

09/53058

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1 de 126



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-053058-00004-0000

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Tra. 11 PATENTEIYI Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 126

FORMULARIO UNICO DE OPOSICION
2000-12

1

OPOSICION A:

☒ Patente de Invención

☐ Patente de Modelo de Utilidad

☐ Diseño Industrial

☐ Esquema de Trazado para Circuitos Integrados

☐ Marcas de Productos o Servicios

☐ Marca Colectiva

☐ Marca de Certificación

☐ Lema Comercial

2

SOLICITUD PUBLICADA

Número del expediente: 09 053.058

Solicitante: WYETH.

Apoderado: ALVARO CORREA ORDOÑEZ.

Título de la nueva creación o denominación del signo:
COMPRÍMIDOS BICAPA DE ESTRÓGENO/SERM Y
ESTRÓGENO/PROGESTINA.

Gaceta 608 de 30 de septiembre 2009, N° de publicación 627.

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OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: TECNOQUIMICAS S.A., Sociedad comercial organizada y existente a las leyes Colombianas, con domicilio y sede principal en la Ciudad de Cali Valle. Dirección: Calle 23 # 7-39 Cali - Valle Teléfono: 882 5555 Fax: 883 8859 E-mail: Domicilio: Cali – Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890.300.466-5
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: (1) 621.26.31 E-mail: info@reyes-abogados.com Fax: (1) 621.25.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44655

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FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los articulos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser suceptibles de aplicación industrial) 16 y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia)). Artículo 30 (Reivindicaciones) y articulo 42 (oposiciones) de la Decisión 486 de la Comisión de la Comunidad Andina.

Justificación: Ver Anexo

5

Comprobante de pago No. 09-97.816(Oposición) Fecha Diciembre 29 de 2009
(Prórroga) Fecha _____

6

Anexos:

Comprobante de pago de la tasa



Poderes, si fuere el caso



Pruebas de los fundamentos de la oposición



Documentos que acrediten el legítimo interés, si fuere el caso



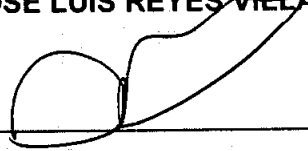
Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas



Copia de la oposición para el traslado al solicitante.

7

NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: 

REYES & REYES
A B O G A D O S

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 09 053.058

TÍTULO SOLICITADO: COMPRIMIDOS BICAPA DE ESTRÓGENO/SERM Y ESTRÓGENO/PROGESTINA.

PUBLICACIÓN: Gaceta 608 de 30 de septiembre 2009, N° de publicación 627.

PRIORIDAD: US 60/867.715 de 29/11/2006.

SOLICITANTE: WYETH.

APODERADO: ALVARO CORREA ORDOÑEZ.

TRÁMITE: PRESENTACIÓN DE OPOSICION

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **09 053.058**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTO DE LA OPOSICIÓN

La solicitud colombiana en trámite **09 053.058**, referida a un comprimido bicapa que comprende una primera capa que comprende por lo menos un estrógeno y una segunda capa que comprende uno o mas agentes terapéuticos seleccionado del grupo que consiste de un modulador del receptor de estrógeno selectivo y un gestágeno; no reúne los requisitos necesarios para otorgársele el privilegio de patente de invención, como se demuestra a través de los siguientes argumentos:

En primer lugar, y refiriéndonos a la carencia de nivel inventivo de la combinación farmacológica que expone la solicitud colombiana en trámite, específicamente entre estrógenos y un modulador del receptor de estrógeno selectivo y/o un gestágeno, es relevante mencionar que existen documentos que exponen con anterioridad la utilidad terapéutica de dicha combinación^{1,2,3,4,5}. Teniendo en cuenta lo anterior, cualquier persona medianamente versada en la materia buscaría la manera de asociar dichos principios activos de una manera mas practica para su administración, en donde la inclusión de los principios activos en

¹ Giovanni Frazzetto. A second chance for hormone replacement therapy? EMBO Rep. 2003 December; 4(12): 1112-1115.doi: 10.1038/sj.embor.7400043.

² MacLaughlin EJ, Sleeper RB, McNatty D, Raehl CL. Management of age-related osteoporosis and prevention of associated fractures. Ther Clin Risk Manag. 2006 Sep;2(3):281-95.

³ Christgau S, Tankó LB, Cloos PA, Mouritzen U, Christiansen C, Delaissé JM, Høegh-Andersen P. Suppression of elevated cartilage turnover in postmenopausal women and in ovariectomized rats by estrogen and a selective estrogen-receptor modulator (SERM). Menopause. 2004 Sep-Oct;11(5):508-18.

⁴ Barnabei VM, Cochrane BB, Aragaki AK, Nygaard I, Williams RS, McGovern PG, Young RL, Wells EC, O'Sullivan MJ, Chen B, Schenken R, Johnson SR; Women's Health Initiative Investigators. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. Obstet Gynecol. 2005 May;105(5 Pt 1):1063-73.

⁵ Patente Americana USRE36247: Method of hormonal treatment for menopausal or post-menopausal disorders involving continuous administration of progestogens and estrogens publicada el 06 de Julio de 1999.

una misma formulación farmacéutica, como por ejemplo en una formulación tipo comprimido bicapa, resulta de evidente utilidad.

En este mismo aspecto es relevante mencionar el concepto de la Doctora en Bioquímica Silvia Susana Giarcovich⁶ en su opinión escrita a cerca de "Asociaciones y Patentes" en donde afirma que las asociaciones farmacológicas están restringidas por ciertos principios y lineamientos preestablecidos por varias entidades, puesto que dichas combinaciones deben estar bajo el precepto de eficacia, seguridad y eficiencia terapéutica, veamos:

"3.3.2. Lineamientos FDA:

A continuación se mencionarán lineamientos que la agencia sanitaria de EEUU ha establecido para el caso de los llamados "*Combination Drug Products*":

3.3.2.1. CFR

El CFR establece la política en relación a las combinaciones de drogas a dosis fija para humanos en 21CFR300.50. Allí se establece que dos o más drogas pueden ser combinadas en una única unidad posológica cuando cada componente hace una contribución al efecto propuesto y la dosis de cada componente es tal que la combinación es segura y efectiva (se consideran casos especiales cuando se busca aumentar la seguridad y eficacia del principal componente o minimizar su potencial abuso).

3.3.2.2. Guía "OTC Combination of Drug Products" [Docket No. 78D-0322]⁷:

Esta guía establece en detalle la política de la agencia para combinar dos o más ingredientes activos OTC, seguros y eficaces y caracteriza diferentes tipos de asociaciones de OTC:

- Ingredientes activos de diferentes categorías terapéuticas para tratar distintos síntomas simultáneamente: Sólo se acepta esta asociación si cada ingrediente está presente dentro de su rango de seguridad y eficacia.
- Ingredientes activos de la misma categoría terapéutica que tienen distintos mecanismos de acción para tratar los mismos síntomas o condición: Sólo se acepta esta asociación si es mejor o

⁶ Profesora Regular Adjunta del Departamento de Farmacología de la Facultad de Farmacia y Bioquímica de la UBA y Directora Técnica y Gerente de Estudios Clínicos de DIFFUCAP-EURAND SACIFI

⁷ Anunciada en el Federal Register (1978), Vol. 43, No. 229.

igual que cada ingrediente solo en su dosis terapéutica y también pueden usarse a dosis subterapéuticas si corresponde.

- Ingredientes activos de la misma categoría terapéutica que tienen el mismo mecanismo de acción: Estos no deberían ser combinados a menos que haya alguna ventaja con respecto a los ingredientes simples (mayor eficacia, seguridad, aceptación del paciente o calidad de la formulación).
- Ingredientes considerados adyuvantes, que aumenten o alteren el efecto de otro ingrediente activo, serán, considerados ingredientes activos.

3.3.2.3. Guía Draft "Current GMP for Combination Products":

Este documento provee una guía para la industria y para el *staff* de la FDA acerca de la aplicabilidad de la cGMP para las asociaciones (*combination products*) y define a un *combination product*, de acuerdo al CFR (21CFR3.2(e)), de forma que no sólo involucra drogas sino *devices*:

Un producto combinado es un producto compuesto de cualquier combinación de una droga y un dispositivo; un producto biológico y un dispositivo; una droga y un producto biológico; o una droga, dispositivo, y un producto biológico. Bajo 21 CFR 3.2 (e), un producto de combinación incluye:

- 1. Un producto que comprende dos o más componentes regulados (i.e., droga/dispositivo, biológico/dispositivo, droga/biológico, o droga/dispositivo/biológico) que son combinados físicamente, químicamente, o de otra forma, o mezclados y producidos como una entidad única;*
- 2. Dos o más productos separados, empaquetados juntos en un solo paquete, o como una unidad comprendiendo droga y productos del dispositivo, dispositivo y productos biológicos, o biológico y productos de droga;*
- 3. Una droga, dispositivo, o producto biológico empaquetado separadamente que, de acuerdo a su plan de investigación o el etiquetado propuesto, es destinado para utilizarse únicamente con una droga, dispositivo, o producto biológico aprobada especificada individualmente, dónde al mismo tiempo ambos son deben estar aceptados para la indicación o efecto y donde, luego de la aprobación del producto propuesto, el etiquetado del producto aprobado necesitaría ser cambiado (e.g., para reflejar un cambio en la indicación, forma farmacéutica, dosis, ruta de administración, cambio significativo en la posología); ó*
- 4. Cualquier droga en investigación, dispositivo, o producto biológico empaquetado separadamente que, de acuerdo al etiquetado propuesto es para utilizarse únicamente*

con otra droga en investigación especificada, dispositivo, o producto biológico, dónde a la vez se requiere que ambos sean aceptados para la misma indicación, uso y efecto.

Además, dentro de esta guía es muy interesante el concepto de "parte constitutiva de un *combination product*" porque especifica su identidad regulatoria como droga, *device* o producto biológico.

3.3.2.4. Guía *Draft "Combination Products Timeliness of Premarket Reviews"*:

Esta guía provee información a un postulante a reclamar la resolución de una disputa acerca de la duración de la revisión de una postulación referida a un producto combinado. Es una guía referida simplemente a un problema administrativo que demuestra cuán regulado se halla este ámbito que tiene una oficina destinada, la Office of Combination Products.

3.3.3. Lineamientos EMEA: Guía *"Fixed Combination Medicinal Products"*:

Esta guía propone evaluar las potenciales ventajas de la asociación en cuanto a mejoramiento de la relación riesgo/beneficio y a simplificación de la terapia. Asimismo, establece criterios a respetar y requisitos a cumplimentar, tanto generales como particulares. Dentro de los particulares hace especial referencia a:

- La indicación.
- Los estudios farmacodinámicos y farmacocinéticos.
- Eficacia y Seguridad: En este caso diferencia dos escenarios concretos:
 - a) *Cuando la combinación fija corresponde exactamente a combinaciones que están ya en uso difundido, un análisis de los datos bibliográficos bien fundamentados debería ser presentado. Con tal que los datos estén bien documentados, este análisis puede ser útil en reducir la cantidad de ensayos clínicos a ser realizada y podría facilitar la selección de dosis para cada sustancia y el rango de dosis propuesto en la combinación fija.*
 - b) *Cuando la combinación fija es esencialmente nueva (las sustancias activas no son usualmente combinadas, la composición cuantitativa es inusual entre sustancias usualmente combinadas o una sustancia enteramente nueva), los datos necesarios son similares a los de una nueva entidad química en la situación donde la combinación fija será propuesta (primero línea o segunda de la línea de terapia). La existencia de experiencia con las sustancias debería ser tenida en cuenta.*

y especifica Régimen de dosis y Composición, Ensayos Terapéuticos y Aspectos de Seguridad.

