

113
#3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 08 - 68,582
FECHA : AGOSTO 28 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-136797-00001-0000
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-136797-00001-0000
Fecha: 2008-08-28 14:07:41 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 32

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	4791509	01/07/2008	532,000.00

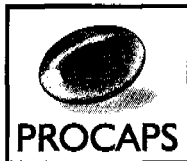
***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEMAS COMERCIALES	266,000.00
		TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



114 12
Hf

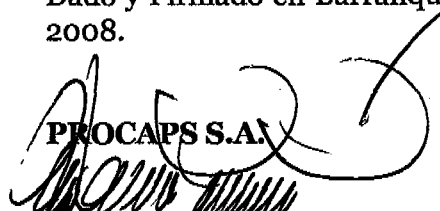
PODER ESPECIAL

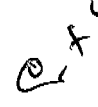
Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 07 136.797, titulada "**COMPOSICIONES Y MÉTODOS PARA EL TRATAMIENTO DE SÍNTOMAS RELACIONADOS CON EL CICLO**", cuyo titular es **WYETH**, publicada en la gaceta No. 592 del 30 de Mayo de 2008.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

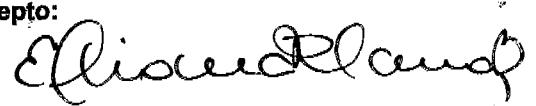
De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 22 días del mes de Agosto de 2008.


PROCAPS S.A.


C.C. N° 16.251.923
NIT: 890.106.527-5
Representante Legal

Acepto:



ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

SEGUNDA NOTARIA LEGAL REPUBLICA DE COLOMBIA NOTARIA SEGUNDA

ADY ISABEL NAMEN SEGURA

NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA

CERTIFICA

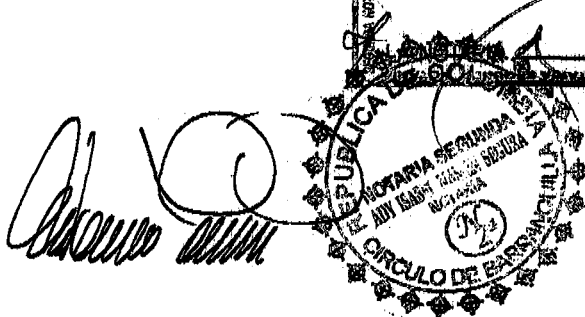
Que la(s) firma(s) que aparece(n) en el documento que antecede se asemeja(n) a la(s) de WALTER
TORRES TATE KOLLE

Que aparece(n) registrada(s) en esta Notaria previa confrontación de la(s) misma(s).

(Decreto 960/70)

Barranquilla 26 de Agosto de 2008

[Signature]



PRESENTACION PERSONAL

El notario describe brevemente el documento que se presenta a la

NOTARIA QUECIENDO DEL CIRCULO DE BOGOTÁ D.C.

personalmente por Elvira Mena

quien exhibió la c.c. 51.975.664

y Tarjeta Profesional No. 83823 C.B.J.

Fecha 28 AGO. 2008

Vicky P

Victoria Pineda Chujillo

NOTARIA

[Circular Seal: REPUBLICA DE COLOMBIA, CIRCULO DE BOGOTÁ D.C.]

Elvira Mena



***** Pag. 1
CAMARA DE COMERCIO
DE BARRANQUILLA
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.

NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

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libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A.

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996,
otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta
Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del
libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras
y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad
se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

***** C O N T I N U A *****



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CAMARA DE COMERCIO
DE BARRANQUILLA
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista,

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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S.A.-----
NIT: 890.106.527-5.

socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,229,071,000	*****1,229,071	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente

***** C O N T I N U A *****



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
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que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zilberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	

***** C O N T I N U A *****



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C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.*****32,748,111

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ----
obrando como Presidente y Representante Legal de la sociedad C.I.
NATURMEGA S.A., que obrando en su condicion de Presidente y -----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo
Organo Social, otorga los siguientes poderes: Otorgar poder -----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO -----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con
las facultades que se transcriben a continuacion: a.- Para que ----
representen a la sociedad PROCAPS S.A, ante todo tipo de -----
autoridades administrativas y jurisdiccionales, en asuntos de ----
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria,
tributaria, policiva, administrativa y fiscal. b.- Contestar y ----
presentar demandas, requerimientos, recursos, pedir y aportar ----
pruebas, recibir, notificarse, ejercer la accion de tutela, -----
tramitar incidente de desacato, comparecer en los procesos que ----
cursen contra la sociedad, allanarse en nombre de la sociedad en
los asuntos que sean necesarios, transigir, desistir, sustituir,
renunciar y reasumir el poder. c.- La facultad expresa de -----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, ----
transaccionales, judiciales o extrajudiciales o extrajudiciales,
cualquiera que sea su cuantia, para lo cual las apoderadas deben
aportar la autorizacion simple y escrita del Representante legal
de la sociedad. d.- Podran presentar solicitudes de devolucion y/o
compensacion de impuestos, ventas y rentas, recibir los pagos por
las devoluciones y adelantar todo tramite o proceso administrativo
ante la DIAN, de tal forma que en ningun momento quede sin -----
representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ----
confiere poder especial amplio y suficiente a las personas que se
determinan seguidamente, que conforman el grupo A y B, para, para
que conjuntamente suscriban contratos de suministros de mercancias
y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS
MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), -----
liquidados a la tasa representativa del mercado vigente en el dia
que se realice la respectiva transaccion. Grupo A. WALTER NANAKA
TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO -----
CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN -----

***** C O N T I N U A *****



***** Pag. 5
CAMARA DE COMERCIO
DE BARRANQUILLA
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA -----
DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO -----
CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME
FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial -----
amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA -----
CC.No.8.715.941, y al señor ANTONIO VARELA DIAZ CC.No.72.004.699,
para que en nombre y representacion de PROCAPS S.A., suscriban -----
declaraciones cambiarias, aduaneras y tributarias a que este -----
obligada la sociedad, en el giro normal de sus negocios y -----
operaciones sociales, por tanto quedan facultados para firmarlas,
como tambien los demas documentos relacionados con ellas, -----
notificarse, aportar y solicitar las pruebas que sean necesarias.
c.-Otorgar poder especial amplio y suficiente al señor MARLON -----
TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
CERRA CC.No.8.715.941, para que en nombre y representacion de -----
PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
documento relacionado con los tramites o registros de Comercio -----
Exterior y o cualquier entidad del Estado que haga sus veces: d)
Otorgar poder especial amplio y suficiente a la doctora CARMEN -----
ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER
TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y -----
representacion de PROCAPS S.A.; endosen los titulos valores de la
sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
(1.000.000.000.00) M.L. CUARTO: El representante legal de la -----
sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta
que la presente reforma fue aprobada por la Asamblea General -----
Extraordinaria de Accionista de PROCAPS S.A., con observancia de
las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 19 de Marzo de 2008.

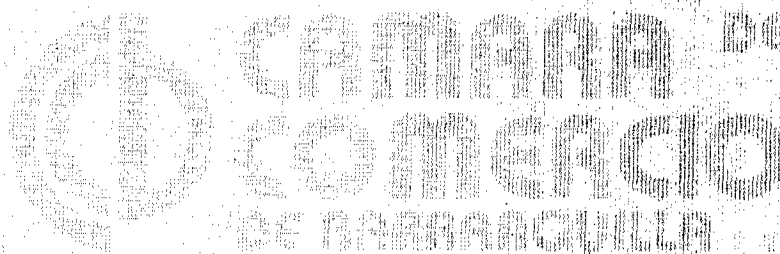
La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

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ANEXO 1

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(54) **ORAL CONTRACEPTIVES TO PREVENT
PREGNANCY AND DIMINISH
PREMENSTRUAL SYMPTOMATOLOGY**

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(52) **U.S. Cl. 514/170; 514/649**

(57) **ABSTRACT**

This invention relates to a method of preventing pregnancy and treating PMS including PMDD. More particularly, the invention relates to a method, which involves administering one of several combination oral contraceptive regimens in combination with an antidepressant and a kit containing the same.

