enalapril maleate.

12 The method of claim 1, wherein the patient is perimenopausal, menopausal or post-menopausal

13 The method of claim 1, wherein said hypertension is mild or severe.

14 The method of claim 1, wherein said amount of DRSP is 3 mg and said amount of 17 β -estradiol is 1 mg.

15 The method of claim 1, wherein said amount of DRSP is 1 mg and said amount of 17 β -estradiol is 1 mg.

AMENDED SHEET

**TRATADO DE COOPERACIÓN DE PATENTES
PCT**

SELLO DE RECIBO DEL PCT – Agosto 17, 2004

De la AUTORIDAD DE EXAMEN PRELIMINAR INTERNACIONAL

Para

Shubin, Harry B

MILLEN, WHITE, ZELANO & BRANIGAN P C

Arlington Courthouse Plaza 1

2200 Clarendon Boulevard Suite 1400

Arlington, Virginia 22201

ESTADOS UNIDOS DE AMÉRICA

**NOTIFICACIÓN DE TRANSMISIÓN DEL REPORTE DE EXAMEN
PRELIMINAR INTERNACIONAL**

(PCT Regla 71 1)

Referencia de archivo del solicitante o agente

BERLX 298 WO NOTIFICACIÓN IMPORTANTE

Solicitud internacional No PCT/US 03/12596

Fecha de presentación internacional (día/mes/año) 24 03 2003

Fecha de prioridad /día/mes/año) 26 04 2002

Solicitante

SCHERING AKTIENGESELLSCHAFT y otros

- 1 Se le notifica al solicitante por este medio que la Autoridad Internacional de Examen Preliminar transmite aquí anexo el reporte de examen preliminar internacional y sus anexos, si hay alguno, establecido en la solicitud internacional
- 2 Una copia de este reporte y sus anexos, si hay alguno, está siendo transmitida a la Oficina Internacional para comunicación a todas las Oficinas elegidas
- 3 Cuando sea requerido por alguna de las Oficinas elegidas, la Oficina Internacional preparará una traducción al Inglés del reporte (pero no de los anexos) y transmitirá dicha traducción a esas Oficinas
- 4 **RECORDATORIO**

El solicitante debe entrar a la fase nacional ante cada Oficina elegida llevando a cabo algunas actuaciones (presentación de traducciones y pago de impuestos nacionales) dentro de los 30 meses desde la fecha de prioridad (o posteriormente en algunas Oficinas) (Artículo 39(1)) (ver también el recordatorio enviado por la Oficina Internacional con la Forma PCT/IB/301)

Cuando una traducción de la solicitud internacional deba ser suministrada por una Oficina elegida, esa traducción debe contener una traducción de cualquier anexo al reporte de examen preliminar internacional, es la responsabilidad del solicitante preparar y suministrar dicha traducción directamente a cada concerniente Oficina elegida.

Para adicionales detalles de los límites de tiempo aplicables y requerimientos de las Oficinas elegidas, ver el Volumen II de la Guía del Solicitante del PCT

Se llama la atención al solicitante del Artículo 33(5), el cual prevé que los criterios de novedad, altura inventiva y aplicabilidad industrial descritos en el Artículo 33(2) a (4) sirven meramente para el propósito del examen preliminar internacional y que "cualquier Estado Contratante puede aplicar adicionales o diferentes criterios con el propósito de decidir si, en ese Estado, las invenciones reivindicadas son patentables o no" (ver además el Artículo 27(5)) Dichos criterios adicionales puede relacionarse, por ejemplo, con excepciones a la patentabilidad, requerimientos para permitir la divulgación, claridad y sustento para las reivindicaciones

Nombre y dirección de envío de la autoridad de examen preliminar internacional
 Oficina Europea de Patentes
 D-80298 Munich
 Tel +49 89 2399 – 0 Tx 523656 epmu d Fax +49 89 2399 – 4465

Funcionario Autorizado

Hutterer, G

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SELLO DE LA OFICINA EUROPEA DE PATENTES

Forma PCT/IPEA/416 (Enero 2004)

**TRATADO DE COOPERACIÓN DE PATENTES
 PCT
 REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL
 (PCT Artículo 36 y Regla 70)**