- Paquetes combinados de diferentes productos medicinales para administración simultánea o secuencial.

Conclusión:

Las diferentes agencias sanitarias a nivel internacional han regulado fuertemente el registro de asociaciones de forma de garantizar la seguridad y eficacia de las mismas y la buena calidad en su elaboración. Todo estudio, investigación o análisis derivados de estos requisitos representan procedimientos de rutina y no originales ideas llevadas a la práctica."

En un segundo aspecto, pero refiriéndonos nuevamente a la carencia absoluta de nivel inventivo de la solicitud en cuestión, es relevante señalar que las formulaciones con las características que describe la solicitud colombiana en trámite, en la totalidad de su capítulo reivindicatorio, corresponden a una tecnología descrita con anterioridad en el estado de la técnica, tecnología que además es reconocible para cualquier persona medianamente versada en la materia como comprimidos multicapas. Dichos comprimidos corresponden a un producto constituido por diferentes granulados, dispuestos uno sobre otro en varias capas paralelas obtenidas por precompresión; el conjunto es sometido a una compresión final para dar lugar a un comprimido estratificado, en donde generalmente se incorporan sustancias activas incompatibles física o químicamente o bien para producir formulaciones de liberación controlada⁸. Prueba de la versatilidad con que se pueden incluir diversas combinaciones de fármacos dentro de estas formulaciones tipo comprimido bicapa, se evidencia en documentos como la publicación internacional WO9520946A1 publicada el 10 de agosto de 1995 en donde se combinan dentro de un comprimido bicapa amoxicilina y clavulanato, la publicación internacional WO03059327A1 publicada el 24 de Julio de 2003 en donde se combinan en un comprimido bicapa telmisartan con hidroclorotiazida y la patente americana US20050220877A1 publicada el 06 de octubre de 2005 en donde se combinan dentro del comprimido bicapa antihistamínicos y descongestionantes.

Siendo más precisos, existen otros documentos donde este tipo de formulaciones farmacéuticas ya se relacionaban con la combinación farmacológica entre

⁸ Vila Jato J.L. Tecnología Farmacéutica. Volumen II. Página 144.

estrógenos y progestinas y/o moduladores del receptor de estrógeno selectivo (SERM). Por ejemplo la publicación internacional WO 03/077923 publicada el 25 de septiembre de 2003 revela:

b) Combining Progesterone and Estrogen in One Dosage Form

A combination dosage form comprising progesterone and estrogen dosage forms can be prepared by first preparing the progesterone and estrogen formulations or dosage forms separately and then combining them. In one aspect, progesterone and estrogen formulations can be compressed together to form one dosage form, for example, a multilayered tablet wherein each layer represents a progesterone or an estrogen formulation. Alternatively, the

La publicación internacional WO 95/17169 publicada el 29 de Junio de 1995 revela:

The method of making pharmaceutical tablets comprising blending a unit dosage quantity of one or more low dosage medicaments with an agglomerated excipient of the group comprising mannitol, maltodextrin or corn syrup solid adding optional tableting aids such as one or more tableting fillers, disintegrating agents or lubricants and drying and compression of said blend.

(...)

The method of claim 7 in which the medicament is a combination of conjugated estrogens and a progestin.

La publicación internacional WO 01/070208 publicada el 27 de diciembre de 2001 revela:

Both components can be incorporated in the compressed tablet core or in a tablet coating formulated to maintain drug stability and provide adequate oral bioavailability. For example, the progestin can be micronized.

(...)

1. Use of conjugated estrogens and medroxyprogesterone acetate in the manufacture of pharmaceutical packs comprising daily dosage units for the treatment or inhibition of menopausal or postmenopausal disorders in a perimenopausal, menopausal, or postmenopausal woman in need thereof, wherein each daily dosage unit comprises a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.

La patente europea EP 0722720 publicada el 24 de Julio de 1996 revela:

One preferred embodiment of this invention is a compressed tablet in which the tablet core contains a unit dose of an estrogenic compound or a mixture thereof in an amount of from about 0.1 to about 5.0 milligrams, or more preferably from about 0.3 to about 2.5 milligrams, in combination with standard excipient compression aids and fillers. Most desirably, the conjugated estrogens found in the tablet core comprises the naturally occurring conjugated estrogen product known as Premarin®. Over a sugar coat on the compressed tablet is applied an additional sugar coat containing about 1 to about 50 milligrams, and preferably about 1.5 to about 30 milligrams, of medroxyprogesterone acetate, a color coat, and finally, a polish coat.

La publicación internacional WO 97/04753 publicada el 13 de febrero de 1997 revela:

A combination tablet containing conjugated estrogens and medroxyprogesterone acetate is made by applying an aqueous based suspension of micronized medroxyprogesterone acetate containing an ethylcellulose dispersion, hydroxypropylmethylcellulose, and dibutylsebacate or triethyl citrate as the film coat. The film coat is applied to the subcoated tablets using an Accela Cota or Wurster apparatus.

en estas tres últimas anterioridades se puede apreciar además que se hace mención explícita de la combinación entre estrógenos conjugados y acetato de medroxiprogesterona en este tipo de formulaciones, tal y como se expone en la solicitud colombiana en las reivindicaciones 3 y 4.

y por ultimo la publicación internacional WO 97/004752 publicada el 13 de febrero de 1997 revela:

1. A pharmaceutical composition in a solid, unit dosage form capable of oral administration for the hormonal
5 treatment of peri-menopausal, menopausal and post-menopausal disorders in a woman comprising:
conjugated estrogens coated onto one or more organic excipients forming a powdered conjugated estrogen composition having less than about 2.5% free water by weight and greater
10 than 2.5% total water wherein said solid unit dosage form is coated with a moisture barrier coating.

(...)

13. The method of claim 12 wherein said gel-forming organic excipient is selected from the group consisting of hydroxypropylmethylcellulose, sodium carboxymethylcellulose and hydroxypropylcellulose.

(...)

21. A pharmaceutical composition of claim 17 further comprising two or more coatings with one outer coating comprising a polymeric film and at least one additional hormone.

22. A pharmaceutical composition of claim 21 wherein said hormone is selected from the group consisting of progesterone, medroxyprogesterone, medroxyprogesterone acetate, testosterone, methyltestosterone, and combinations thereof.

en donde además de la combinación entres estrógenos conjugados y acetato de medroxiprogesterona, se hace mención de la inclusión de polímeros que pueden formar geles, específicamente hidroxipropilmetilcelulosa, tal y como lo expone la solicitud colombiana en sus reivindicaciones 6 a 9.

En el mismo sentido, todos los excipientes que hacen parte de la formulación reivindicada en la solicitud colombiana en cuestión, son excipientes convencionalmente utilizados en este tipo de formulaciones sólidas para administración oral, por ejemplo, cualquier persona medianamente versada en la materia debe reconocer que la lactosa puede utilizarse como diluyente, que la celulosa microcristalina puede usarse como aglutinante, que el estereato de magnesio es uno de los lubricantes mas comunes, que la croscarmelosa de sodio se puede utilizar como desintegrante, y que el acido ascórbico es uno de los antioxidantes mas comunes; por lo tanto las reivindicaciones 10 a 36 y 47 a 53 carecen irrefutablemente de nivel inventivo.

Finalmente y teniendo en cuenta lo mencionado en los cursos sobre patentes dictados por la Dra. ZAMUDIO, Teodora, profesora de la Universidad de Buenos Aires⁹:

⁹ PROCESO 88-IP-2005 Interpretación prejudicial de los artículos 1 y 4 de la Decisión 344 de la Comisión del Acuerdo de Cartagena con fundamento en la consulta formulada por el Consejo de Estado de la República

“Se podría diferenciar la combinación de elementos de la simple agregación. La primera es la sinergia de los elementos de forma tal que se genera uno nuevo con propiedades distintas, de tal manera que el nuevo elemento sólo es resultado de dicha combinación sin que puedan determinarse los elementos por separado; la segunda se da cuando los elementos se mantienen intactos en cuanto a su efecto fundamental y, por lo tanto, son claramente distinguibles unos de otros, es decir, no hay una sinergia o combinación intrínseca de los elementos.”

podemos concluir que la solicitud colombiana en trámite es una simple agregación de elementos, todos ellos conocidos en el estado de la técnica, elementos dentro de los que se incluyen tanto la formulación farmacéutica tipo tableta bicapa, los excipientes que hacen parte de la misma formulación, y la combinación farmacológica incluida en dicha formulación; agregación que resulta en una formulación farmacéutica convencional y reconocida por cualquier persona medianamente versada en la materia, y que se puede llegar a ella aplicando los ensayos básicos de las etapas de preformulación y formulación correspondientes a este tipo de formulaciones, y que son indispensables para asegurar la seguridad, estabilidad, eficiencia y eficacia de cualquier medicamento, y por lo tanto podemos afirmar que dicha solicitud carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16 y 18 (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- ❖ Abstracts de todas las publicaciones científicas mencionadas en el acápite de Fundamentos de la Oposición.
- ❖ Portadas de las Patentes: Americana USRE36247: Method of hormonal treatment for menopausal or post-menopausal disorders involving continuous administration of progestogens and estrogens publicada el 06 de Julio de 1999, la publicación internacional WO9520946A1 publicada el 10 de agosto de 1995, la publicación internacional WO03059327A1 publicada el 24 de Julio de 2003 y la patente americana US20050220877A1 publicada el 06 de octubre de 2005 en donde se combinan dentro del comprimido bicapa antihistamínicos y descongestionantes.
- ❖ La publicación internacional WO 03/077923 publicada el 25 de septiembre de 2003 pagina 16 y capítulo reivindicatorio.
- ❖ La publicación internacional WO 95/17169 publicada el 29 de Junio de 1995 capítulo reivindicatorio.
- ❖ La publicación internacional WO 01/070208 publicada el 27 de diciembre de 2001 pagina 17 y capítulo reivindicatorio.
- ❖ La patente europea EP 0722720 publicada el 24 de Julio de 1996 pagina 6 y capítulo reivindicatorio.
- ❖ La publicación internacional WO 97/004752 publicada el 13 de febrero de 1997 capítulo reivindicatorio.
- ❖ La publicación internacional WO 97/04753 publicada el 13 de febrero de 1997 ejemplos 5 a 9 y capítulo reivindicatorio.
- ❖ Copia del PROCESO 88-IP-2005 Interpretación prejudicial de los artículos 1 y 4 de la Decisión 344 de la Comisión del Acuerdo de Cartagena con fundamento en la consulta formulada por el Consejo de Estado de la República de Colombia, Sala de lo Contencioso Administrativo, Sección Primera. Expediente Interno N° 2001-00039 (6787).

VI. ANEXOS

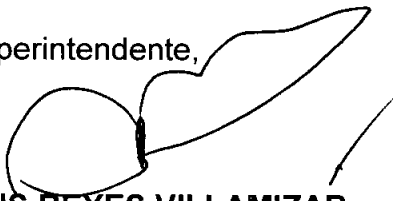
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Tecnoquímicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. El mencionado en el acápite de pruebas.

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A., las recibirá en la secretaría de su Despacho o en su sede localizada en la Calle 23 # 7-39, de la ciudad de Cali.