ORAL CONTRACEPTIVES TO PREVENT PREGNANCY AND DIMINISH PREMENSTRUAL SYMPTOMATOLOGY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/335,807, filed Dec. 5, 2001, the disclosure of which is hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This invention relates to oral contraceptives that prevent pregnancy and diminish or eliminate premenstrual symptomatology, including PMS and PMDD, and to a method of preventing pregnancy and diminishing or eliminating premenstrual symptomatology, including PMS and PMDD.

[0004] 2. Background Art

[0005] The human menstrual cycle involves a repetitive sequence of hormonal changes that result in episodic uterine bleeding. Normally, each menstrual cycle has a mean interval of 21 to 35 days, conventionally beginning with the first day of menstrual flow and ending on the day before the next onset of bleeding. Duration of the menstrual flow is usually 2 to 6 days with loss of 20 to 60 ml of blood.

[0006] The menstrual cycle is divided into follicular and luteal phases, each corresponding to changes occurring in the ovary. These phases may also be described as proliferative or secretory, corresponding to changes observed in the uterine endometrium. Variations in the length of the cycle are usually due to alterations in the follicular phase, because the luteal phase length remains relatively constant at 12 to 16 days.

[0007] During the follicular phase, several primary follicles are recruited for further growth and development. Granulosa cells in primary follicles possess follicle stimulating hormone (FSH) and estradiol receptors. Upon FSH stimulation, granulosa cells produce aromatase. This enzyme converts the androgens androstenedione and testosterone, made in response to luteinizing hormone (LH) by thecal cells, to estrone and estradiol, respectively. Granulosa cells respond to estradiol by undergoing mitosis to increase the number of granulosa cells and estradiol production. By day 7 of the cycle, one enlarging primary follicle is selected by unknown processes to be the follicle that will release the oocyte at ovulation.

[0008] The midcycle rise in plasma estradiol stimulates the large midcycle LH surge. This midcycle LH surge triggers resumption of meiosis within the oocyte and luteinization of the granulosa cells within the preovulatory follicle. Immediately before ovulation, the outer follicular wall begins to dissolve and an oocyte is released approximately 24 to 36 hours from the onset of the LH surge.

progesterone. LH maintains the corpus luteum during the luteal phase and, acting via the adenyl cyclase system, stimulates progesterone production. If pregnancy does not occur, lutein cells degenerate, and diminished hormone secretion precedes menstruation. Menstruation is immediately followed by the onset of another menstrual cycle.

[0010] Because endometrial proliferation serves to prepare the uterus for an impending pregnancy, manipulation of hormones and of the uterine environment can provide contraception. For example, estrogens are known to decrease FSH secretion by feedback inhibition. Under certain circumstances, estrogens can also inhibit LH secretion, once again by negative feedback. Under normal circumstances, the spike of circulating estrogen found just prior to ovulation induces the surge of gonadotropic hormones that occurs just prior to and results in ovulation. High doses of estrogen immediately post-coitally also can prevent conception probably due to interference with implantation.

[0011] Progestins can also provide contraception. Endogenous progesterone after estrogen is responsible for the progestational changes of the endometrium and the cyclic changes of cells and tissue in the cervix and the vagina. Administration of progestin makes the cervical mucus thick, tenacious and cellular which is believed to impede spermatozoal transport. Administration of progestin also inhibits LH secretion and blocks ovulation in humans.

[0012] The most prevalent form of oral contraception is a pill that combines both an estrogen and a progestin, a so-called combined oral contraceptive preparation. Alternatively, there are contraceptive preparations that comprise progestin only. However, the progestin-only preparations have a more varied spectrum of side effects than do the combined preparations, especially more breakthrough bleeding. As a result, the combined preparations are the preferred oral contraceptives in use today (Sheth et al., *Contraception* 25:243 (1982)).

[0013] In establishing an estrogen-progestin regimen for oral contraceptives, two principal issues must be confronted. First, efficacy must be maintained and second, there must be avoidance of further erosion in the control of endometrial bleeding. In general, even the lowest dose oral contraceptive products commercially available have demonstrated efficacy but the overall instances of bleeding control problems have increased as the doses were reduced, as manifested both in breakthrough bleeding (untimely flow or spotting) or withdrawal amenorrhea during the "pill free" week (expected menses).

[0014] During the luteal phase of the menstrual cycle, as many as 75% of women with regular menstrual cycles experience some symptoms of premenstrual syndrome (PMS), a recurring, cyclical disorder involving behavioral, emotional, social and physical symptoms (Steiner et al., *Annu. Rev. Med.* 48:447-455 (1997)). Behavioral, emotional and social symptoms include, but are not limited to, irritability, mood swings, depression, hostility and social withdrawal. Physical symptoms include, but are not limited to, bloating, breast tenderness, myalgia, migraines or headaches

disorder. In these women, the diagnosis of Premenstrual Dysphoric Disorder (PMDD), which is defined in the Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) can be applied. According to the DSM-W, a woman with PMDD must have at least five premenstrual symptoms during the luteal phase, with at least one of the symptoms being an emotional or "core" symptom. The core symptoms must be irritability, anger, mood swings, tension or depression (and interfere with daily activities), and must be confirmed by a prospective daily rating for at least two cycles. Three to five percent of women with PMS report to have PMDD.

[0016] There is also a subgroup of women who experience severe PMS, which accounts for about 20% of the PMS population. These women experience severe emotional symptoms that do not fall under the strict criteria of PMDD as defined in DSM-IV but require medical attention.

[0017] Symptoms of PMDD may begin at any age after menarche, but the average age at onset appears to be around 26 years and several researchers found that symptoms, such as estrogen withdrawal symptoms, associated with the premenstrual phase gradually become worse, and perhaps more protracted, over time. It has been suggested that worsening could occur because of the recurring increases and decreases in ovarian hormones. This is supported by data from other cultures: when menstruation is infrequent, premenstrual symptoms are rare. It is also supported by data associating low parity with the risk of PMDD. Low parity yields a greater number of hormonal cycles, and, thus, a woman has more exposure to and withdrawal from massive amounts of progesterone. Further, several studies find lower rates of premenstrual symptoms among users of oral contraceptives, again suggesting that briefer exposure to peaks and troughs of endogenous progesterone is protective against PMDD (Yonkers, K., *J. Clin. Psychiatry* 58(Suppl. 14):4-13 (1997)).

[0018] Suppression of ovulation has been an important rationale for the use of hormonal treatments for PMS. One method of inhibiting ovulation is by using oral contraceptives (OCs). Combination oral contraceptives inhibit ovulation by suppressing gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). To date, only two controlled studies of the oral contraceptive treatment of PMS have been published. The results indicate that combination oral contraceptives effectively reduce physical symptoms (especially breast pain and bloating), but the response on the relief of psychological symptoms has been less clear.

[0019] Therapeutic interventions for women who meet the criteria for PMDD include selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants and anxiolytics, as well as the antidepressant alprazolam (XANAX®). These interventions have demonstrated efficacy with minimal side effects. Recent investigations of SSRI have also demonstrated success at low doses.

[0020] Antidepressants that are active at serotonin receptors include clomipramine (ANAFRANIL®), fluoxetine

(SARAFEM®). The effectiveness of fluoxetine for the treatment of PMDD was established in four randomized, placebo-controlled trials. Fluoxetine at a daily dose of either 20 mg or 60 mg proved to be superior to placebo in reducing symptoms (Steiner et al., *New Engl. J. Med.* 332:1529-34 (1995)). However, the combination of oral contraceptive and fluoxetine was not examined, as women who were taking oral contraceptives were excluded from the trial.