Referencia de archivo del solicitante o agente

BERLX 298 WO

PARA ACCIÓN ADICIONAL Ver Notificación de Transmisión del Reporte de Examen Preliminar Internacional (Forma PCT/IPEA/416)

Solicitud internacional No PCT/US 03/12596

Fecha de presentación internacional (día/mes/año) 24 03 2003

Fecha de prioridad /día/mes/año) 26 04 2002

Clasificación Internacional de Patentes (IPC) o tanto clasificación nacional como IPC
 A61K31/585

Solicitante

SCHERING AKTIENGESELLSCHAFT y otros

- 1 Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad Internacional de Examen Preliminar y es transmitida al solicitante de acuerdo con el Artículo 36
- 2 Este REPORTE consiste de un total de 8 hojas, incluyendo esta hoja de cubierta

X Este reporte también está acompañado por ANEXOS, es decir, hojas de la descripción, reivindicaciones y/o dibujos que ha sido corregidos y son la base para este reporte y/o hojas que contienen rectificaciones hechas ante esta Autoridad (ver Regla 70 16 y Sección 607 de las Instrucciones Administrativas bajo el PCT)

Estos anexos consisten de un total de 1 hojas

- 3
- I

X

Base de la opinión
- II

Prioridad
- III

X

No establecimiento de opinión con respecto a novedad, paso inventivo y aplicabilidad industrial
- IV

Falta de unidad de invención
- V

X

Declaración con motivada bajo la Regla 66 2(a)(ii) con respecto a novedad, paso inventivo o aplicabilidad industrial
- VI

citaciones y explicaciones que soportan cada declaración
- VII

Algunos documentos citados
- VIII

Algunos defectos en la solicitud internacional
- VIII

Algunas observaciones sobre la solicitud internacional

Fecha de presentación de la solicitud 19 11 2003

Fecha de completado este reporte 4 Febrero 13 08 2004

Nombre y dirección de envío de la autoridad de examen preliminar internacional

Oficina Europea de Patentes

D-80296 Munich

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Funcionario autorizado

Hornich, E

Teléfono No +49 89 2399-8721

Forma PCT/IPEA/409 (Hoja de cubierta) (Enero 2004)

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No PCT/US 03/12596

- I
- Base del reporte
- 1
- Con respecto a los elementos de la solicitud internacional (Las hojas de reemplazo que han sido suministradas a la Oficina receptora como respuesta a una invitación bajo el Artículo 14 son referidas en este reporte como “presentadas originalmente” y no están anexas a este reporte debido a que no contienen correcciones (Reglas 70 16 y 70 17))
- Descripción, páginas 1-14
- como se presentaron originalmente
- Reivindicaciones, números 1-15
- presentadas por telefax el 16 07 2004
- Dibujos, hojas 1-8
- como se presentaron originalmente

2 Con respecto al idioma, todos los elementos marcados arriba estaban disponibles o fueron suministrados a esta Autoridad en el idioma en el cual fue presentada la solicitud internacional, a menos que se indique de otra forma bajo este ítem

Estos elementos estaban disponibles o fueron suministrados a esta Autoridad en el siguiente idioma , el cual es el idioma de una traducción suministrada para el propósito de la búsqueda internacional (bajo la Regla 23 1(b)),

el idioma de la publicación de la solicitud internacional (bajo la Regla 48 3(b)),
el idioma de una traducción suministrada para el propósito del examen preliminar internacional (bajo la Regla 55 2 y/o 55 3),

3 Con respecto a cualquier nucleótido y/o secuencia de aminoácidos divulgados en la solicitud internacional, el examen preliminar internacional se llevó a cabo en la base del listado de secuencias

contenido en la solicitud internacional en forma escrita
presentado conjuntamente con la solicitud internacional en forma legible por computador,

suministrado subsecuentemente a esta Autoridad en forma escrita,

suministrado subsecuentemente a esta Autoridad en forma legible por computador,

Se ha suministrado la declaración de que el listado de secuencias escrito suministrado subsecuentemente no entra más allá de la divulgación en la solicitud internacional como se presentó

Se ha suministrado la declaración de que la información registrada en forma legible por computador subsecuentemente es idéntica al listado de secuencias escrito

4 Las correcciones han dado como resultado la cancelación de la descripción, páginas las reivindicaciones, Nos los dibujos, hojas