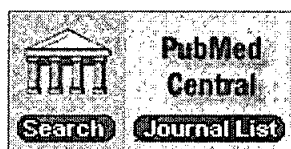
Señor Superintendente,



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Science and Society
Analysis

A second chance for hormone replacement therapy?

Vicki Brower

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Summary

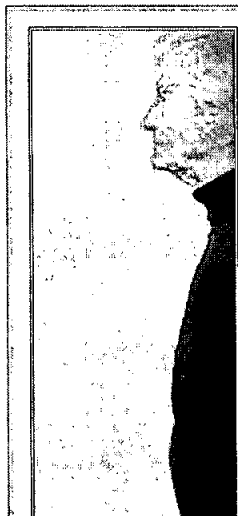
Hormone replacement therapy for older women has been vilified after two major studies showed that it increased their susceptibility to various diseases. But scientists maintain that, used differently, it can still help to protect against neurological and cardiovascular diseases

The results of two large-scale studies on the health risks and benefits of hormone replacement therapy (HRT) for post-menopausal women dropped a bombshell of bad news this year. The Women's Health Initiative (WHI) study, sponsored by the US National Institutes of Health (NIH), and the UK's Million Women Study, sponsored by the British Medical Research Council (MRC) and Cancer Research UK, both found that HRT significantly increases the risk of invasive breast cancer. The US study also found higher risks of heart attack, stroke and blood clotting. The NIH took the unusual step of halting the WHI trial and recommended that women stop taking HRT for mild menopausal symptoms. However, many researchers maintain that these studies tell only one side of the story and that HRT, if the right drugs are used with the right regimen in the right patients, can indeed be beneficial to women's health.



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The WHI reported in several publications (Anderson *et al.*, 2003; Shumaker *et al.*, 2003; Rapp *et al.*, 2003; Wassertheil-smoller *et al.*, 2003) that for the 16,608 women in the study who took a combination of oestrogen and progesterone, the risk of breast cancer increased by 26%, heart attack by 24% and stroke by 41%. Combination therapy also doubled the risk of ovarian cancer and all types of dementia, including Alzheimer's disease. Although the study found a reduction in colon cancer risk and osteoporosis (Cauley *et al.*, 2003), the WHI concluded that the risks outweigh the benefits and stopped its study after five years. The oestrogen-only part of the study is still underway, with results expected in 2005. The British study similarly showed that women between the ages of 50 and 64 taking a combination therapy had a 22% higher risk of death from breast cancer compared with women taking a placebo (Million Women Study Collaborators, 2003). All told, these two major trials show that the risks by far outweigh the benefits of treating post-menopausal symptoms, such as hot flashes, sleep disruption and vaginal atrophy, with combination HRT. The US and UK governments immediately issued new guidelines stating that the only reason to consider HRT is for treatment of moderate-to-severe symptoms at the lowest possible dose and for the shortest amount of time, while taking the patient's individual risk factors into consideration. For most physicians and patients, HRT is now no longer considered a 'lifestyle' drug for women, but a choice that comes with considerable risk.



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For the approximately 50 million post-menopausal women in the USA and millions of others in Europe, however, the debate has first and foremost caused a great deal of confusion and fear. Bruno Muller-Oerlinghausen, chairman of the German Commission on the Safety of Medicines (Berlin) called the thousands of breast cancer deaths from HRT “a national and international tragedy” and stated in the UK *Sunday Herald* that “more women have probably died from the hormone therapy than damaged children were born in the wake of the thalidomide scandal.” The UK's MRC estimates that HRT has caused 20,000 deaths from breast cancer over the past ten years in the UK alone. Sales of Wyeth's (Madison, NJ, USA) Premarin® (conjugated equine oestrogen) and PremPro™ (a combination of Premarin and synthetic progesterone) dropped precipitously over the past 18 months and the *British Medical Journal* recently reported that 40% of women in New Zealand had stopped taking HRT after results from the WHI study were published (Lawton *et al.*, 2003).

The controversy was further fuelled by women's health journalist and activist Barbara Seaman's best-selling book *The Greatest Experiment Ever Performed on Women: Exploding the Estrogen Myth* (Hyperion, New York) that blamed drug companies, such as Wyeth and Schering in Berlin, Germany, for putting profits above the well-being of women. She details the development and marketing of Premarin and diethylstilbestrol, a synthetic oestrogen once prescribed to pregnant women to prevent miscarriage and later found to cause gynaecological cancers in their daughters. Premarin in particular has been marketed as a 'lifestyle' drug, helping women to stay 'forever feminine' and avoid the emotional and physical tolls of menopause, despite early evidence that the drug could cause breast and cervical cancer. Although the Nurses' Health Study (Grodstein & Stampfer, 1996) and the 2002 Cache County Study (Zandi *et al.*, 2002) showed that HRT might help to prevent heart disease and dementia, these observations have been interpreted as the 'healthy user effect'—the fact that women in this study were healthier and took better care of themselves—according to Nananda Col in the Department of Medicine at Brigham & Women's Hospital and Harvard Medical School (Boston, MA, USA).

For most physicians and patients, HRT is now no longer considered a 'lifestyle' drug for women, but a choice that comes with considerable risk

A similar controversy over hormone replacement therapy for men is also heating up. Approximately 5.6 million men in the USA now take testosterone to treat a range of age-related symptoms, including diminished libido, and loss of muscle mass and strength, in spite of evidence that testosterone replacement may fuel prostate cancer and atherosclerosis. On the basis of the results with HRT for women and the scientific literature on testosterone, the Institute of Medicine (Washington, DC, USA) is now considering a large, government-sponsored study in the USA to investigate whether testosterone treatment creates health risks for men.

Despite the damning trial results, the debate over HRT has not been resolved. While many scientists, including Marcia Stefanick, Associate Professor at Stanford University's School of Medicine (Stanford, CA, USA) and Chair of the WHI Steering Committee, say that the case is closed for treating women with HRT, others disagree. They believe that the studies only show that treating post-menopausal women with certain forms of oestrogen and progesterone is harmful, but maintain that there is strong scientific evidence that younger women could in fact benefit from other formulations of hormones that reduce the risk of cardiovascular and neurological diseases. This will be difficult to prove. Stefanick said that "additional studies would be a waste of taxpayers' dollars," and Wyeth is not planning any new trials with Premarin or PremPro, said company spokesperson Natalie DeVane. It is, however, starting a phase III trial with the next-generation SERM (selective oestrogen-receptor modulator) bazedoxifene combined with Premarin in post-menopausal women with osteoporosis and menopausal symptoms. Unlike oestrogen, SERMs do not have proliferative effects on the uterus, but they may actually produce some menopausal-like vasomotor symptoms, such as hot flashes. "In principle, there should be new large-scale trials, but in practice, I doubt they will happen," said Wulf Utian, head of the North American Menopause Society (Cleveland, OH, USA).

One small trial is being planned, however. S. Mitchell Harman, head of the Kronos Longevity Research Institute (Phoenix, AZ, USA), is designing a study that will test different forms of hormones in younger women for the prevention of cardiovascular disease, KEEPS (Kronos Early Estrogen Prevention Study). According to Harman, 450 women, aged 45–55, will be studied for five years, beginning this summer: 150 will receive transdermal oestradiol and oral placebo, 150 will get conjugated equine oestrogen and a placebo skin patch, and 150 will receive a placebo tablet and skin patch. "Ideally, we should study 24,000 women for 10 years, but we don't have that kind of funding," he said. The trial will cost US \$12 million.

Approximately 5.6 million men in the USA now take testosterone to treat a range of age-related symptoms [...] in spite of evidence that testosterone replacement may fuel prostate cancer and atherosclerosis

Harman believes that HRT has benefits for women and that the WHI's failure to show protection against cardiovascular diseases can be blamed on the age of women tested (median age 63) and on the hormones used. "The WHI was based on the premise that if oestrogen is good earlier [in life], it's good later; we don't believe that. [...] Intervening for heart disease 10 years after menopause is simply too late. It takes 5–10 years after menopause for rates of heart attacks in women to rise, and by then, the damage is done and it can't be reversed," he said. Harman also noted that cardiovascular disease in older women occurs about five times as frequently as breast cancer and that there is a pressing need to find a way to protect them even if it raises breast

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cancer risk in a small number of women. By using transdermal oestrogen, he believes that the carcinogenicity of oestrogen can be reduced or eliminated, because oral oestrogen is metabolized by the liver and results in extremely high concentrations in the blood. Harman also noted that oestrogen raises levels of endogenous pro-coagulants and lowers anticoagulants, which creates a higher risk for women after the age of 55–60.

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He also cited data from experiments with female monkeys that had their ovaries removed and were given a high-fat diet to induce atherosclerosis, which showed a reduction in the number of heart attacks in animals given HRT. But Stefanick disagrees that such an animal model is relevant to humans. "Women at menopause and even 10–15 years later are more similar to each other than they are to teenage monkeys who have had their ovaries removed [and are put on hormones]," she remarked. She doubts that testing 1,500 younger women with other types of hormone will yield data any different to the WHI study, which had included younger women who did not test better than the older women.

Another reason for the discouraging results in the WHI and UK trials may be the use of artificial progesterone, some researchers believe. "The real culprit in WHI was the synthetic progesterone used," according to C. Dominique Toran-Allerand, a professor in the Department of Anatomy and Cell Biology at Columbia University (New York, NY, USA). "Provera [methoxyprogesterone acetate (MPA), the synthetic progesterone in PremPro] is a promiscuous compound, binding to many other receptors, including some in the breast which can cause cell division and cause harm if one is at risk for cancer." Synthetic progestin is not a good substitute for natural progesterone, she continued, because it also antagonizes the effect of oestrogen, whereas under normal physiological conditions, the natural forms of these hormones work synergistically.

Moreover, there is "ample literature showing that oestrogen and progesterone given at the onset of menopause have neurological benefits if given in a cyclical manner—for memory, mood disorders and depression," Toran-Allerand said, but if the treatment is started too late, cognitive deficits can no longer be corrected. Research on oestrogen's neuroprotective abilities applies mostly to younger women, echoed Roberta Diaz Brinton of the University of Southern California (Los Angeles, CA, USA). In 2002, Brinton showed how MPA negates the potential benefits of oestrogens on cognitive function and prevention of Alzheimer's disease (Nilsen & Brinton, 2002a), which further supports her earlier research, which showed that oestradiol and progesterone—but not MPA—can protect neurons (Nilsen & Brinton, 2002b). A more recent article (Nilsen & Brinton, 2003) investigated how and why natural progesterone and MPA have such different effects.

Oestrogen exerts its neuroprotective effects by acting as a free-radical scavenger and regulating calcium levels in neurons, but it can do so only if another enzyme, extracellular receptor kinase (ERK), is activated. Brinton's work showed that only oestradiol and progesterone, but not MPA, activate nuclear ERK in hippocampal neurons; in fact, MPA blocks oestradiol-induced nuclear activation.

"Oestrogen is a 'Goldilocks' molecule."

"Oestrogen is a 'Goldilocks' molecule," explained Brinton. "It has to be given at a dose that is 'just right'—too much or too little has the same effect: none." Consequently, there is a narrow window of dose response for the hormone's beneficial effects on memory function and protection of neurons. In addition, oestrogen has a 'healthy-cell bias'—it confers a survival advantage to healthy neurons challenged with a neurotoxin, but not in patients whose supply of oestrogen has been attenuated for an extended duration. "In the past, women have been treated with oestrogen a year after their last menstrual cycle; but during perimenopause, their brains are likely to be more responsive," Brinton said. Furthermore, women with a healthy uterus cannot take an oestrogen-only formulation because of the hormone's proliferative effects on the endometrium, the blood-rich mucous membrane that lines the inside of the uterus.