[0022] It is the object of the present invention to provide estrogen-progestin combinations and/or regimens for oral contraceptive use, including estrogen-progestin combinations and/or regimens that contain an antidepressant, to concurrently diminish or eliminate premenstrual symptoms (PMS) including PMDD. Two regimens are proposed, the so-called 28-day regimen and the 91-day regimen. The 28-day regimen will allow women the option of maintaining the customary 13 menstrual cycles per year while diminishing or alleviating premenstrual symptoms (PMS) including PMDD. The 91-day regimen will allow women the option of maintaining only 4 menstrual cycles per year while diminishing or alleviating premenstrual symptoms (PMS) including PMDD. Thus, the 91-day regimen enhances compliance by involving fewer stop/start transitions per year and also results in less blood loss, and hypothetically, will diminish premenstrual symptoms, including PMDD. Having fewer menstrual intervals can also enhance lifestyles and convenience. This and other objects of the invention will become apparent to those skilled in the art from the following detailed description.

BRIEF SUMMARY OF THE INVENTION

[0023] This invention relates to female oral contraceptives that will prevent pregnancy and treat PMS including PMDD. This invention further relates to a method of preventing pregnancy and treating PMS including PMDD, by avoiding complete withdrawal of estrogen at the end of the treatment period, or between treatment periods, by administering oral contraceptives. Premenstrual symptoms are rare when menstruation is infrequent. Further, users of oral contraceptives have lower rates of premenstrual symptoms, again suggesting that briefer exposure to peaks and troughs of endogenous progesterone is protective against PMDD. More particularly, the invention relates to a method of preventing pregnancy, which involves administering one of two combination oral contraceptive regimens. Additionally, the invention relates to a method of preventing pregnancy, which involves administering one of two combination oral contraceptive regimens that contain an antidepressant.

DETAILED DESCRIPTION OF THE INVENTION

[0024] The invention relates to oral contraceptives that will prevent pregnancy and diminish or eliminate PMS including PMDD. Methods of using these oral contraceptives to prevent pregnancy and diminish or eliminate PMS including PMDD are also provided. More particularly, the methods involve administering one of several combination

with the present invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasically, for 21 to 26 consecutive days, preferably about 22-25 days, followed by administration of low-dose estrogen for 2 to 10 days, preferably about 3-7 days, more preferably about 2-7 days, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μ g of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively.

[0026] In a preferred embodiment, women will be administered an oral contraceptive on days 1 through 21 of the menstrual cycle containing 150 μ g levonorgestrel and 30 μ g ethinyl estradiol, followed by a dosage form on days 22-28 of the cycle, which contains 30 μ g ethinyl estradiol. A typical administration schedule is illustrated in Table 1. Thus, in a 28-day regimen schedule, there are about 13 treatment and menstrual cycles per year.

TABLE 1

Administration schedule for a 28-day regimen		
Days	Hormone	Antidepressant
1-21	150 μ g levonorgestrel and 30 μ g ethinyl estradiol	none
22-28	30 μ g ethinyl estradiol	none

[0027] In another embodiment of the invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasically, for 21 to 26 consecutive days, preferably about 22-25 days, followed by administration of low-dose estrogen for 2 to 10 days, preferably about 3-7 days, more preferably about 2-7 days, in combination with the antidepressant fluoxetine hydrochloride, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μ g of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively, and the fluoxetine hydrochloride is in an amount of about 5-120 mg. Oral contraceptives with initial doses of fluoxetine at either 5 mg or 10 mg/day can be started to avoid any activating side effects that may lead to noncompliance. The dose can then be increased as needed. Fluoxetine can also be given intermittently during the late luteal phase, which is typically 1-2 weeks before menses. In addition, a one-time or once-weekly dose of about 90 mg of fluoxetine can be administered.

[0028] In a preferred embodiment, women will be administered an oral contraceptive on days 1 through 21 of the menstrual cycle containing 150 μ g levonorgestrel and 30 μ g ethinyl estradiol, followed by a dosage form on days 22-28

TABLE 2

Administration schedule for a 28-day regimen with an antidepressant		
Days	Hormone	Antidepressant
1-21	150 μ g levonorgestrel and 30 μ g ethinyl estradiol	none
22-28	30 μ g ethinyl estradiol	20 mg fluoxetine hydrochloride daily OR a one-time dose of 90 mg fluoxetine hydrochloride OR a once-weekly dose of 90 mg fluoxetine hydrochloride

[0029] An additional embodiment of the invention is a long-term regimen that allows women the option of limiting their menstrual periods to about four times per year. In accordance with the present invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasically, for 60 to 110 consecutive days, preferably about 81 to 89 days, followed by administration of estrogen for 2 to 10 days, preferably about 5 to 8 days, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μ g of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively.

[0030] In a preferred embodiment, the 91-day regimen, women will be administered an oral contraceptive on days 1 through 84 of the menstrual cycle containing 150 μ g levonorgestrel and 30 μ g ethinyl estradiol, followed by a dosage form on days 85-91 of the cycle, which contains 30 μ g ethinyl estradiol. A typical administration schedule is illustrated in Table 3. Thus, in a 91-day regimen, there are only four treatment and menstrual cycles per year.

TABLE 3

Administration schedule for a 91-day regimen		
Days	Hormone	Antidepressant
1-84	150 μ g levonorgestrel and 30 μ g ethinyl estradiol	none
85-91	30 μ g ethinyl estradiol	none

[0031] In an additional embodiment of the invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasically, for 60 to 110 consecutive days, preferably about 81 to 89 days, followed by administration of low-dose estrogen and fluoxetine hydrochloride for 2 to 10 days, preferably about 5 to 8 days, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μ g of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively, and the fluoxetine hydrochloride is in an amount of about 5-120 mg. Oral contraceptives with initial doses of fluoxetine at either 5 mg or 10 mg/day can be started to avoid any activating side effects that may lead to noncompliance. The dose can then be increased as needed. Fluoxetine can also be given intermittently during the late luteal phase, which is typically 1-2 weeks before menses. In addition, a one-time or once-weekly dose of about 90 mg of fluoxetine can be administered.

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[0032] In a preferred embodiment, women will be administered an oral contraceptive on days 1 through 84 of the menstrual cycle containing 150 μ g levonorgestrel and 30 μ g ethinyl estradiol, followed by a dosage form on days 85-91 of the cycle, which contains 30 μ g ethinyl estradiol and 20 mg fluoxetine hydrochloride. A typical administration schedule is illustrated in Table 4. Thus, in a 91-day regimen, there are only four treatment and menstrual cycles per year.

TABLE 4

Administration schedule for a 91-day regimen with an antidepressant		
Days	Hormone	Antidepressant
1-84	150 μ g levonorgestrel and 30 μ g ethinyl estradiol	none
85-91	30 μ g ethinyl estradiol	20 mg fluoxetine hydrochloride daily OR a one-time dose of 90 mg fluoxetine hydrochloride OR a once-weekly dose of 90 mg fluoxetine hydrochloride

[0033] The estrogens which may be employed as a component in the regimens of this invention may be any of those conventionally available. Typically, the estrogen may be selected from the group comprising synthetic and natural estrogens, including steroidal and nonsteroidal estrogens. The synthetic estrogens may be selected from, for example, ethinyl estradiol, ethynodiol diacetate, mestranol and quinestranol. Particularly of interest are 17 α -ethinyl estradiol and esters and ethers thereof. The preferred estrogen is 17 α -ethinyl estradiol. The natural estrogens may include, for example, conjugated equine estrogens, esterified estrogens, 17 β -estradiol, estradiol valerate, estrone, piperazine estrone sulphate, estriol, estriol succinate and polyestrol phosphate.

[0034] The progestin component may be any progestationally active compound. Thus, the progestin may be selected from progesterone and its derivatives such as, for example, 17-hydroxy progesterone esters, 19-nor-17-hydroxy progesterone esters, 17 α -ethinyltestosterone and derivatives thereof, 17 α -ethinyl-19-nor-testosterone and derivatives thereof, norethindrone, norethindrone acetate, ethynodiol diacetate, dydrogesterone, medroxy-progesterone acetate, norethynodrel, allylestrenol, lynoestrenol, fuingestanol acetate, medrogestone, norgestrienone, dimethiderone, ethisterone, cyproterone acetate, levonorgestrel, dl-norgestrel, d-17 α -acetoxy-13 β -ethyl-17 α -ethinyl-gon-4-en-3-one oxime, cyproterone acetate, gestodene, desogestrel and norgestimate. The preferred progestin is levonorgestrel.