5 Este reporte ha sido establecido como si (alguna de) las correcciones no se hayan hecho, pues han sido consideradas como más allá de las divulgaciones como se presentaron (Regla 70 2(c))
(Se debe hacer referencia a cualquier hoja de reemplazo que contiene dichas correcciones como bajo el ítem 1 y anexas a este reporte)

6 Observaciones adicionales, si son necesarias

III No establecimiento de opinión con respecto a novedad, altura inventiva y aplicabilidad industrial

1 Las preguntas acerca de si la invención reivindicada parece ser novedosa, involucra altura inventiva (no es obvia), o es industrialmente aplicable no se han examinado con respecto a

la solicitud internacional completa

X las reivindicaciones Nos 1-15 (con respecto a la aplicabilidad industrial)

debido a que

X la mencionada solicitud internacional, o las mencionadas reivindicaciones Nos 1-15 (con respecto a la aplicabilidad industrial) se relacionan con la siguiente materia sujeto que no requiere de un examen preliminar internacional (especificar)

Ver hoja separada

la descripción, reivindicaciones o dibujos (indicar abajo los elementos particulares) o dichas reivindicaciones Nos son tan poco claras que no se puede formar una opinión importante (especificar)

las reivindicaciones, o las mencionadas reivindicaciones Nos están tan inadecuadamente sustentadas en la descripción que no se puede formar una opinión importante

no se ha establecido un reporte de búsqueda internacional para las mencionadas reivindicaciones Nos

- 2 No se puede llevar a cabo un examen preliminar internacional significativo debido a la falta del nucleótido y/o listado de secuencia de aminoácidos para cumplir con el estándar provisto en el anexo C de las instrucciones administrativas
no se ha suministrado la forma escrita o no cumple con el estándar
la forma legible por computador no se ha suministrado o no cumple con el estándar

V Declaración motivada bajo el Artículo 35(2) con respecto a la novedad, el paso inventivo o la aplicabilidad industrial, citaciones y explicaciones que sustentan dicha declaración

1 Declaración

Novedad (N)	Si	Reivindicaciones	2-8, 11
	No	Reivindicaciones	1, 9, 10, 12-15
Paso inventivo (IS)	Si	Reivindicaciones	
	No	Reivindicaciones	1-15
Aplicabilidad Industrial (IA)	Si	Reivindicaciones	
	No	Reivindicaciones	

- 2 Citaciones y explicaciones
Ver hoja separada

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL HOJA SEPARADA
Solicitud internacional No PCT/US 03/12596

SECCIÓN III

- 1 Las reivindicaciones 1-15 se relacionan con materia sujeto considerada por esta Autoridad como cubiertas por las previsiones de la Regla 67 1(iv) PCT. Consecuentemente, no se formulará opinión con respecto a la aplicabilidad industrial de la materia sujeto de estas reivindicaciones (Artículo 34(4)(a)(I) PCT)

SECCIÓN V

- 2 Referencias

D1 PRESTON RICHARD A Y OTROS 'Efecto aditivo de drospirenona/17-beta estradiol (DRSP/E2) en la presión sanguínea ambulatoria 24 horas en mujeres hipertensas post menopáusicas que reciben enalapril maleato' DIARIO AMERICANO DE HIPERTENSIÓN, volumen 15, no 4 parte 2, Abril 2002 (2002-04-16), página 235A. Decimoséptimo Encuentro Científico Anual de la Sociedad Americana de Hipertensión, New York, NY, USA, Mayo 14-18, 2002, Abril, 2002 ISSN, 0895-7061

- D2 WO 02 52857 A
- D3 OELKERS W 'Drospirenona-un nuevo progestógeno con actividad anti-mineral-corticoide, que se asimila a la progesterona natural' EL DIARIO EUROPEO DE LA CONTRACEPCIÓN, INGLATERRA DICIEMBRE 2000, volumen 5, Suplemento 3, Diciembre 2000 (2000-12), páginas 17-24, ISSN 1362-5187
- D4 NORMAN P Y OTROS 'Drospirenona. Contraceptivo, terapia de reemplazo hormonal, aldosterona antagonista, progestógeno 1,2-dihidrospirorenona, SH-470, ZK-30595, 'DROGAS DEL FUTURO, volumen 25, nol 12, Diciembre 2000 (2000-12), páginas 1247-1256, ISSN 0377-8282
- D5 WO 01 15701 A