What scientists, such as Brinton, Harman and others, say is that the book on HRT is not closed—it has potential health benefits for women. However, more research is needed to determine what route of administration, oral or local, and which formulations for which patient groups are most effective to benefit the heart and brain while not damaging other organ systems. This may be difficult to show. Even if scientific evidence points to beneficial aspects of hormone treatment, these can only be determined in large-scale studies. After the huge controversy and public reaction to the WHI and Million Women Study debacles, it may be difficult to lure women into clinical trials again.

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Management of age-related osteoporosis and prevention of associated fractures

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Abstract: Osteoporosis and related fractures are a significant concern for the global community. As the population continues to age, morbidity and mortality from fractures due to low bone mineral density (BMD) will likely continue to increase. Efforts should be made to screen those at risk for osteoporosis, identify and address various risk factors for falls and associated fractures, ensure adequate calcium and vitamin D intake, and institute pharmacological therapy to increase BMD when indicated. Agents which increase BMD and have been shown to decrease fractures, particularly at the hip, should be considered preferentially over those for which only BMD data are available. Drugs which have been shown to decrease the risk of age-related osteoporotic fractures include oral bisphosphonates (alendronate, ibandronate, and risedronate), intranasal calcitonin, estrogen receptor stimulators (eg, estrogen, selective estrogen receptor modulators [raloxifene]), parathyroid hormone (teriparatide), sodium fluoride, and strontium ranelate. Data are beginning to emerge supporting various combination therapies (eg, bisphosphonate plus an estrogen receptor stimulator), though more data are needed to identify combinations which are most effective and confer added fracture protection. In addition, further research is needed to identify ideal regimens in special populations such as nursing home patients and men.

Keywords: osteoporosis, fracture, prevention, treatment

Background

Epidemiology and economic impact

Osteoporosis, defined as a skeletal disorder characterized by decreased bone strength and increased susceptibility of fractures (NIH 2001), is a significant health concern for the international community. Hip fractures, considered to be the most debilitating fragility fracture secondary to osteoporosis, are associated with an approximately 2-fold increased risk of mortality the year following the fracture (Center et al 1999; Empana et al 2004). In 1990 it was estimated that approximately 1.3 million hip fractures occurred globally (Johnell and Kanis 2004). These fractures were associated with 740 000 deaths and 1.75 million disability adjusted life-years lost, with the highest rates occurring in established market economies such as North America, Japan, Australia, and Western Europe. In the US alone, it is estimated that over 1.5 million fractures occur annually due to osteoporosis, with over 300 000 occurring at the hip (NOF 2005b).

While hip fractures are considered to be the most debilitating osteoporosis-related fracture, other fracture types are common. In the US, it is estimated that wrist fractures occur at almost the same rate as hip fractures with approximately 250 000 annually, and the vertebral fracture rate is more than double that of hip fractures with approximately 700 000/year (NOF 2005b). These fractures lead to numerous adverse sequelae include chronic pain, deformity, and disability, decreased quality of life, decreased mobility, increased risk of pressure ulcers, and decreased pulmonary function (Nevitt et al 1998; Schlaich et al 1998; Lips et al 1999; Fink et al 2003; Margolis et al 2003; Hallberg et al 2004).

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As the global population ages, the prevalence of age-related osteoporosis (ie, postmenopausal osteoporosis, male osteoporosis) and related fractures is likely to increase considerably. In the US, the prevalence of osteoporosis is expected to grow from an estimated 10 million in 2002 to 14 million by 2020 (NOF 2005a). In the EU, the total number of hip fractures is estimated to increase from 414 000 to 972 000 from year 2000 to 2050 (Compston et al 1998). Vertebral fractures are estimated to increase during this time from 23.7 million to 37.3 million.

The economic consequences of osteoporosis with its associated morbidity and mortality due to fractures are staggering. While total world-wide estimates are not readily available, there are data that describe the costs in various countries. In Belgium (population ~10 million), the total cost of hip fractures in 1996 was almost US\$126.2 million per year (Reginster et al 1999). The estimated cost of osteoporotic fractures in females greater than 50 years of age using 1997 figures cost the UK £727 million (US\$1.23 billion); or an estimated £942 million (US\$1.6 billion) including men, assuming the cost of treatment was the same as females (Dolan and Torgerson 1998). The annual cost of osteoporotic fractures to the US healthcare system in 2001 was approximately US\$17 billion, with a single hip fracture costing approximately US\$40 000 (NOF 2004).

Diagnosis and classification

The gold standard for diagnosis of osteoporosis is measurement of bone mineral density (BMD) using central dual-energy x-ray absorptiometry (Lewiecki et al 2004). Bone mineral density is defined as the average concentration of mineral per unit of area (g/cm^2) measured (Cummings et al 2002). This figure is then reported as the number of standard deviations (SD) between the value of an individual and the mean value for a reference population. The World Health Organization (WHO) classification for diagnosis is based on comparison of BMD to a young-adult mean (T-score) for postmenopausal women and men >50 years. Normal is considered a T-score greater than -1.0 , osteopenia is a T-score between -1.0 and -2.5 , and osteoporosis is a T-score less than -2.5 . Severe osteoporosis may be considered when the T-score is less than -2.5 in the presence of one or more fragility fractures (Kanis and Gluer 2000). For children, premenopausal women, and men younger than 20 years, Z-scores, which are SD comparisons based on age and gender, should be used instead rather than T-scores (Lewiecki et al 2004). Because BMD declines with age, T-scores are lower than Z-scores, particularly for patients with

advanced age. For instance, a 70 year old female with a Z-score of -1.0 may have a T-score of -3.0 and thus be considered osteoporotic.

Bone mineral density is a surrogate marker for bone strength and fragility fractures. It is estimated that BMD accounts for approximately 70% of bone strength (NIH 2001) and correlates well with fracture risk. For every 1 SD decline in femoral-neck BMD it is estimated that the risk of an osteoporotic fracture at the hip increases by 2.5-fold (Cummings et al 1993; Marshall et al 1996). While BMD is useful to evaluate risk of fracture, it should be noted that a significant portion of bone strength may be derived from other sources (eg, genetics). Thus, while BMD is a useful tool to evaluate risk of osteoporotic fractures, choice of medication used for prevention or treatment should ideally be based on data demonstrating reduction in fractures, recognizing that other factors such as past medical history and adherence may also play a role.

Risk assessment and prevention of fractures

To identify patients at risk of fractures and optimize pharmacotherapy, a thorough risk factor analysis is recommended. Two major areas of risk factor assessment that should be considered, particularly for older individuals, include an assessment of both "bone" and "non-bone" related risks. "Bone-related" risk factors are those factors associated with bone density. "Non-bone" risk factors are variables associated with fracture risk unrelated to bone density, and may increase fracture risk irrespective of osteoporosis diagnosis. However they compound the risk of an osteoporosis end-point in a patient who has decreased bone density.

Traditional risk factor assessment focuses on "bone" related factors. These are variables that increase the risk of fracture by affecting BMD and include physical frame, genetics, lifestyle, hormonal changes, and medication effects (NOF 2004). Prior to obtaining BMD measurements, a full assessment of these "bone" related risk factors should include complete medical history including family history of osteoporosis and fracture and any personal history of fracture as an adult. For women, this should include a gynecological history including history of menses, pregnancies, surgeries, or menopause. Physical exam should reveal weight, height (particularly if height has changed from known adult maximum) and curvature of the spine. Patient interview can reveal diet (including dairy and supplemental calcium/vitamin D intake), exercise, smoking, alcohol use,

and current medication use. Tools such as the Osteoporosis Risk Assessment Instrument (ORAI) and the Simple Calculated Osteoporosis Risk Assessment (SCORE) are validated instruments which take into account these "traditional" risk factors (Lydick et al 1998; Cadarette et al 2000). It has also been reported that the WHO will soon release an instrument to quantify the contribution of various osteoporosis risk factors and calculate an individuals' anticipated 10-year fracture risk (Tucci 2006).

In addition to traditional risk factor assessment, clinicians should be mindful of additional "non-bone" risk factors. While these variables are not directly related to bone density, they can increase risk of fractures by increasing the risk of fall-related injury. Fall-related injuries are a leading cause of morbidity and mortality in older individuals. While falls can cause a range of injuries not limited to fracture, including pain, swelling, bruising, lacerations, sprains, concussions, or subdural hematomas, the combined risk of falls and low BMD puts older individuals at particular risk of functional decline due to fracture. In the US, falls are a significant cause of admission to long term care facilities, and are a leading cause of both injury and death in older individuals (Granek et al 1987; Tinetti and Williams 1997).

While only 5%–10% of falls in the community setting result in fracture and subsequent hospitalization (van Weel et al 1995), this percentage is magnified by the sheer prevalence of falls. It has been estimated that one third of community dwelling individuals over the age of 65 will fall in one year (Tinetti and Williams 1997; Cumming 1998). This estimate increases to 50% when considering the population over the age of 85 years.

It may be difficult to elucidate the cause and effect relationship between falls and fractures. While fractures can certainly result from a fall, the fall can likewise be a consequence of a fracture. This can occur when a pathologic

fracture of the hip is the precipitating cause. If there is no clear patient history to shed light on circumstances surrounding a fall event, it may be difficult to determine which event, the fall or the fracture, preceded the other. For that reason, both "bone" and "non-bone" risks for fracture should be assessed in all older individuals. Risk factors for falls can be generally categorized as intrinsic or extrinsic as described in Table 1 (Sleeper et al 2000).

A component of both bone and non-bone risk factor assessment that deserves special attention is the drug regimen review including: 1) medications for the prevention or treatment of osteoporosis, 2) medications associated with drug-induced osteoporosis, and 3) medications or environmental factors predisposing to falls. Other areas which may be evaluated include whether a BMD evaluation has been performed, intake of calcium and vitamin D, as well as their respective formulations, doses, and administration regimens. While the presence of an osteoporosis treatment regimen suggests a BMD evaluation has occurred, it should not be assumed that fracture risk has been optimally managed. The presence of pharmacotherapy for an established osteoporosis diagnosis is in fact a surrogate marker that indicates the need for ongoing assessment of both bone and non-bone related risk. Medications associated with drug-induced osteoporosis such as glucocorticoids, chronic heparin, excessive thyroid replacement, immunosuppressants, or anticonvulsants can also be identified (NOF 2004). Concurrent medications may also be important non-bone risk factors for falls. Medications traditionally associated with fall risk include psychoactive medications (eg, antipsychotics, antidepressants, benzodiazepines, sedative hypnotics), opioids, nonsteroidal antiinflammatory drugs (NSAIDs), anticholinergic medications, and cardiovascular medications (Kannus et al 2005). Mechanisms by which these agents can cause falls include sedation, dizziness, cognitive impairment, ataxia,

Table 1 Intrinsic and extrinsic risk factors for fall-related fractures

Intrinsic risk factors	Sensory	Visual impairment, vestibular disorders, peripheral neuropathy
	Musculoskeletal	Muscle weakness, pain, gait/balance disturbances, range of motion, endurance
	Behavioral–cognitive	Cognitive impairment, depression, impaired daily activities, fear of falling
	Medication-related	Antipsychotics, antidepressants, benzodiazepines and other sedative hypnotics, Narcotics, NSAIDs, anticholinergic medications, cardiovascular medications, and the use of multiple medications
	Disease-state related	Parkinson's Disease, Alzheimer's disease, stroke, depression, arrhythmias, hypoglycemia, orthostatic hypotension, seizures, glaucoma, syncope, mobility dependence, history of falls
Extrinsic risk factors	Environment	Steps or unmarked floor rises, uneven or loose carpeting, obstacles in path, low light or excessive glare, ill-fitting footwear
	Activity	Need for or inappropriate use of assistive devices, "furniture cruising"

Abbreviations: NSAIDs, nonsteroidal antiinflammatory drugs.

blurred vision, agitation, extrapyramidal movements, psychomotor slowing, orthostatic hypotension, increased postural sway, arrhythmias, and delirium. Drug regimen review should reveal not only the presence of a potentially problematic drug, but the daily dosage, frequency and duration of use, and cumulative number of high-risk agents. Optimal management of various comorbidities which may increase the risk of dizziness or instability (eg, prevention of hypoglycemic episodes in patients with diabetes) may decrease the risk for fall-related fractures.