[0035] The weight ratio of the active ingredients, e.g., ethinyl estradiol and levonorgestrel, is at least 1:45 and preferably at least 1:50. The preferable amount of ethinyl estradiol is about 10-50 μ g and the preferable amount of levonorgestrel is about 0.15-1.5 mg. Other estrogens vary in potency from ethinyl estradiol. For example, 30 μ g of ethinyl estradiol is roughly equivalent to 60 μ g of mestranol or 2 g of 17 β -estradiol. Likewise, other progestins vary in potency from levonorgestrel. Thus, 1 mg of levonorgestrel is roughly equivalent to 2 mg of norgestrel or 4 mg of norgestimate.

the relative potency should be made. The correlations in potency between the various estrogens and progestins are known. See for example European Patent Application No.0 253 607, which is hereby incorporated in its entirety by reference hereto.

[0036] The preferred antidepressant is fluoxetine hydrochloride although other antidepressants can be employed. For example, the antidepressants alprazolam (XANAX®), clomipramine (ANAFRANIL®), paroxetine (PAXIL®), sertraline (ZOLOFT®), nefazodone (SERZONE®), fenfluramine (PONDIMIN®) and venlafaxine (EFFEXOR®) can also be used. The daily amounts of these antidepressants can vary, depending on the antidepressant used, from 0.75 to 2 mg, 10 to 20 mg or 50 to 100 mg.

[0037] Each of the described regimens will prevent pregnancy and additionally diminish or eliminate debilitating premenstrual symptomatology.

[0038] Other useable estrogens include the esters of estradiol, estrone and ethinyl estradiol such as the acetate, sulfate, valerate or benzoate, conjugated equine estrogens, agnostic anti-estrogens, and selective estrogen receptor modulators. The formulations of the invention may be administered orally, preferably in tablet form, parenterally, sublingually, transdermally, intravaginally, intranasally or buccally. The method of administration depends on the types of estrogens and progestins used in the formulation, as well as the amounts per unit dosage. Most estrogens are orally active and that route of administration is therefore preferred. Methods for transdermal administration including the associated methods for manufacturing such systems are well known in the art. In this connection, reference may be had to U.S. Pat. Nos. 4,752,478, 4,685,911, 4,438,139 and 4,291,014, which are hereby incorporated in their entirety by reference hereto.

[0039] Pharmaceutical formulations or preparations containing the formulations of the invention and a suitable carrier can be solid dosage forms which includes tablets, dragees, capsules, cachets, pellets, pills, powders or granules; topical dosage forms which include solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels or jellies, foams and controlled release depot entities; transdermals, vaginal rings, buccal formulations; and parenteral dosage forms which includes solutions, suspensions, emulsions or dry powder comprising an effective amount of estrogen, progestin and antidepressant as taught in this invention.

[0040] It is known in the art that active ingredients can be contained in such formulations in addition to pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, "Modern Pharmaceutics", Banker & Rhodes, Marcel Dekker, Inc. (1979); "Goodman & Gilman's The Pharmaceutical Basis of Therapeutics", 6th Edition,

dance with the method of administration. Thus, the active ingredients are prepared according to known methods in a pharmaceutically acceptable form for administration. These ingredients, in their required quantities are combined with the appropriate pharmaceutical carriers such as additives, vehicles and/or flavor ameliorating substances. These substances may be referred to as diluents, binders and lubricants. Gums, starches and sugars are also common terms. Typical of these types of substances or excipients are pharmaceutical grades of mannitol, lactose starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate and the like. The active ingredient(s) may comprise from about 0.01% by weight to about 99.99% by weight of the total formulation and the remainder comprises the pharmaceutically acceptable carrier. The percentage of active ingredient(s) may vary according to the delivery system or method of administration and is chosen in accordance with conventional methods known in the art.

[0042] In the oral form of the formulation, the contraceptive preparations are preferably produced in the form of a kit or package, with the daily dosages arranged for proper sequential administration. Thus, in another aspect, the present invention also provides a pharmaceutical package which contains combination-type contraceptives in multiple dosage units in a synchronized, fixed sequence, wherein the sequence or arrangement of the dosage units corresponds to the stages of daily administration.

[0043] For example, the pharmaceutical formulations may be provided in kit form containing for the 28 -day regimen at least about 18, and preferably at least about 21 tablets, and up to 26 tablets, intended for ingestion on successive days. Preferably administration is daily for at least 21 days using tablets containing both the estrogen and the progestin and then for at least 7 days using tablets containing only estrogen. In another preferred embodiment, administration is daily for at least 21 days using tablets containing both the estrogen and the progestin and then for at least 7 days using tablets containing both estrogen and an antidepressant, e.g., fluoxetine hydrochloride. For the long-term regimen, the pharmaceutical formulation may be provided in kit form containing at least about 60, and preferably at least about 81 to 89 tablets, and up to 110 tablets, intended for ingestion on successive days. Preferably administration is daily for at least 84 days using tablets containing both the estrogen and the progestin and then for at least 7 days using tablets with only estrogen. In another preferred embodiment, administration is daily for at least 84 days using tablets containing both the estrogen and the progestin and then for at least 7 days using tablets with both estrogen and an antidepressant, e.g., fluoxetine hydrochloride.

[0044] Efficacy of the 28 -day and 91 -day regimens on premenstrual symptomatology are measured by psychometric scales that include self-administered Visual Analogue Scales (VAS) and a prospective daily symptoms chart or diary to evaluate psychological and somatic symptoms. Total score of the psychological and somatic symptoms is

however, that these examples are illustrative only and are not intended to limit the scope of the invention.

EXAMPLES

Example 1

[0046] Multicenter Randomized Phase III Clinical Trial to Evaluate Two Continuous Oral Contraceptive Regimens in Women Diagnosed with Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)

[0047] Clinical Design and Summary

[0048] In a multicenter, randomized, clinical trial the efficacy and safety of three combination oral contraceptives regimens in the prevention of pregnancy in sexually active women, ages 18 through 40 years, will be evaluated. Patients will be randomized in a 1:1:1 fashion to one of the following regimens:

[0049] Levonorgestrel 150 μ g/ethinyl estradiol (EE) 30 μ g administered once daily for 84 days as a combination oral tablet followed by ethinyl estradiol 30 μ g administered once daily for 7 days (DP3-84/30);

[0050] Levonorgestrel 150 μ g/ethinyl estradiol 30 μ g administered once daily for 84 days as a combination oral tablet followed by ethinyl estradiol 10 μ g administered once daily for 7 days (DP3-84/10); or

[0051] Levonorgestrel 150 μ g/ethinyl estradiol 30 μ g administered once daily for 25 days as a combination oral tablet followed by ethinyl estradiol 30 μ g administered once daily for 3 days (DP3-25/30).

[0052] Patients randomized to either DP3-84/30 or DP3-84/10 will receive 4 cycles of study drug. Patients randomized to DP3-25/30 will receive 13 cycles of study drug. All patients will receive approximately 1 year of therapy.

[0053] The study coordinator or designated personnel will register the patient. Patients will be randomly assigned to one of the treatment regimens. The treatment group assignment will not be revealed to the patient prior to signing of the informed consent.

[0054] All patients, regardless of randomization, will initiate study OC therapy on the first Sunday following the beginning of their menstrual period ("Sunday starters") and will remain as Sunday starters throughout the study. Each of the dose packs will be dispensed with an abbreviated patient information sheet and a more detailed patient package insert (PPI).