3 Novedad (Artículo 33(2) PCT)

D2 divulga el uso de una composición que comprende un estrógeno (estradiol) y drospirenona para terapia de reemplazo de hormonas. Las dosificaciones de los compuestos corresponden a las dosificaciones definidas en la presente solicitud. El uso de la composición para la terapia del reemplazo de hormonas es especialmente útil cuando la mujer sufre de otros desórdenes no compatibles con el uso de una fuente de exógenos de estrógeno (tal como hipertensión), 'muy bajas cantidades de estrógeno pueden estar en la composición. En dichas modalidades, la dosis de drospirenona puede ser tal que el desorden, enfermedad o síntoma se alivia.' (Página 9, segundo párrafo). El pasaje citado arriba está en claro contexto con las composiciones divulgadas en D2 y consecuentemente igualmente con las dosificaciones divulgadas en D2.

Se considera que D2 anticipa la materia sujeto de las reivindicaciones 1, 9, 10 y 12-15.

4 Paso inventivo

D1 divulga el efecto anti hipertenso de una composición que comprende drospirenona y 17 beta estradiol en mujeres hipertensas post menopáusicas que reciben enalapril maleato.

La diferencia entre D1 y las reivindicaciones de la presente solicitud que pueden parecer novedosas es la dosificación de los compuestos, sin embargo, las dosificaciones definidas en las presentes reivindicaciones son comunes para HRT (ver por ejemplo D2).

No podría entonces reconocerse actividad inventiva para la materia sujeto de las reivindicaciones 2-8 y 11.

5 Aplicabilidad industrial (Artículo 33(4) PCT)

Para la aceptación de las presentes reivindicaciones 1-15 con respecto a la pregunta de si son industrialmente aplicables. No hay un criterio unido en los Estados Contratantes del PCT. La patentabilidad puede además ser dependiente de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como industrialmente aplicable la materia sujeto de las reivindicaciones al uso de un compuesto en tratamiento médico, pero puede permitir, sin embargo, reivindicaciones a un compuesto conocido para un

primer uso en tratamiento médico y el uso de un compuesto tal para la
fabricación de un medicamento para un nuevo tratamiento médico



PATENT COOPERATION TREATY

RECEIVED AUG 15 2003 INTERNATIONAL BUREAU	PCT/US03/12596 100
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PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To

Millen, White, Zelano & Branigan P.C.

SHUBIN, Harry, B.
 Millen, White, Zelano & Branigan,
 P.C.
 Suite-1400
 Arlington Courthouse Plaza 1
 2200 Clarendon Boulevard
 Arlington, VA 22201
 United States of America

Date of mailing (day/month/year) 22 July 2003 (22 07 03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference BERLX 288 (VQ)	International application No. PCT/US03/12596

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below

Name(s) of the applicant(s) and State(s) for which they are applicants

SCHERING AKTIENGESSELLSCHAFT (for all designated States except US)
 KARARA, Adel, H (for US)

International filing date

24 March 2003 (24.03.03)

Priority date(s) claimed

28 April 2002 (28 04 02)

Date of receipt of the record copy by the International Bureau

28 May 2003 (28 05 03)

List of designated Offices

AP, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW
 EA - AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 EP - AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR
 OA - BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 National: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EQ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KB, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to

☒ time limits for entry into the national phase - see updated important information (as of April 2002)

☒ confirmation of precautionary designations (if applicable)

☐ requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority

The International Bureau of WIPO 34, chemin des Colombettes 1211 Genève 28, Switzerland	Authorized officer Laurence NICOLO
Facsimile No. (41-22) 338-70-80	Telephone No. (41-22) 338 8849

Form PCT/IB/301 (April 2002)

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8/15/03-LD

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office where a demand for international preliminary examination is filed before the expiration of 18 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(J) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 18826, 18832 and 18834, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limits), Office by Office, refer to the PCT Gazette ("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site including those of the Gazette, Newsletter and Guide, at <http://www.wipo.int/pct/en/index.html>.

Information about the requirements for filing a demand for international preliminary examination is set out in the PCT Applicant's Guide, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.8(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.8(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.8(c) before the expiration of 15 months from the priority date (this time limit may not be extended). If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. The Notice of confirmation and payment must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 18 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 18-month time limit (Rule 17 1(d)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 18-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17 1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 18-month time limit is the filing date of the earliest application whose priority is claimed.