Pharmacological treatment

Pharmacological goals for osteoporosis include halting bone loss, improvement of BMD, and reduction in fragility fractures. Whenever possible, drug therapies that have been shown to decrease fractures, particularly at the hip, should be used as hip fractures have the greatest impact from a patient and societal perspective (Figure 1).

Bone remodeling involves both resorptive and anabolic processes. Drugs that have traditionally been used for the treatment of osteoporosis have largely focused on inhibition of bone resorption. More recently however, medications which stimulate bone formation or that both inhibits resorption and stimulate anabolic processes have been developed or are under investigation.

Calcium and vitamin D

Adequate intake of both calcium and vitamin D are an essential part of osteoporosis prevention, and no treatment regimen should be considered complete without these adjunctive therapies. There are numerous studies that have reported outcomes of supplemental calcium, vitamin D, or both on BMD and fractures (Table 2).

Calcium

The majority of the body's calcium is stored in bone, and as such, is the primary source when dietary sources are insufficient. For this reason, adequate calcium intake is a first-line defense against bone loss. A variety of calcium regimens have been studied to assess the effects on BMD and fractures (Table 2). While not every evaluation of calcium has consistently demonstrated a clear reduction in fracture risk, guidelines recommend 1000–1500 mg elemental calcium daily, whether from diet or from supplements (NIH 1994; NAS 1997; NOF 2004), with higher doses (eg, 1200–1500 mg) for those greater than 50 years or who have low BMD.

Vitamin D

Vitamin D is an essential component that, along with parathyroid hormone (PTH), regulates serum calcium concentrations. Inadequate vitamin D intake may be a greater concern than poor calcium intake, as vitamin D may not be as prevalent in the diet as calcium, and patients may be less aware of vitamin D requirements than calcium. In addition, low exposure to sunlight and poor renal function may also lead to decreased concentrations. Yet supplemental vitamin D, with or without calcium, has been shown to reduce fracture rates and may also have effects on muscle strength and risk of falling. A recent meta-analysis of double-blinded, randomized controlled trials evaluating various doses of vitamin D found that while lower doses (eg, 400 IU) were not associated with a significant benefit, 700–800 IU daily was associated with 26% reduction in hip fractures (number needed to treat [NNT]=45) and 23% reduction in nonvertebral fracture (NNT=27) when compared with calcium alone or placebo (Bischoff-Ferrari et al 2005). Recently, the investigators for the Women's Health Initiative released results of a 7 year follow up of over 30 000 women

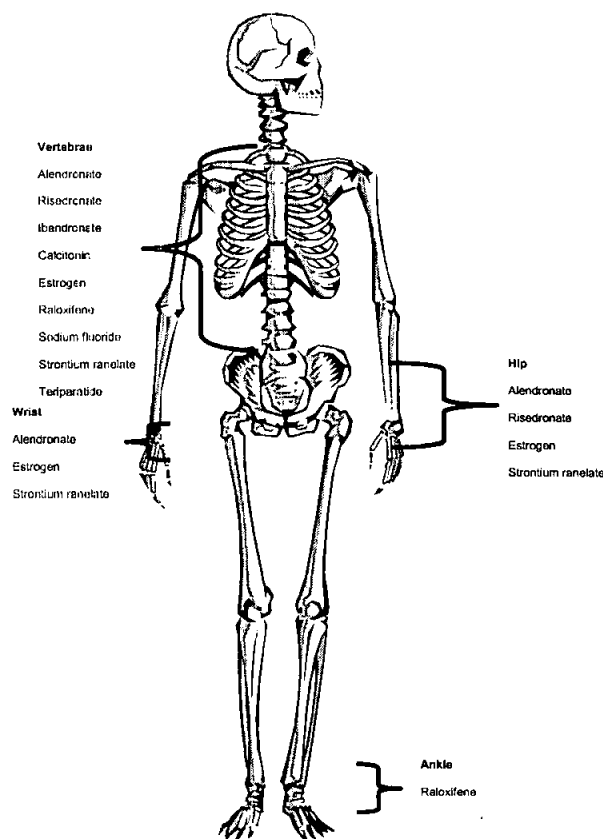


Figure 1 Fracture reduction data available by agent and site.

Note: Please see text for discussion of studies demonstrating fracture reduction and references.

aged 50–79 (Jackson et al 2006). Despite a 1.06% increase in BMD, this study did not show a statistically significant reduction in hip fractures among women who received 1000 mg calcium carbonate and 400 IU vitamin D₃, and a 17% increase in risk of renal calculi. However, there are several important points that should be noted about this study. In addition to the use of a daily dose of vitamin D lower than currently advocated, the average T score at baseline was normal (−0.65). Only 3% of subjects for whom bone density was measured at baseline had a T score below −2.5. In addition, it was noted that the reduction in hip fracture risk was statistically significant after non-adherent patients were excluded.

Vitamin D supplementation, particularly with the active form (ie, calcitriol) may be theoretically important for frailer, institutionalized individuals or those with chronic health conditions (eg, PTH disorders, chronic renal failure, and dialysis) due to the inability or reduced capacity to convert vitamin D to the active form. Clinical trials with calcitriol evaluating BMD and fracture outcomes have had mixed results. However, in one trial of 50 women with vertebral fractures, spinal BMD increased 1.94% after 2 years of treatment with calcitriol 0.62 mcg/day plus 1000 mg calcium versus a 3.92% decrease for placebo ($p=0.001$) (Gallagher and Goldgar 1990). In another trial of 622 women with

compression fractures, 0.25 mcg calcitriol BID given for 3 years to women with a history of ≤ 5 fractures decreased the rate of new vertebral fractures compared with 1000 mg calcium alone (4.2 vs 31.0 fractures per 100 patient years, $p<0.0001$) (Tilyard et al 1992). In both of these studies, serum or urine calcium monitoring was necessary to identify subjects requiring dose adjustment due to hypercalcemia or hypercalcuria. Moreover, the true benefit of calcitriol over other vitamin D-containing agents has not been established, and activated vitamin D has not been evaluated against first line therapies such as bisphosphonates. Therefore, further data is needed before the optimal place of calcitriol in osteoporosis therapy is established.

Monitoring of serum vitamin D concentrations is intriguing, and has been suggested as a means of clinically identifying individuals in need of additional supplementation (Holick et al 2005). The reported range of normal values may vary by laboratory, but is typically 16–120 ng/ml (Wallach 1986). Opinion varies as to the threshold for deficiency, but on average is around 15 ng/ml (LeBoff et al 1999). Various studies have demonstrated that deficiency of vitamin D is associated with decreased BMD and increased fractures (Aaron et al 1974; Bischoff-Ferrari et al 2004). It is also clear that vitamin D supplementation confers benefit with respect to both BMD and fracture risk (Bischoff-

Table 2 Clinical trials of calcium and vitamin D

Authors/year	Study design	Intervention	Outcomes	NNT
Chapuy et al 1992	32 70 postmenopausal women (mean age 84)	1200 mg elemental calcium (calcium triphosphate) 800 IU vitamin D given for 18 months	43% reduction in hip fracture ($p=0.043$) 32% reduction in nonvertebral fractures ($p=0.015$)	56 29
Dawson-Hughes et al 1997	389 ambulatory men and women >65 years	500 mg of calcium (calcium citrate) plus 700 IU vitamin D ₃ daily for 3 years	50% reduction in nonvertebral fractures ($p=0.02$)	14
Grant et al 2005	5292 elderly men and women (mean age 77 years) with history of low trauma fracture	1000 mg calcium (calcium carbonate), 800 IU vitamin D ₃ , the combination, or placebo for 45 months	NS (high rate of non-compliance)	
Shea et al 2002	Meta-analysis of 15 trials totaling 1806 patients	Various formulations of calcium ranging from 500–2000 mg (two studies contained vitamin D supplementation, 400 IU daily or 300 000 IU at study start). Average follow-up = 2 years	2.1% increase in total body BMD 23% decrease in vertebral fractures (95% CI 0.54–1.09) 14% decrease in nonvertebral fractures (95% CI 0.43–1.72)	NS NS
Jackson et al 2006	36 282 women aged 50–79 with average baseline T score of −0.65 (± 1.03)	1000 mg calcium (calcium carbonate), 400 IU vitamin D ₃ for 7 years	1.06% increase in BMD ($p<0.01$) Non-significant reduction in hip fracture in primary analysis; 29% reduction in hip fracture among adherent subjects (95% CI 0.52–0.97).	NS

Abbreviations: BMD, bone mineral density; CI, confidence index; NNT, number needed to treat; NS, not significant.

Ferrari et al 2005). However, it is not clear if laboratory assessment is routinely necessary or cost effective in all patients. Monitoring may be useful in those individuals for whom severe deficiency or coexisting hyperparathyroidism is suspected. For instance, several studies have demonstrated improvements in elevated PTH concentrations in patients with established vitamin D deficiency who receive supplemental vitamin D (Malabanan et al 1998; Need et al 2004). However, while studies evaluating the efficacy of vitamin D for osteoporosis often report data regarding subjects' 25-hydroxyvitamin D levels, not all studies consistently report an association between the change in serum level and the amelioration of fracture risk (Lips et al 1996; Dawson-Hughes et al 1997; Adams et al 1999; Jackson et al 2006). Further, an optimal target vitamin D concentration has not been universally established. Despite this, there is sufficient evidence to recommend vitamin D supplementation as a routine part of osteoporosis prevention and treatment (Bischoff-Ferrari et al 2005). Therefore, an individual patient's eligibility for such therapy should not be contingent upon laboratory assessment of deficiency.

Product recommendations

As the quantities and formulations of calcium or vitamin D products have varied from study to study, there is currently no clear consensus which agent or regimen should be recommended to all patients. Based upon preponderance of data from multiple studies, a total daily intake of 1200–1500 mg calcium and 600–800 IU of vitamin D is recommended for those with age-related osteoporosis or who are at risk. As these total daily doses can be achieved by a variety of products, clinicians need to be prepared to answer questions regarding product selection. Patients should be counseled that the recommended daily amount of calcium refers to the elemental form, and this may vary depending upon the form chosen (Table 2). Second, there are potential concerns regarding bioavailability of various formulations based upon gastric absorption. It has been suggested that acid-dependent forms of calcium, such as calcium carbonate, are not as efficiently absorbed as acid-independent forms, such as calcium citrate. The clinical significance of this has not been clearly determined but may be worth considering, particularly in patients with age-related changes in gastric pH or who are on acid suppression therapy. Regardless of formulation selected, patients should also be counseled that bioavailability can be maximized by administering calcium supplements in divided doses, limiting intake at a single dosing interval to 500–600 mg, and giving with meals,

particularly with calcium carbonate. The administration intervals of calcium supplements should also be timed so as to avoid absorption interactions with other products such as iron salts, fiber laxatives, quinolones, or tetracyclines.