[0055] All patients will complete and download information entered into an electronic diary. Assessments will include study drug compliance, use of additional forms of contraception, bleeding patterns, weight, assessment of the incidence and severity of menstrual related symptoms and medication taken to relieve these symptoms. Information will be self-recorded on the electronic diary via a series of

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[0057] Patient Eligibility

[0058] Inclusion Criteria

[0059] Patients must meet the following criteria to be included in the study:

[0060] 1. Sexually active adult females (age 18 through 40), of child bearing potential, in a heterosexual relationship, at risk for pregnancy, who are in good health and who

[0061] have a history of OC use for an interval of at least three successive cycles with regular withdrawal bleeding (bleeding during the pill-free interval or during the first three days of the subsequent cycle) prior to enrollment (Continuous Users)

[0062] OR

[0063] have no prior history OC use (Fresh-Starts)

[0064] OR

[0065] have no history of OC use in the 6 months prior to enrollment (Prior Users)

[0066] 2. Negative urine pregnancy test.

[0067] 3. Signed informed consent.

[0068] 4. Agree to use study oral contraceptive therapy as their primary birth control method (BCM).

[0069] Exclusion Criteria:

[0070] Patients will be excluded from the study if any of the following criteria are met:

[0071] 1. History of hypersensitivity to estrogen or progestin components of OCs.

[0072] 2. History of alcohol or drug abuse which, in the opinion of the investigator, makes the patient unfit for participation in the study.

[0073] 3. Active smoker age >34 years.

[0074] 4. Chronic use of any medication that may interfere with the efficacy of oral contraceptives.

[0075] 5. History of being HIV or Hepatitis C positive.

[0076] 6. History of persistent noncompliance with any chronic medication.

[0077] 7. History of having received injectable hormone therapy (e.g., Depo-Provera® (Pharmacia and Upjohn)) within the 10 months prior to enrollment or having a progestin-releasing intrauterine device (IUD) in place within 3 months prior to enrollment or has had a contraceptive implant removed within one month prior to enrollment or has received any other form of hormonal contraception within 3 months prior to enrollment.

delivery must have had at least two normal menstrual cycles prior to enrollment.

[0080] 10. History of abnormal bleeding (break-through or withdrawal bleeding that lasts ≥ 10 consecutive days or excessive spotting that lasts ≥ 10 consecutive days) while on conventional oral contraceptives.

[0081] 11. History of thromboembolic disorder, vascular disease, cerebral vascular or coronary artery disease.

[0082] 12. Uncontrolled or untreated hypertension (systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mmHg on more than two occasions).

[0083] 13. Known or suspected carcinoma of the breast, endometrial carcinoma or known or suspected estrogen dependent neoplasia.

[0084] 14. Undiagnosed abnormal genital bleeding.

[0085] 15. History of hepatic adenomas or carcinomas.

[0086] 16. History of cholestatic jaundice of pregnancy or jaundice with prior OC use.

[0087] 17. Known or suspected pregnancy or currently breastfeeding.

[0088] 18. Hyperlipidemia requiring active treatment with antihyperlipidemic agents.

[0089] 19. History of diabetes mellitus, glucose intolerance or gestational diabetes.

[0090] 20. History of abnormal laboratory value at screening

[0091] 21. Any clinically significant abnormal finding or condition on history, screening, physical exam, pelvic exam or any laboratory finding which contraindicates the use of oral contraceptives.

[0092] 22. Has participated in any clinical investigation within the 30 days prior to enrollment.

[0093] 23. Has donated or had a loss of more than 500 cc of blood within the 30 days prior to enrollment.

[0094] Treatment Regimen

[0095] Description of Study Medication

[0096] DP3-84/30

[0097] All tablets in the DP3-84/30 regimen; 84 tablets each containing 150 μ g levonorgestrel/30 μ g EE and 7 tablets each containing 30 μ g of EE will be white unembossed tablets. One combination tablet will be taken each day for 84 days followed by 7 days of EE tablets in 91-day cycles repeated consecutively for approximately one year (4 cycles). Each DP3-84/30 dose kit will be packaged in a 3-part fold-out white blister card pack where each of the first two blister packs has 28 active tablets each and the third

clinic visit one foil pouch, a patient information sheet, a PPI and a child resistant pouch will be dispensed.

[0099] DP3-84/10

[0100] All tablets in the DP3-84/10 regimen; 84 tablets each containing 150 μg levonorgestrel/30 μg EE and 7 tablets each containing 10 μg of EE will be white unembossed tablets. One combination tablet will be taken each day for 84 days followed by 7 days of EE tablets in 91 -day cycles repeated consecutively for approximately one year (4 cycles). Each DP3-84/10 dose kit will be packaged in a 3-part fold-out white blister card pack where each of the first two blister packs has 28 active tablets each and the third blister pack has 28 active tablets and 7 ethinyl estradiol tablets (35 tablets total) for each 91 -day cycle.

[0101] Each blister card pack will be sealed into a foil pouch, which will be labeled with a patient-specific label. Each foil pouch will contain an oxygen absorber. At each clinic visit one foil pouch, a patient information sheet, a PPI and a child resistant pouch will be dispensed.

[0102] DP3-25/30

[0103] All tablets in the DP3-25/30 regimen; 25 tablets each containing 150 μg levonorgestrel/30 μg EE and 3 tablets each containing 30 μg of EE will be white unembossed tablets. One combination tablet will be taken each day for 25 days followed by 3 days of EE tablets in 28 -day cycles repeated consecutively for approximately one year (13 cycles). Each DP3-25/30 blister card will have 25 active tablets followed by 3 ethinyl estradiol tablets (28 tablets total) for each 28 -day cycle.

[0104] Each blister card will be sealed into a foil pouch, which will be labeled with a patient-specific label. Each foil pouch will contain an oxygen absorber. At clinic visits one through three, 3 foil pouches, a patient information sheet, a PPI and a child resistant pouch will be dispensed. At clinic visit four, 4 foil pouches, a patient information sheet, a PPI and a child resistant pouch will be dispensed.

[0105] All patients, regardless of randomization, will be instructed to initiate OC therapy on the first Sunday following the beginning of their menstrual period ("Sunday starters"). Patients will be instructed to take their study medication at the same time each day. Day 1 of the study will be defined as the first day of study medication.

[0106] Administration

[0107] Designated personnel will dispense all study drugs. All study medications must be kept in a secured area at temperature ranging from approximately 15-25° C. (59-77° F.). All patients will be instructed to take one tablet per day at approximately the same time each day. All patients will be "Sunday starters"; that is all patients will begin study drug therapy on the first Sunday following the start of their previous menstrual cycle or completion of prior oral contraceptive regimens. All patients enrolled in the study will maintain Sunday starts for each successive cycle.

control during the interval between when they have finished study medication until they have completed the final study visit.

[0109] Patients randomized to DP3-84/30 or DP3-84/10 will receive a 13 -week supply (single cycle) of study drug at each clinic visit during Weeks 13, 26 and 39. Patients randomized to DP3-25/30 will receive a 12 -week supply (three-cycles) of study drug at the initiation of the study and at clinic visits during Weeks 12 and 24. During the clinic visit at Week 36 patients randomized to DP3-25/30 will receive 16 -week supply (four cycles) of study medication.

[0110] Examinations/Tests

TABLE 5

Parameter	Study Schedule			
	Screening	Visit 1	Visits 2-4 ^a	Completion of Therapy
Informed consent	X			
Medical and contraceptive history	X			
Physical exam including pelvic exam	X			X
Weight, vital signs	X	X	X	X
Pap smear	X			X
Randomization		X		
Clinical laboratory tests ^b	X			X
Urine pregnancy test ^c	X	X	X	X
Study drug distribution ^d		X	X	
Electronic diary distribution		X		
Study drug compliance measurement			X	X
Adverse event recording			X	X

^aPatients randomized to DP3-84/30 or DP3-84/10 will be seen at Weeks 13, 26 and 39. Patients randomized to DP3-25/30 will be seen at Weeks 12, 24, and 40.