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

SHUBIN, Harry, B.
Millen, White, Zelano & Branigan,
P C
Suite 1400
Arlington Courthouse Plaza 1
2200 Clarendon Boulevard
Arlington, VA 22201
United States of America

Date of mailing (day/month/year) 22 July 2003 (22 07 03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference BERLX 288 WO	
International application No. PCT/JS03/12596	International filing date (day/month/year) 24 March 2003 (24.03.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 26 April 2002 (26 04.02)
Applicant SCHERING AKTIENGESELLSCHAFT et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17 1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17 1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17 1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
26 April 2002 (26.04.02)	60/375,439	US	27 May 2003 (27 05 03)

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

Facsimile No. (41-22) 338 70 90

Authorized officer

Laurence NICOLO

Telephone No. (41-22) 338 89 48

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47 1(c) first sentence)

To

SHUBIN Harry B.
Millen White Zelano & Branigan, P.C. NOV 18 2003
Suite 1400
Arlington Courthouse Plaza 1
2200 Clarendon Boulevard
Arlington VA 22201
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
29 October 2003 (29 10 03)

Applicant's or agent's file reference
BERLX 298(WO)

IMPORTANT NOTICE

International application No
PCT/US03/12596

International filing date (day/month/year)
24 March 2003 (24 03 03)

Priority date (day/month/year)
26 April 2002 (26 04 02)

Applicant

SCHERING AKTIENGESELLSCHAFT et al

- 1 Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice

AU, AZ, BY, CH, CN, CO, DE, DZ, HU JP, KG KP KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47 1(c) third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s)

- 2 The following designated Offices have waived the requirement for such a communication at this time.

AE AG AL, AM AP, AT, BA, BB, BG, BR, BZ, CA, CR CU, CZ DK, DM EA EC EE EP, ES, FI, GB, GD GE, GH
GM, HR, ID IL, IN, IS, KE KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW MX, NO, NZ, OA, OM PH PL, PT, RO,
SC, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49 1(a-bis))

- 3 Enclosed with this notice is a copy of the international application as published by the International Bureau on 06 November 2003 (06 11 03) under No 03/090755

4. TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter* October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide* Volume II, National Chapters, all available from WIPO's Internet site at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide* Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

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

Authorized officer

Judith Zahra

Facsimile No.(41 22) 740 14.35

Telephone No.(41 22) 338.91 11

Dtd 11/24/03-HR

IN THE U. S. PATENT AND TRADEMARK OFFICE AS IPEA
OR
IN THE EUROPEAN PATENT OFFICE AS IPEA

International Application No PCT/US03/12596
 International Filing Date 24 March 2003

Priority Date Claimed
 26 April 2002

Title of Invention

**TREATMENT OF HYPERTENSION IN WOMEN RECEIVING HORMONE
 REPLACEMENT THERAPY**

Applicant(s)

SCHERING AKTIENGESELLSCHAFT et al.

Assistant Commissioner for Patents
 Box PCT
 Attn IPEA/US
 Washington, D C 20231

OR

European Patent Office
 Attn IPEA/EP
 D-80298 Munich
 GERMANY
 VIA FACSIMILE -011-49-89-23994465

**RESPONSE TO WRITTEN OPINION IN THE
 INTERNATIONAL APPLICATION**

Sir

In response to the Written Opinion in the International Application, dated January 21, 2004, Applicant requests that claims 1-18 be cancelled and replaced with attached new claims 1-15

The new claims are novel For example, all now contain the limitation of original claim 13 which was found to be novel in the written opinion

These claims also reflect an inventive step because the blood pressure lowering effect is unexpectedly higher for the combination, e.g , than drospirenone alone For example, the lowest effective dose of the conventional blood pressure lowering agent, spironolactone, is 100 mg Drospirenone is known to be roughly equivalent to about 7 mg of spironolactone Thus, 3 mg of drospirenone are equivalent to 21 mg of spironolactone well less than the minimum effective dose of spironolactone For lowering of blood pressure, 200 mg of

Our File No. BERLX-298-WO

spironolactone is typically used. Thus, the amount of drospirenone used is many times less. Nevertheless, the claimed combination of drospirenone and 17 β -estradiol has a more pronounced effect than drospirenone alone, or 17 β -estradiol alone, suggesting a synergistic effect for the combination product. This is precisely opposite to, and thus unexpected from, the passage quoted in the written opinion from page 9 of D2.