Bisphosphonates

The bisphosphonates are a first line therapy for most patients with age-related osteoporosis. The nitrogen-containing bisphosphonates alendronate, risedronate, and ibandronate, are the most common agents used for treating and preventing age-related osteoporosis. While other bisphosphonates are available (eg, etidronate, pamidronate, tiludronate, and zoledronic acid) for other indications (eg, Paget's disease, hypercalcemia of malignancy, corticosteroid-induced osteoporosis), these agents are not first-line therapy for age-related osteoporosis (Licata 2005).

The nitrogen-containing bisphosphonates increase BMD by inhibiting several key enzymes in the mevalonate pathway (Licata 2005). This leads to increased BMD through several antiresorptive mechanisms including inhibition of osteoclast recruitment, osteoclast activity on the bone, induction of osteoclastic apoptosis, and alteration of the bone or bone mineral to reduce dissolution rate. Through inhibition of bone resorption, the bisphosphonates increase BMD approximately 2%–8% depending upon the agent, dose, and site measured and are effective for both the prevention and treatment of age-related osteoporosis (Cummings et al 1998; Harris et al 1999; Black et al 2000; Orwoll et al 2000; Reginster et al 2000; McClung et al 2001; Chesnut et al 2004).

Table 3 Characteristics of various calcium preparations. Data from Wickersham and Novak (2002)

Calcium salt	% elemental calcium	Elemental calcium in example dosage forms	Absorption acid dependent
Carbonate	40%	1500 mg tablet contains 500 mg	Yes
Triphosphate	39%	1565.2 mg tablets contain 600 mg elemental calcium	Yes
Citrate	21%	950 mg tablets contain 200 mg elemental calcium	No
Lactate	13%	650 mg tablets contain 84.5 mg elemental calcium	No
Gluconate	9.3%	500 mg tablets contain 45 mg elemental calcium	No

Table 4 Approved drug regimens in the US and EU for management of osteoporosis

Drug regimen (Listed alphabetically by class)	Prevention of postmenopausal osteoporosis	Treatment of postmenopausal osteoporosis	Treatment of male osteoporosis
Bisphosphonates			
Alendronate			
5 mg PO daily or 35 mg PO once weekly	X		
10 mg PO daily or 70 mg PO once weekly		X	X
Ibandronate			
2.5 mg PO daily or 150 mg PO once monthly	X	X	
Risedronate			
2.5 mg PO daily or	X		
5 mg PO daily or 35 mg PO once weekly		X	
Calcitonin 200 IU intranasally once daily		X	
Estrogen receptor stimulators			
Estrogen replacement therapy (various dosage forms)	X		
Raloxifene 60 mg PO daily	X	X	
Tibolone 2.5 mg PO daily ^a	X ^a		
Teriparatide (PTH 1-34) 20 mcg subcutaneous daily		X	X
Strontium ranelate 2 g PO daily ^a		X ^a	

Note: ^aNot approved in the US.

Abbreviations: PO, by mouth; PTH, parathyroid hormone.

Alendronate is an oral bisphosphonate that has been shown to decrease both vertebral and non-vertebral fractures. In the Fracture Intervention Trials (FIT), the effects of alendronate 5 mg daily for 2 years followed by 10 mg daily for 2 years in women with low BMD and no history of fracture or at least one-vertebral fracture was assessed. In the arm of the trial that included women with at least one prior vertebral fracture, 2027 women were followed to assess the risk of new vertebral and nonvertebral fractures (Black et al 2000). After an average follow-up of 2.9 years, alendronate increased BMD at the femoral neck 4.1%, total hip 4.7%, and posterior-anterior lumbar spine 6.2% compared with placebo ($p < 0.001$ for all) and decreased the risk of new radiographic fractures by 47% (NNT=14), clinical vertebral fractures 55% (NNT=37), hip fractures 51% (NNT=91), wrist fractures 48% (NNT=53), and any non-vertebral fracture by 20% (NNT=36; $p < 0.05$ for all). In the FIT arm that included women with low BMD but without a prior history of fracture, 4432 women were followed for an average of 4.2 years (Cummings et al 1998). At the end of the study, alendronate increased BMD at the femoral neck 4.6%, total hip 5.0%, and lumbar spine 6.6% compared with placebo ($p < 0.001$ for all) and decreased the rate of any clinical fracture by 36% (NNT=15), though this effect was only significant in patients with osteoporosis at baseline (initial femoral neck T-score ≤ -2.5). Alendronate decreased the rate of radiographic vertebral fractures overall by 44% (NNT=60).

Vertebral and non-vertebral fracture data is available for risedronate. In the Vertebral Efficacy with Risedronate Therapy in North American (VERT-NA) and Multi-National (VERT-MN) studies, the effects of risedronate 2.5 mg daily and 5 mg daily for 3-years was compared with placebo in postmenopausal women with osteoporosis and prior vertebral fractures (Harris et al 1999; Reginster et al 2000). After 3 years, risedronate 5 mg daily decreased the rate of new vertebral fractures similarly in the two studies; 41% (NNT=10) and 49% (NNT=20) in the VERT-NA and VERT-MN studies respectively. Nonvertebral fractures were reduced in the VERT-NA study 40% (NNT=31) and 33% (NNT=20; $p=0.06$) in the VERT-MN trial.

Risedronate has also been studied in patients at very high risk for fracture. In the Hip Intervention Program (HIP) study, the effects of risedronate 2.5 mg or 5 mg daily in 5455 elderly women with osteoporosis (femoral neck T-score ≤ -4 or ≤ -3 plus a non-skeletal risk for falls) was compared with placebo (McClung et al 2001). After mean follow-up of 2.3 years, risedronate decreased the overall rate of hip fracture 30% (NNT=90), 40% in women 70–79 years of age (NNT=77), and 60% in those 70–79 years of age with at least 1 vertebral fracture at baseline (NNT=29).

Ibandronate, an oral bisphosphonate with an extended dosing interval, is the newest agent in this class to be approved for both the prevention and treatment of postmenopausal osteoporosis. In the oral ibandronate osteoporosis vertebral fracture trial in North America and

Europe (BONE) study, ibandronate 2.5 mg daily or 20 mg every other day for 12 doses every 3 months was compared with placebo in 2946 osteoporotic women with 1–4 prior vertebral fractures (Chesnut et al 2004). After 3 years, vertebral fractures were significantly reduced 62% (NNT=20) and 50% (NNT=21) respectively for the daily and intermittent doses compared with placebo. Ibandronate did not decrease clinical non-vertebral fractures or hip fractures. However, a possible reason for this lack of benefit was the relatively high femoral neck T-score of patients at baseline (mean T-score –2.0). Post hoc analyses of patients at greater risk for hip fracture (ie, femoral-neck T-scores <–3.0) demonstrated that daily ibandronate was effective in decreasing nonvertebral fractures by 69%.

Traditionally, oral bisphosphonates had been given on a daily basis. More recently however, intermittent regimens (eg, once weekly with alendronate and risedronate and once monthly with ibandronate) have been developed in an attempt to increase patient adherence. It is important to note that fracture data are not available for these intermittent regimens, though studies are available that have demonstrated equivalent effects on BMD compared with daily dosing (Brown et al 2002; Rizzoli et al 2002; Miller et al 2005). However, while fracture data are not specifically available for these intermittent regimens, data are beginning to emerge that suggest these regimens do increase patient adherence. In an administrative claims study of 30 health plans, once weekly bisphosphonate use was associated with greater medication persistence than once daily users (69% vs 58%, $p<0.001$) and had higher rates of retention on treatment (44% vs 32%) at one year of use (Cramer et al 2005). However, it is important to note that long-term adherence (eg, 1 year) was still very poor with these intermittent regimens. Thus, continued research on modalities to increase patient adherence to osteoporosis therapies is warranted.

Calcitonin

Calcitonin is a 32-amino acid peptide that can be obtained from numerous animals, including a human form through recombinant technology. However, salmon calcitonin is the most potent and therefore most frequently used isolate (Zaidi et al 2002). The primary effect of calcitonin is to decrease bone resorption by inhibiting the function of mature osteoclasts. Calcitonin works via both cAMP and calcium-dependent pathways to accomplish this effect (Zaidi et al 2002).

There are data supporting the efficacy of nasal calcitonin in reducing vertebral fractures, however non-vertebral fracture data is lacking. The prevent recurrence of osteoporotic fractures (PROOF) study consisted of 1255 postmenopausal women with pre-existing vertebral fractures who were randomized to 200 IU of intranasal salmon calcitonin or placebo (Chesnut et al 2000). Patients were followed for a total of five years to assess incidence of new vertebral fractures. The calcitonin group had a 33% reduction in the risk of vertebral fractures (NNT=33) compared with placebo.

In addition to antiresorptive properties, calcitonin has also been shown to be effective for managing the pain associated with acute vertebral compression fractures (Lyritis et al 1991). Thus, this agent may be useful in patients who have experienced a recent osteoporosis-related vertebral fracture. However, there are limitations with use of this agent. First, data regarding antifracture efficacy is significantly less when compared with other agents used for osteoporosis. Secondly, data are available that suggest the antiresorptive effects of calcitonin may diminish significantly with time. Between 19–26 months, a plateau effect has been demonstrated, which is likely due to down-regulation of calcitonin receptors (Gruber et al 1984). Thus, due to the availability of agents with more favorable fracture data, particularly when used long-term, calcitonin should not be a first line agent in the treatment of osteoporosis.

Estrogen receptor stimulators

Stimulation of estrogen receptors is another method by which BMD may be increased. Agents which stimulate estrogen receptors include estrogen (various forms), selective estrogen receptor modulators (SERMs), and tibolone. Estrogen receptors are located in various tissues throughout the body, including breast, uterine, intestinal, and bone tissues. In bone tissue estrogen receptors are located on osteoblasts and osteoclasts, and stimulation of these receptors by estrogen decreases osteoclast activity, thereby decreasing bone resorption. In addition, estrogen is also associated with peripheral inhibition of PTH, increased intestinal absorption of calcium, and decreased renal excretion of calcium (Notelovitz 1997).

Estrogen

Estrogen, with or without a progesterone, has beneficial effects on surrogate markers of bone turnover and on fracture risk, and has been used extensively for the prevention of

osteoporosis. There is evidence that estrogen increases BMD at the hip, lumbar spine, and peripheral body sites (Wells et al 2002). However, there has been relatively less data with respect to fracture outcomes. In 2 meta-analyses of 13 and 22 trials, estrogen was associated with an overall 13% reduction in vertebral fracture and a 27% reduction in non-vertebral fractures respectively (Torgerson and Bell-Syer 2001a, 2001b).

Two large, randomized, placebo controlled trials, the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI), evaluated the combination of estrogen plus progestin (Hulley et al 1998; WGWHI 2002; WHISC 2004). The HERS and its open label follow-up HERS II (Cauley, Black, et al 2001) did not report a reduction in fractures for hip, wrist, vertebral or total fractures (hazard ratio [HR] 1.04, 95%CI 0.87–1.25). The WHI was a much larger study evaluating 0.625 mg conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate versus placebo (WGWHI 2002). The estrogen-only arm evaluated 0.625 mg daily CEE or placebo in women with a hysterectomy (WHISC 2004). In the estrogen plus progesterone arm, there was a 33% reduction (NNT=345) in the risk of hip fracture (Cauley et al 2003). The reduction in hip fracture risk was greater for those individuals receiving estrogen plus progesterone who also received at least 1200 mg of daily calcium at baseline. Estrogen plus progesterone was also associated with a 36% reduction in vertebral fractures (NNT=387), and a 30% reduction in lower arm/wrist fractures (NNT=125). The results of the estrogen-only arm likewise decreased the risk of hip and vertebral fractures slightly (NNT=216 and NNT=225 respectively).