^bClinical laboratory tests include CBC, serum chemistry, lipid profile, urinalysis

^cRepeated on Visit 1 if the screening was completed more than 2 weeks prior to enrollment

^dFor patients randomized to DP3 25/30, three (3) cycle supply will be dispensed at Weeks 12 and 24; a four (4) cycle supply will be dispensed at Week 40.

[0111] Study Procedures by Visit

[0112] Screening and Enrollment

[0113] Patients will sign informed consent. Prior to enrollment, within four weeks prior to initiation of study therapy, all patients will undergo a screening evaluation that will include prior medical and contraceptive history, smoking history, physical examination including pelvic exam and Pap smear, vital signs and weight, and clinical laboratory tests including complete blood count (CBC), serum chemistry, lipid profile, urinalysis, and urine pregnancy test.

[0114] All clinical laboratory evaluations (blood and

pregnancy test must be repeated at Visit 1. Patients with a report of an abnormality on Pap smear will be disqualified for enrollment unless investigator decides the results are not clinically significant and will not interfere with conduct of the study. Investigator's decision must be documented. Patients who have had a normal Pap smear within the three months prior to enrollment in the study will not be required to have the test repeated. A copy of the results must be available in the patient's medical record. Any patient with a report of insufficient cells must have the test repeated and documented as normal prior to enrollment. Patients will then be enrolled in the study.

[0116] Visit 1

[0117] Visit 1 will take place during the final week of the menstrual cycle prior to beginning study therapy (i.e., during menses for those patients not taking oral contraceptives or during Week 4 for those patients taking oral contraceptives). During Visit 1 patients will be randomized to one of the following treatment groups:

[0118] DP3-84/30; levonorgestrel 150 µg/EE 30 µg for 84 days+EE 30 µg for 7 days

[0119] OR

[0120] DP3-84/10; levonorgestrel 150 µg/EE 30 µg for 84 days+EE 10 µg for 7 days

[0121] OR

[0122] DP3-25/3; levonorgestrel 150 µg/EE 30 µg for 25 days+EE 30 µg for 3 days

[0123] The treatment regimen assignment will be ascertained by randomization via Interactive Voice Response System (IVRS). The treatment group assignment will not be revealed to the patient prior to signing of the informed consent.

[0124] A urine pregnancy test will be re-administered to those women who were screened more than two weeks prior to Visit 1. Study medication will be dispensed with patient instructions. An electronic diary will be given to each patient. Each patient will be trained regarding the use and care of the electronic diary. Patients will be instructed to take each dose of study medication and to complete all diary entries at approximately the same time each day.

[0125] Visits 2-4

[0126] All visits should take place within seven days prior to completion of study medication for that cycle. Any visit that takes place prior to the final week of the cycle will be recorded as a protocol deviation. Any visit that takes place following the final week of the cycle resulting in a lapse in study medication intake will be recorded as a protocol violation and will result in the patient being withdrawn from the study. Any visit that takes place following the final week of the cycle but does not result in a lapse in study medication (c.g., the patient received an emergency supply of study medication) will be recorded as a protocol deviation.

recorded. A urine pregnancy test will be conducted. Used study medication will be returned and counted by the study pharmacist or designated personnel.

[0128] Completion of Therapy

[0129] The end-of-study evaluation will take place 1 week following completion of last cycle of the study drug. Patients will be counseled to use birth control during the interval between when they have finished study medication until they have completed the final study visit. Patients will undergo physical exam, including pelvic exam and pap smear. Vital signs and weight will be recorded. Blood and urine samples for clinical laboratory tests including CBC, serum chemistry, lipid profile, urinalysis and urine pregnancy test will be obtained. Used study medication cards will be returned and counted by the study pharmacist or designated personnel. Patients will be queried regarding adverse events, concomitant medications, change in smoking history and compliance. The electronic diary will be returned.

[0130] Post-Study Visit

[0131] After study completion/withdrawal, patients will be followed via a phone call for occurrence of pregnancy and until the menstrual cycle returns to normal. The patient based on the cycle pattern prior to the study entry will determine return to normal menstrual cycle. The minimum period of follow up will be 3 months. Patients who decide to use a contraceptive method that regulates/alters menstrual cycle after study completion/withdrawal will be followed for 3 months via a phone call.

[0132] Only those patients who have an on-going serious adverse event that has not resolved or those who become pregnant during the course of the study will be followed via clinic visits after completion of the study. Patients with on-going serious adverse events will be followed until the event has been satisfactory managed or resolved. Patients who are pregnant will be followed for eight weeks following delivery or termination of the pregnancy. Infants' health assessment will be followed for eight weeks following delivery. This follow-up may be in the form of a written report from a family physician, obstetrician or pediatrician. All serious adverse events that occur in the three months following discontinuation of therapy will be reported. SAEs that occur at any time after study completion/discontinuation will be reported if investigator determines it is drug-related.

[0133] Early Termination

[0134] Any patient who withdraws or is withdrawn from the study must return the investigational medication and electronic diary and will be required to complete all procedures for the final visit. All patients will be followed via a phone call for 3 months for the occurrence of pregnancy and until the menstrual cycle return to normal. All patients will be followed via a phone call for three months for the occurrence of serious adverse events.

[0135] Examinations and Procedures

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disqualified for enrollment unless investigator decides the results are not clinically significant and will not interfere with conduct of the study. The Investigators decision must be documented. Patients who have had a Pap smear reported as within normal limits within the three months prior to enrollment in the study will not be required to have the test repeated. A copy of the results must be available in the patient's medical record. Any patient with a report of insufficient cells must have the test repeated and documented by the investigator as within normal limits prior to enrollment.

[0138] Laboratory Safety Tests

[0139] Clinical laboratory tests will be performed at screening and at the completion of therapy or upon early withdrawal. All clinical laboratory tests will be done at one central laboratory. Laboratory tests will include CBC, serum chemistry, lipid profile, urinalysis, and urine pregnancy test. In addition, urine pregnancy tests will be conducted at every clinic visit and at the completion of therapy or upon early withdrawal from the study. All urine pregnancy tests will be performed using the Sure Step® Pregnancy Test kit (Applied Biotech, Inc.).

[0140] Pregnancy

[0141] All patients will be followed for the occurrence of pregnancy for three months following completion of the study. This follow-up may be in the form of a telephone call. All pregnancies that occur during the course of the study or in the three months following completion of the study will be dated using ultrasound to establish the gestational age of the fetus. Patients who become pregnant during the course of the study due to method failure will be followed for eight weeks following delivery or termination of the pregnancy. Infants' health assessment will be followed for eight weeks following delivery. This follow-up may in the form of a documented telephone conversation with associated pediatrician or written report from the associated pediatrician.

[0142] Electronic Diaries

[0143] Patients will be asked to complete electronic diaries. The diary will be programmed to ask specific questions related to the study compliance, bleeding pattern and occurrence of symptoms that are commonly associated with the hormone fluctuation during the menstrual cycle. The questions will address dosage, compliance, bleeding pattern and hormone-related symptoms either on the scale from 0-3 or using 10 cm Visual Analogue Scale (VAS).

[0144] Hand-held data acquisition devices will be used to collect patient responses. The electronic diary will provide patients with a menu-driven, graphical interface to enter diary information (as well as objective data) using a hand-held stylus. Data entry will be electronic and key fields must be completed properly before allowing patient to finish the report. Each report will be downloaded by dial-up network connection.

Once each question is completed the patient will confirm the response and will not be permitted to return to that question for modification.

[0146] Information on the hormone-related symptoms to be collected is from the Calendar of Premenstrual Experiences (COPE) and Diagnostic and Statistical Manual of Mental Disorders Forth Edition (DSM-IV).

[0147] The validity and reliability of the COPE instrument was assessed by Mortola, et al., *Obstet. Gynecol.* 89:179-83 (1990), who administered it throughout two consecutive ovulatory cycles to 36 rigidly screened women with PMS and to 18 controls. The validity of the visual analogue scales applied to the psychological symptoms associated with the PMDD has been previously documented.