Respectfully submitted,



Anthony J. Zelano, Reg No 27,969
Attorney for Applicants

MILLEN, WHITE, ZELANO
& BRANIGAN, P C
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2200 Clarendon Blvd Suite 1400
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Attorney Docket No BERLX-0298-WO

Date July 16, 2004

AJZ bcf

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NEW CLAIMS 1-15 - PCT/US03/12596

1 A method to lower blood pressure and effect hormone replacement therapy (HRT) in a hypertensive human female patient, comprising administering to said patient drospirenone (DRSP) in an amount of 1-3 mg/day and 17 β -estradiol in an amount of 1-3 mg/day

2 The method of claim 1, further comprising administering antihypertensive medication to said patient

3 The method of claim 2, wherein said patient began taking the antihypertensive medication before initiation of the administration of said DRSP and 17 β -estradiol

4 The method of claim 2, wherein said antihypertensive medication is administered in conjunction with the administration of said DRSP and 17 β -estradiol

5 The method of claim 2, wherein administration of said antihypertensive medication is initiated after initiation of administration of said DRSP and 17 β -estradiol

6 The method of claim 2, wherein said antihypertensive medication is a diuretic, an α -adrenergic blocking agent, a β -adrenergic blocking agent, a CNS-acting agent, an adrenergic neuron blocking agent, a vasodilator, an angiotensin I converting enzyme (ACE) inhibitor, a calcium channel blocker, a renin inhibitor or a combination thereof

7 The method of claim 6, wherein said antihypertensive medication is an ACE inhibitor

8 The method of claim 7, wherein said ACE inhibitor is benazepril, captopril, enalapril, enalaprilat, fosinopril, lisinopril, pentopril, quinapril, quinaprilat, ramipril, transolapril, or zofenopril

9 The method of claim 1, wherein said DRSP and 17 β -estradiol are administered orally, transdermally or by injection

10 The method of claim 9, wherein said DRSP and 17 β -estradiol are administered orally

11 The method of claim 2, wherein said antihypertensive medication is enalapril maleate

12 The method of claim 1, wherein the patient is perimenopausal, menopausal or post-menopausal

13 The method of claim 1, wherein said hypertension is mild or severe

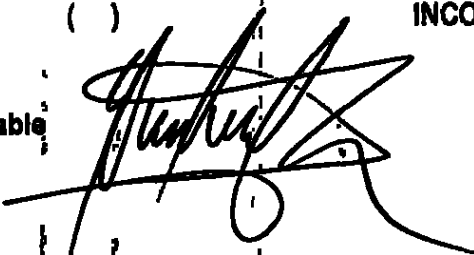
14 The method of claim 1, wherein said amount of DRSP is 3 mg and said amount of 17 β -estradiol is 1 mg

15 The method of claim 1, wherein said amount of DRSP is 1 mg and said amount of 17 β -estradiol is 1 mg.

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
- Indicación de que se solicita la concesion de una patente	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud	()	()
- Descripción de la invención	()	()
- Dibujos de ser estos pertinentes	()	()
- Comprobante de Pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
DISEÑO INDUSTRIAL	()	()
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO	()	()
- Indicación de que solicita el registro de un Esquema de trazado	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud	()	()
- Representación grafica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable



Fecha

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04117322 00000000 Folios: 106
Fecha (MD) 2004-11-23 11:04:35
Tramite : 011 PCT-PATENT 379 FASE MACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

108
108

2020

Bogotá D C

Doctor(a) A
GUSTAVO HOLLMANN RESTREPO
Apoderado(a)
SCERING AG

11477

REFERENCIA	Radicación N°	04-117322
	Solicitud internacional	PCT/US03/12596
	Fecha inicio fase nacional	2004-11-26
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art 26-k Decisión 486)
- La solicitud no contiene la traducción de los anexos del reporte de examen preliminar internacional (Art 36 2 b) del tratado PCT)

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e), del capítulo quinto del título primero de la Circular Unica N° 10 de 2001.


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

El anterior requerimiento fue notificado por fijación en lista de fecha,
17 DIC. 2004
202063