Despite the benefit of hormone replacement therapy for osteoporosis, there are many concerns with chronic use. The estrogen plus progesterone arm of the WHI was stopped after an average follow-up of 5.2 years due to increased risk of breast cancer (number needed to harm [NNH]=237). Safety analysis also revealed a slight increase in risk of coronary heart disease events (NNH=237), pulmonary embolism (NNH=227), stroke (NNH=225), and deep vein thrombosis (NNH=141). Similar results were reported in the estrogen-only arm of the WHI, which was stopped after an average follow-up of 6.8 years. While there did not appear to be an increased risk of breast cancer or pulmonary events, there was no benefit reported for the primary outcome of coronary heart disease events (CHD) and an increased risk of stroke (NNH=125) and deep vein thrombosis (NNH=220).

Based on findings from the WHI, HERS, and other meta-analyses of estrogen or estrogen plus progestin, the 2005 US Preventive Services Task Force (USPSTF) recommended against routine use of estrogen with or without a progestin for the prevention of chronic conditions in older women (USPSTF 2005). While citing good evidence for increased BMD, and fair to good evidence for reducing fracture risk, the task force concluded that the risk of breast cancer, venous thromboembolism, CHD, stroke, and cholecystitis "likely to exceed the chronic disease prevention benefits in most women." After the completion of the estrogen-only arm of the WHI, the task force updated its recommendations to recommend against the routine use of unopposed estrogen for the treatment of chronic conditions in women who have had a hysterectomy. As with estrogen and progestin therapy, they cited good evidence for osteoporosis benefit, but fair evidence for risks associated with thromboembolism, stroke, lower cognitive function, and dementia. For women with an intact uterus, unopposed estrogen is associated with an increased risk of endometrial cancer (Grady et al 1995).

While the Task Force recommendations provide general guidance on the use of estrogen with or without a progestin, there are several clinical considerations that should be evaluated when weighing the risks and benefits of hormone replacement therapy (HRT). The Task Force concedes that while the risks of HRT are statistically significant, the absolute risk is small. For women aged 50–79 years, treatment of 10 000 women with HRT for 1 year might result in 8 additional cases of breast cancer, 8 additional strokes, 8 additional pulmonary emboli, and 7 CHD events, while resulting in five fewer hip fractures. A woman at high risk of fracture with a low risk of breast cancer or cardiovascular disease may consider the benefits of estrogen more compelling.

In contrast, HRT has not demonstrated superiority with respect to increased BMD or reductions in fracture risk compared with bisphosphonates in patients with osteoporosis. Thus, it should generally not be considered first line therapy for osteoporosis in bisphosphonate-eligible individuals, irrespective of the risk-benefit controversies previously described.

Emerging questions that remain unanswered about estrogen therapy include the roles of either low-dose or transdermal formulations in osteoporosis prevention or treatment. These forms of estrogen therapy were not evaluated in the large randomized trials upon which much of the current risk-benefit analysis is based, and are therefore

not formally associated with the same risks as traditionally dosed HRT. While there are data demonstrating the efficacy of these forms in maintaining or improving bone density (Lindsay et al 2002; Ettinger et al 2004), conclusive evidence of reduced fracture risk is lacking.

Selective estrogen receptor modulators (SERMs)

For women who are not candidates for bisphosphonate therapy and in whom the risk of estrogen outweighs the potential benefits, other options may include selective estrogen receptor modulators (SERMs). The mechanism of action for these agents is to act as an estrogen receptor agonist on bone and uterine tissues, but as an antagonist in breast tissues (Riggs and Hartmann 2003). Therefore, SERMs have a similar effect on bone density as estrogen, but carry a different risk profile.

Raloxifene is the most commonly used SERM for prevention and treatment of osteoporosis, and is associated with a 2%–3% increase in BMD (Delmas et al 1997). Raloxifene has also demonstrated benefits on vertebral fractures, though data supporting a fracture benefit at non-vertebral sites is generally lacking. In the 36 month Multiple Outcomes of Raloxifene Evaluation (MORE) study, raloxifene 60 mg daily given for 3 years was associated at 30% (NNT=29) reduction in vertebral fractures (Ettinger et al 1999). The risk of breast cancer may be as much as 72% lower with raloxifene compared with placebo (Cauley, Norton, et al 2001). Because raloxifene is not associated with some of the traditional side effects of HRT such as breast tenderness and vaginal bleeding (Ettinger et al 1999), it is not necessarily an alternative for those women wishing to mitigate some of the cardiovascular risks of HRT, such as deep vein thromboembolism, which is increased approximately 1.7–3-fold compared with placebo (Ettinger et al 1999; Martino et al 2005). It also does not provide the symptom relief from hot flashes associated with menopause for which some women may still elect short term HRT, and may actually be associated with an increased incidence (Martino et al 2005).

There is interest in new SERMs for osteoporosis. Agents such as lasofoxifene, ospemifene, and bazedoxifene, as well as other novel SERM are in development. Most are primarily being evaluated for breast cancer prevention, however data describing their effects on bone density are emerging (Lasofoxifene 2005; Ronkin et al 2005; Wurz et al 2005).

Tibolone

Another agent active at the estrogen receptor is tibolone. Tibolone is a prodrug that must be converted to active metabolites 3 α -hydroxytibolone, 3 β -hydroxytibolone, and a Δ 4-isomer, and is available in several countries, though not the US. Tibolone is classified as a non-estrogen synthetic steroid which may have estrogenic, progestogenic, or androgenic effects. In osteoporosis, the effect on trabecular bone density is thought to be related to activity at the estrogen receptor (Rubin and Bilezikian 2003).

Tibolone is used for the treatment of postmenopausal symptoms, and has been evaluated for the prevention and treatment of osteoporosis. The effects of 1.25–2.5 mg daily have been studied for improvements in surrogate markers of bone turnover and bone density improvements at the hip and lumbar spine. Increases in bone density have ranged from 3.6% to 7.2% at the lumbar spine and 2.6% to 4.6% at the femoral neck, though data on fracture reduction is currently lacking (Thiebaud et al 1998; Pavlov et al 1999; Rymer et al 2001; Roux et al 2002).

Clear comparisons between tibolone and estrogen replacement are not available. In one study, the magnitude of BMD increase was greater with tibolone than with conjugated equine estrogen/medroxyprogesterone after 3 years (Thiebaud et al 1998). However, in another study the BMD improvements with tibolone were not superior to estradiol and norethindrone after 2 years (Roux et al 2002). These authors did report though, that the incidence of side effects such as vaginal bleeding and breast tenderness was lower in the tibolone group. Thus, tibolone may be an alternative to estrogen in postmenopausal women for the amelioration of menopausal symptoms, osteoporosis prevention and possibly for osteoporosis treatment. However, considering the lack of fracture data, this agent should not be used first line for osteoporosis prevention or treatment, particularly in bisphosphonate-eligible women.

Strontium ranelate

Strontium ranelate is a di-strontium salt that has been shown to act as both a bone-forming and antiresorptive agent (Marie 2005). A proposed mechanism for increased bone formation is via stimulation of replication of osteoprogenitor cells and collagen. In addition, strontium has been shown to inhibit osteoclast activity and differentiation in vitro (Reginster, Sarlet, et al 2005). It is currently approved in Europe for the treatment of postmenopausal osteoporosis, though it is not yet available in the US.

The effects of strontium ranelate on BMD and fractures have been studied. The strontium ranelate for treatment of osteoporosis (STRATOS) trial evaluated the effects of 0.5 g, 1 g, or 2 g strontium ranelate compared with placebo over 3 years in 353 postmenopausal women with at least one previous vertebral fracture and a lumbar T-score <-2.4 (Meunier et al 2002). Lumbar BMD increased in a dose-dependent manner from a mean annual slope of 1.4% with 0.5 g/day to 3.0% with 2 g/day ($p<0.01$ for both doses vs placebo). In a phase 3 study, 1649 postmenopausal women with osteoporosis and at least one prior vertebral fracture were given strontium ranelate 2 g/day or placebo and followed for three years (Meunier et al 2004). The relative risk of new vertebral fractures decreased 41% compared with placebo (NNT=9). In the Treatment of Peripheral Osteoporosis Study (TROPOS), strontium ranelate 2 g/day or placebo was given to 5091 postmenopausal women with osteoporosis (Reginster, Seeman, et al 2005). After a mean follow up of 3 years, nonvertebral fractures were reduced 16% (NNT=59) and major fragility fractures by 19% (NNT=59) with strontium therapy versus placebo. Although strontium ranelate has been shown to be beneficial in postmenopausal osteoporosis, it is not generally considered a first line agent at this time due to less clinical experience and fracture data compared with bisphosphonates.

Sodium fluoride

Although sodium fluoride has been available for several years, it is not generally considered a routine therapy for age-related osteoporosis. While sodium fluoride has been shown to increase BMD by stimulating osteoblasts (Farley et al 1983), concerns have been raised regarding strength and quality of new bone formed as well as tolerability. In a 4-year, prospective study of 202 postmenopausal women with osteoporosis and vertebral fractures who were randomized to either 75 mg/day of sodium fluoride or placebo, the incidence of nonvertebral fractures increased 3-fold compared with placebo (Riggs et al 1990). The postulated mechanism for this increase in fracture is overstimulation of bone formation by sodium fluoride, leading to excessive production of weaker bone. In addition, sodium fluoride has been associated with other adverse events such as gastrointestinal disturbances likely as a result of conversion of sodium fluoride to hydrofluoric acid in the stomach, and lower extremity pain possibly due to excessive bone remodeling (Rubin et al 2001).

Due to previously noted adverse effects, systemic sodium fluoride has not gained wide use or acceptance. However, more recent data in which sodium fluoride is given on an intermittent basis and in sustained release form may change this agent's place in therapy. Sustained-release sodium fluoride given on an intermittent basis has been shown to decrease vertebral fractures and increase BMD (Rubin et al 2001). In a randomized, double-blind, placebo-controlled trial of 85 postmenopausal women with 1 or more vertebral compression fractures, 25 mg sustained-release sodium fluoride given twice daily in 3, 12-week cycles with a 2-month drug-free period in between was compared with placebo. After a mean follow up of 42 months, BMD in L2-L4 increased by 5.4% compared with placebo and decreased vertebral fractures decreased by 68% (NNT=8). Thus, while intermittent therapy with sustained release sodium fluoride may be a viable treatment option for osteoporosis, it is currently not recommended as a first or second line therapy due to lack of definitive, long-term data.

Teriparatide (recombinant parathyroid hormone 1-34)

Parathyroid hormone may be anabolic or catabolic in the skeleton depending on the mode of administration. When PTH is given as a once-daily injection, its primary affect is to increase bone mass (Hodsman et al 2005). The mechanism by which PTH is thought to stimulate bone production is by increasing the remodeling rate. PTH increases the amount of new bone that is laid down in each remodeling unit, which leads to a net gain in bone mass. In addition, it is also thought that PTH initially uncouples formation from resorption and is able to directly stimulate bone formation independent of resorption (Hodsman et al 2005).