[0148] Treatment Modifications Based on Toxicity

[0149] No significant toxicity is expected from the study medication. However, if the patient develops any symptoms or any abnormal laboratory parameter attributed to the drug, which are considered by the patient and/or physician to be of unacceptable severity, then the study medication should be discontinued.

[0150] Concomitant Medications

[0151] Patients will be queried regarding concomitant medication use at monthly phone calls and quarterly clinic visits. All concomitant medication use (both prescription and over-the-counter (OTC), including herbal medications and nutritional supplements) must be reported during the study, and recorded on the patient's Case Report Form (CRF).

[0152] Patients who require the initiation of chronic therapy with drugs that are known to interact with OCs will be withdrawn from the study. Patients who require intermittent therapy with drugs known to interact with OCs (e.g. antibiotic therapy) will remain in the study and will receive counseling regarding the need for additional contraceptive protection during the entire cycle. Patients will be provided with the list of medications that are known to interact with OC and will be instructed to notify study coordinator as soon as medication is prescribed to receive proper counseling. Notification and counseling can be conducted via the phone and must be documented in the patient's CRF. Those cycles in which drugs known to interact with OC therapy are taken will not be used in the calculation of the pregnancy rate.

[0153] The use of emergency contraceptive pills ("morning after pills") is prohibited in the study. Data from any patient who utilizes contraceptive pills others than those provided for the study will not be included in the calculation of the pregnancy rate for that cycle.

[0154] Adverse Event Reporting

[0155] An Adverse Event (AE) is any reaction, side effect, or other undesirable event that occurs in conjunction with the use of a drug, biological product or diagnostic agent in humans, whether or not the event is considered drug related.

[0159] Results in persistent or significant disability/incapacity

[0160] Congenital anomaly

[0161] The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical and scientific judgment should be exercised in deciding whether an important medical event is serious. Although the event may not be immediately life threatening, fatal, or result in hospitalization, it should be considered serious when it jeopardizes the patient, or requires an intervention to prevent a serious outcome as defined above.

[0162] The AE reporting period for this study begins at the Enrollment Visit and ends at the final clinic visit. The SAE reporting period will continue for 3 month after the final clinic visit. All SAEs will be followed through resolution or until investigator assesses the SAE as chronic or stable.

[0163] A preexisting condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical form) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

[0164] During the study AEs will be recorded through monthly phone calls and quarterly clinic visits. A call-in number will be provided to the patients who wish to report an adverse event between the scheduled phone calls and clinic visits.

Example 2

[0165] Multicenter Randomized Phase III Clinical Trial to Evaluate Two Continuous Oral Contraceptive Regimens in Combination with Fluoxetine Hydrochloride in Women Diagnosed with Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)

[0166] Overview of the Study Design

[0167] In a three-arm, parallel, randomized, multicenter, placebo-controlled, double-blinded study, the efficacy and safety of continuous oral contraceptive therapy as a ninety-one day regimen (84 days active combination therapy followed by low dose estrogen for 7 consecutive days (DP3-91)), or as a twenty-eight day regimen (21 day active combination therapy followed by low dose estrogen for 7 consecutive days (DP3-28)), in combination with fluoxetine hydrochloride administered for approximately 6 consecutive months to women diagnosed with PMS and/or PMDD who desire contraception, will be evaluated.

[0168] A cohort of approximate 40-100 patients enrolled in each of the study arms will undergo endometrial biopsy (to test incidence of hyperplasia and carcinoma) prior to the initiation of study drug therapy and at the conclusion of the study or withdrawal.

[0169] Efficacy of the 28 -day and 91 -day regimens on

weight gain symptoms. Total score of the psychological and somatic symptoms will be computed. The patient and blind observer will also complete the PMTS at each visit.

[0170] Study Population

[0171] Females ages 18 through 49 who are fluent in English and capable of giving informed consent, without contraindication to the use of oral contraceptives and selective serotonin reuptake inhibitors (SSRIs), and meet the criteria for PMS including PMDD as defined in the diagnostic and statistical manual of mental disorders (DSM-IV). All patients will be counseled at the beginning of the study and at each study visit to use an alternative form of contraception. All patients will be followed for the occurrence of pregnancy during the course of the study. Patients who become pregnant during the course of the study will be followed for eight weeks following delivery or termination of the pregnancy. Infants will be followed for eight weeks following delivery.

[0172] Dosage

[0173] Patients will be randomized to one of the following:

[0174] (1) Ninety-one day oral contraceptive therapy with ethinyl estradiol (DP3-91) and fluoxetine hydrochloride administered for two cycles where each cycle consists of: 150 μ g levonorgestrel and 30 μ g ethinyl estradiol (days 1-84 of the first cycle and days 92-175 of the second cycle, 30 μ g ethinyl estradiol (days 85-91 of the first cycle and days 176-182 of the second cycle), 20 mg fluoxetine hydrochloride (days 1-182), and placebo to preserve blinding (days 183-196);

[0175] (2) Twenty-eight day oral contraceptive therapy with ethinyl estradiol (DP3-28) administered for 7 cycles where each cycle consists of: 150 μ g levonorgestrel and 30 μ g ethinyl estradiol (days 1-21 for seven cycles), 30 μ g ethinyl estradiol (days 22-28 for seven cycles), and 20 mg fluoxetine hydrochloride (days 1-196); or

[0176] (3) Fluoxetine hydrochloride administered daily for 196 days: 20 mg fluoxetine hydrochloride per day (days 1-196) or placebo to preserve blinding (days 1-196).

[0177] Study Management

[0178] The study will utilize electronic case report forms and remote system management. Each investigator will be provided a programmed laptop computer dedicated to the study. This system allows the investigator to download and view patient diary data during clinic visits and also allows for rapid data queries by the study monitors. The system will also allow real-time on-line tracking of study site accrual rates, serious adverse events, pregnancies and study progress.

[0179] Outcomes Measurement Scales

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ness symptoms. Patients will be prompted to rate how they feel each day using 100 mm scales in which the descriptors range from "no symptoms" (0 mm) to "severe or extreme symptoms" (100 mm). The PMTS consists of a 36 item scale that will be completed by the patient and a 10-item scale completed by the blinded observer. Both scales rate premenstrual symptoms for a particular day; the total score can range from 0 (no symptoms) to 36 (all symptoms present and severe).

[0181] The secondary outcome will be defined as reduction in symptoms of PMS including PMDD as measured by the sub-score of somatic symptoms on VAS. The VAS will measure headache, bloating, pain and breast tenderness and weigh gain symptoms. Patients will be prompted to rate how they feel each day using 100 mm scales in which the descriptors range from "no symptoms" (0 mm) to "severe symptoms" (100 mm). In addition to information recorded in paper diaries, a standardized questionnaire will be used to determine whether the patient had any side effects.

[0182] Statistical Analysis

[0183] For the primary analysis, the mean of the VAS scales will be derived to obtain a single VAS score, which evaluates composite psychological and symptomatic outcomes. Mean percent reduction from baseline at the luteal phase will be compared using an analysis of covariance (ANCOVA) approach that evaluates the effects of the treatment group, center and treatment-by-center interaction, after adjusting for the effect of the baseline VAS score. All statistical tests will be two-sided at the 0.05 level of significance. Pairwise comparisons will be made for each active treatment to placebo. Secondary analyses will include a set of statistical tests for the PMTS and 10-item blinded observer-based measures.

[0184] Application of the compounds, compositions and methods of the present invention for the medical or pharmaceutical uses described can be accomplished by any clinical, medical, and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. It will therefore be appreciated that the various embodiments which have been described above are intended to illustrate the invention and various changes and modifications can be made in the inventive method without departing from the spirit and scope thereof.

What is claimed is:

1. A method of diminishing premenstrual symptoms in a female, comprising continuously administering a combination of estrogen and progestin for 81-89 consecutive days, followed by administration of estrogen for a period of 2-10 consecutive days.

2. The method of claim 1, in which the daily amount of estrogen administered for 81-89 consecutive days is equivalent to about 5-50 μ g of ethinyl estradiol.

3. The method of claim 2, in which the daily amount of progestin administered for 81-89 consecutive days is equivalent to 0.05-1.5 mg of levonorgestrel.

4. The method of claim 3, wherein the combination of

7. The method of claim 3, in which the progestin is levonorgestrel.

8. A method of diminishing premenstrual symptoms in a female, comprising continuously administering a combination of estrogen and progestin for 21-26 consecutive days, followed by administration of estrogen for a period of 2-7 days.

9. The method of claim 8, in which the daily amount of estrogen administered for 21-26 consecutive days is equivalent to about 5-50 μ g of ethinyl estradiol.

10. The method of claim 9, in which the daily amount of progestin administered for 21-26 consecutive days is equivalent to 0.05-1.5 mg of levonorgestrel.

11. The method of claim 10, wherein the combination of estrogen and progestin is administered for at least 21 consecutive days.

12. The method of claim 8, wherein the estrogen is administered for at least 7 consecutive days.

13. The method of claim 9, in which the estrogen is ethinyl estradiol.

14. The method of claim 10, in which the progestin is levonorgestrel.

15. A method of diminishing premenstrual symptoms in a female, comprising continuously administering a combination of estrogen and progestin for 81-89 consecutive days, followed by administration of a combination of estrogen and an antidepressant for a period of 2-10 days.

16. The method of claim 15, in which the daily amount of estrogen administered for 81-89 consecutive days is equivalent to about 5-50 μ g of ethinyl estradiol.

17. The method of claim 16, in which the daily amount of progestin administered for 81-89 consecutive days is equivalent to 0.05-1.5 mg of levonorgestrel.

18. The method of claim 17, in which the daily amount of antidepressant administered for 2-10 consecutive days is equivalent to about 5-120 mg of fluoxetine hydrochloride.

19. The method of claim 15, wherein the combination of estrogen and progestin is administered for at least 84 consecutive days.

20. The method of claim 15, wherein the combination of estrogen and antidepressant is administered for at least 7 consecutive days.

21. The method of claim 16, in which the estrogen is ethinyl estradiol.

22. The method of claim 17, in which the progestin is levonorgestrel.

23. The method of claim 18, in which the antidepressant is fluoxetine hydrochloride.

24. The method of claim 15, wherein said combination of estrogen and antidepressant is administered in a single tablet.

25. A method of diminishing premenstrual symptoms in a female, comprising continuously administering a combination of estrogen and progestin for 21-26 consecutive days, followed by administration of a combination of estrogen and an antidepressant for a period of 2-7 days.

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28. The method of claim 27, in which the daily amount of antidepressant administered for 2-7 consecutive days is equivalent to about 5-120 mg of fluoxetine hydrochloride.

29. The method of claim 25, wherein the combination of estrogen and progestin is administered for at least 21 consecutive days.

30. The method of claim 25, wherein the combination of estrogen and antidepressant is administered for at least 7 consecutive days.

31. The method of claim 26, in which the estrogen is ethinyl estradiol.

32. The method of claim 27, in which the progestin is levonorgestrel.

33. The method of claim 28, in which the antidepressant is fluoxetine hydrochloride.

34. The method of claim 25, wherein said combination of estrogen and antidepressant is administered in a single tablet.

35. A kit to diminish premenstrual symptoms consisting of:

(a) tablets comprising estrogen and progestin; and

(b) tablets comprising estrogen.

36. The kit of claim 35, wherein said estrogen and progestin tablets include about 84 tablets and wherein said estrogen tablets include about 7 tablets.

37. The kit of claim 35, wherein said estrogen and progestin tablets include about 21 tablets and wherein said estrogen tablets include about 7 tablets.

38. The kit of claim 35, in which the amount of estrogen in the tablets is equivalent to about 5-50 μ g of ethinyl estradiol.

39. The kit of claim 38, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

40. The kit of claim 38, in which the estrogen is ethinyl estradiol.

41. The kit of claim 39, in which the progestin is levonorgestrel.

42. A kit to diminish premenstrual symptoms consisting of:

(a) tablets comprising estrogen and progestin; and

(b) tablets comprising estrogen and an antidepressant.

43. The kit of claim 42, wherein said estrogen and progestin tablets include about 84 tablets and wherein said estrogen and antidepressant tablets include about 7 tablets.

44. The kit of claim 42, wherein said estrogen and progestin tablets include about 21 tablets and wherein said estrogen and antidepressant tablets include about 7 tablets.

45. The kit of claim 42, in which the amount of estrogen in the tablets is equivalent to about 5-50 μ g of ethinyl estradiol.

46. The kit of claim 45, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

47. The kit of claim 46, in which the amount of antidepressant in the tablets is equivalent to about 5-120 mg of fluoxetine hydrochloride.

48. The kit of claim 46, in which the amount of antidepressant in the tablets is equivalent to about 90 mg of

51. The kit of claim 47, in which the antidepressant is fluoxetine hydrochloride.

52. A preparation for diminishing premenstrual symptoms in a female comprising about 84 tablets consisting of a combination of estrogen and progestin and about 7 tablets consisting of estrogen.

53. The preparation of claim 52, in which the amount of estrogen in the tablets is equivalent to about 5-50 μ g of ethinyl estradiol.

54. The preparation of claim 53, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

55. The preparation of claim 53, in which the estrogen is ethinyl estradiol.

56. The preparation of claim 54, in which the progestin is levonorgestrel.

57. A preparation for diminishing premenstrual symptoms in a female comprising about 21 tablets consisting of a combination of estrogen and progestin and about 7 tablets consisting of estrogen.

58. The preparation of claim 57, in which the amount of estrogen in the tablets is equivalent to about 5-50 μ g of ethinyl estradiol.

59. The preparation of claim 58, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

60. The preparation of claim 58, in which the estrogen is ethinyl estradiol.

61. The preparation of claim 59, in which the progestin is levonorgestrel.

62. A preparation for diminishing premenstrual symptoms in a female comprising about 84 tablets consisting of a combination of estrogen and progestin and about 7 tablets consisting of a combination of estrogen and an antidepressant.

63. The preparation of claim 62, in which the amount of estrogen in the tablets is equivalent to about 5-50 μ g of ethinyl estradiol.

64. The preparation of claim 63, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

65. The preparation of claim 64, in which the amount of antidepressant in the tablets is equivalent to about 5-120 mg of fluoxetine hydrochloride.

66. The preparation of claim 64, in which the amount of antidepressant in the tablets is equivalent to about 90 mg of fluoxetine hydrochloride.

67. The preparation of claim 63, in which the estrogen is ethinyl estradiol.

68. The preparation of claim 64, in which the progestin is levonorgestrel.

69. The preparation of claim 65, in which the antidepressant is fluoxetine hydrochloride.

70. A preparation for diminishing premenstrual symptoms in a female comprising about 21 tablets consisting of a combination of estrogen and progestin and about 7 tablets consisting of a combination of estrogen and an antidepressant.

71. The preparation of claim 70, in which the amount of

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73. The preparation of claim 72, in which the amount of antidepressant in the tablets is equivalent to about 5-120 mg of fluoxetine hydrochloride.

74. The preparation of claim 72, in which the amount of antidepressant in the tablets is equivalent to about 90 mg of fluoxetine hydrochloride.

75. The preparation of claim 71, in which the estrogen is ethinyl estradiol.

76. The preparation of claim 72, in which the progestin is levonorgestrel.

77. The preparation of claim 73, in which the antidepressant is fluoxetine hydrochloride.

78. The method of claim 5, whereby a one-time dose of an antidepressant is administered in combination with the estrogen.

79. The method of claim 78, in which the antidepressant is fluoxetine hydrochloride.

80. The method of claim 79, in which the amount of fluoxetine hydrochloride administered is about 90 mg.

81. The method of claim 12, whereby a one-time dose of an antidepressant is administered in combination with the estrogen.

82. The method of claim 81, in which the antidepressant is fluoxetine hydrochloride.

83. The method of claim 82, in which the amount of fluoxetine hydrochloride administered is about 90 mg.

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