The effects of PTH 1-34 (teriparatide) on BMD and fractures have been studied. In a placebo controlled study of 1637 postmenopausal women with at least 1 prior vertebral fracture, teriparatide 20 mcg and 40 mcg given as a once-daily subcutaneous injection was compared with placebo (Neer et al 2001). After a median follow-up of 21 months, teriparatide increased BMD by 9% and 13% in the lumbar spine and 3 and 6% at the femoral neck compared with placebo for the 20 mcg and 40 mcg groups respectively. This increase in BMD led to a significant decreases in both vertebral fractures (65% and 69%) and nonvertebral fractures (53% and 54%) for the PTH groups respectively.

While teriparatide does increase BMD and has been shown to be effective in reducing the risk of fractures, there

are significant limitations to its use. First, it must be given once daily as an injection. Thus, patient acceptance and adherence to therapy may be significantly diminished, particularly when compared with an intermittent oral bisphosphonate regimen. In addition, the extremely high cost of this agent is also a limitation. Teriparatide is approximately US\$17.50/day (€15/day) for the 20 mcg/day dose (Selby 2004).

Another limitation of teriparatide may be the slight increased risk of osteosarcoma. This risk is postulated based on the induction of osteosarcoma in a rat model. Teriparatide therapy is not recommended for more than a two year period and should not be used in patients with an increased risk of malignancies of the bone (Hodsman et al 2005). Thus, although teriparatide has been shown to be effective for osteoporosis, it should generally be reserved for patients who are unable to tolerate a bisphosphonate and who have severe/established osteoporosis.

Combination therapy

Use of combination therapies that have different mechanisms of action is a potential treatment option for those at high risk for osteoporotic fracture. Data are available that demonstrate an approximate 1% additional increase in BMD with combination of a bisphosphonate and estrogen or raloxifene versus a bisphosphonate alone (Bone et al 2000; Harris et al 2001; Johnell et al 2002; Greenspan et al 2003). However, there are some theoretical concerns that over-suppression of bone formation may occur with utilization of two or more antiresorptives, thus potentially increasing the risk for fractures.

The combination of a bisphosphonate with PTH has had mixed results. In two randomized, controlled trials, the combination of alendronate with PTH failed to increase BMD in men and women (Black et al 2003; Finkelstein et al 2003). Alendronate attenuation of PTH-induced stimulation of bone formation was postulated as a potential etiology for this lack of benefit. However, in the continuation study by Black et al (2005), patients who were assigned alendronate for 1 year after receiving 1-year of PTH, BMD at the lumbar spine increased significantly more in the combination group (12.1% vs 4.1%). Thus, although fracture data are not available for the combination of PTH followed by a bisphosphonate, this may be a reasonable intervention.

Treatment in special populations

As many as 85% of American nursing home residents suffer from osteoporosis (Zimmerman et al 1999). Comorbidities,

inadequate nutrition, multiple medications, immobility, difficulty transferring, disabilities, and fragility all contribute to a much higher fracture rate among nursing home dwelling elderly as compared with community dwelling elderly. Osteoporosis treatment and prevention of related fractures among nursing home residents involves multiple perspectives including fall prevention, adequate nutrition, strength and balance training, and frequent medication review. Environmental modifications to nursing home floors, doors, and hallways are often the best method to reduce fall rates and therefore fractures.

Unfortunately, the majority of nursing home residents with osteoporosis receive inadequate drug therapy. Calcium and vitamin D supplements are prescribed for approximately 60% of nursing home residents with osteoporosis and only 25% of residents with hip fractures (Kamel 2004). Bisphosphonate use is also low among nursing home residents with documented hip fractures. The pharmacologic foundation for osteoporosis treatment in elderly nursing home residents should include adequate calcium and vitamin D supplements and bisphosphonate therapy, taking into account individual patient considerations such as swallowing function, mobility/position, and esophageal function.

Osteoporosis is increasingly recognized as a serious men's health issue with 25%–30% of hip fractures occurring in men (Elliott et al 2004). One in four men over aged 50 will experience an osteoporosis-related fracture in their life time (NOF 2005b). Male nursing home residents have a 5–10-fold increase in fracture risk compared with males residing in the community. Men experience higher morbidity and mortality after hip fracture with one year mortality post hip fracture approximately double in men when compared with women (Amin and Felson 2001). After sustaining a hip fracture, up to 50% of men require institutional care. Thus, fall prevention is an important concern for both community dwelling men and nursing home male residents. Aged-related osteoporosis in men may be exacerbated by lifestyle habits including low physical activity, low body weight, excessive alcohol intake, and smoking. The pharmacologic foundation for osteoporosis treatment in men, as well as women, includes adequate calcium and vitamin D supplementation. First line therapy includes oral bisphosphonates (eg, alendronate). Teriparatide is indicated for men with idiopathic or hypogonadism-related (associated low levels of estradiol and testosterone) osteoporosis who are at high risk of fracture (Orwoll et al 2003; Teriparatide 2003). Public relations campaigns of the National

Osteoporosis Foundation are now directed specifically toward men to help patients and practitioners understand that both genders are susceptible to the devastating effects of age-related bone loss.

Conclusions

Osteoporosis is a significant problem for the global community. With the aging of the population, osteoporosis and related fractures will likely continue to increase. Various interventions are available to decrease the morbidity, mortality, and economic impact of age-related osteoporosis. This includes identification of risk factors for low BMD and falls, screening patients at risk, and instituting pharmacological therapy for those with documented osteoporosis. All patients should receive adequate calcium and vitamin D. Medications which have proven to decrease fractures should be used preferentially over medications for which there is only positive BMD data. Further research is needed to determine if combination therapies have additive effects on fracture reduction. In addition, attention should be paid to patients who may be at significant risk of age-related osteoporosis and related fractures, but are often neglected, such as men and those in the nursing homes.

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Suppression of elevated cartilage turnover in postmenopausal women and in ovariectomized rats by estrogen and a selective estrogen-receptor modulator (SERM)

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ABSTRACT

Objective: Several observational studies indicate that estrogen deficiency increases the incidence of osteoarthritis in postmenopausal women. To validate this observation, we investigated the effects of ovariectomy (OVX) on cartilage erosion in rats using histology and an established bioassay of cartilage-specific collagen type II degradation products (CTX-II). Furthermore, we investigated whether estrogen and levormeloxifene, a selective estrogen-receptor modulator (SERM), can prevent the OVX-induced changes in cartilage degradation. The clinical relevance was assessed in postmenopausal women by measuring the changes in CTX-II during 12-month treatment with levormeloxifene versus placebo.

Design: Sixty 6-month-old rats were divided in five groups. One group was subjected to sham and the others to OVX, followed by treatment with vehicle alone, estradiol or 0.2 mg/kg/day or 5 mg/kg/day of levormeloxifene. The rats were treated for 9 weeks with biweekly blood and urine sampling for measurement of bone resorption and cartilage turnover. After study termination, hind knees were removed for histological analysis of erosions. The effect of levormeloxifene in postmenopausal women was assessed by measuring CTX-II in samples from 301 women who were participating in a phase II study of this SERM.

Results: OVX rats showed significant increases in the urinary excretion of CTX-II. After 9 weeks this was manifested as increased surface erosion of knee articular cartilage compared with sham-operated rats. Treatment with estrogen or levormeloxifene prevented the OVX-induced changes. There was a significant correlation between the 4-week changes in CTX-II and cartilage erosion at week 9 ($r = 0.64$, $P < 0.001$). In postmenopausal women treated with levormeloxifene, the urinary excretion of CTX-II was decreased by approximately 50% and restored CTX-II levels to the premenopausal range.

Conclusions: This study is the first to demonstrate that a SERM suppresses cartilage degradation in both rodents and humans, suggesting potential therapeutical benefits in the prevention of destructive joint diseases such as osteoarthritis.

Key Words: Cartilage – Articular – Erosion – Selective estrogen-receptor modulators – Osteoarthritis – Biochemical markers.

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Osteoarthritis (OA) is a chronic joint disease that accompanies aging. As the number of older people is expected to increase dramatically in the Western world in upcoming decades, the number of people with OA will also increase.¹ The social and economic impact of the disease

is tremendous as OA is a major reason for disability and reduced quality of life among older people.

The majority of therapies commonly used in the clinical management of OA—such as nonsteroidal anti-inflammatory drugs (NSAIDs) and the newer COX-2 inhibitors—act predominantly through relieving symptoms, with no or minimal documented effect in terms of slowing or halting the underlying cartilage degradation. Therefore, there is an unmet clinical need for identification of therapeutic compounds that act on cartilage cells and enzyme systems, slowing or halting structural degradation.

Some reports have indicated that estrogen and compounds acting through the estrogen receptor exert a chondro-protective effect.^{2,3} The beneficial effect of estrogen-like substances in OA treatment is also supported by the observation that women experience a marked increased incidence of knee OA after cessation of endogenous estrogen production.^{4,5} A few histological studies of articular cartilage in postmenopausal women have suggested that, after menopause, women lose cartilage faster than men of the same age.⁶ The anatomical prerequisites for the beneficial effects of estrogen-like drugs have been demonstrated by *in vitro* studies revealing the presence of alpha- and beta-estrogen receptors (ERs) in human chondrocytes.⁷ *In vivo* animal studies have demonstrated that these ERs are functionally active and involved in the regulation of cartilage matrix synthesis.⁸ Furthermore, a recent study in cynomolgus monkeys demonstrated OA-like pathological changes within articular joints three years after OVX,⁹ and these structural changes could be effectively prevented by estrogens. In humans, most but not all observational studies suggest that postmenopausal estrogen use is associated with a decreased prevalence of OA.¹⁰⁻¹² In a recent study, we measured degradation products of type II collagen (CTX-II) as a marker of cartilage degradation in pre- and postmenopausal women.¹³ We observed a highly significant increase in this marker after menopause. Furthermore, hormone therapy (HT) use was associated with a suppression of CTX-II levels, further suggesting that estrogen levels influence cartilage turnover.¹³

In light of the recent report from the Women's Health Initiative trial,¹⁴ there is increased focus on the potentials of selective estrogen-receptor modulators (SERMs) in primary prevention of menopause-related diseases. A large number of nonsteroid compounds have been identified that are able to bind to the estrogen receptors with high affinity and exert estrogen agonistic effects in some tissues and antagonistic effects in other tissues.¹⁵ These compounds have been ex-

tensively studied for their effects on estrogen responsive tissues such as breast, endometrium, and bone. There is, however, scarce information available regarding their potential for the prevention of cartilage degradation.¹⁶

The present study was designed to investigate: (1) the effect of OVX on cartilage erosion assessed by histology and a specific immunoassay measuring degradation products of collagen type II (CTX-II);¹⁷ and (2) the effect of estrogen and a potent SERM, levormeloxifene, on changes in biomarkers and histological measures of cartilage degradation in OVX rats. The clinical relevance of the findings from the OVX study was further explored by measuring the changes in cartilage turnover in generally healthy postmenopausal women treated with various doses of levormeloxifene for 12 months in a previously published, randomized, double-blind, placebo-controlled trial.¹⁸

METHODS

Materials and buffers

All chemicals were of analytical grade and purchased from either Sigma (USA) or Merck (Switzerland). Peptides used in the study were more than 95% pure and obtained from Chimex Ltd. (St. Petersburg, Russia). Cell culture reagents were obtained from Life Technologies (UK). Compositions of the buffers used in immunoassays have been described previously.^{17,19} Levormeloxifene was provided by Drs. Karsten Wasserman and Poul Jacobsen of Novo Nordisk A/S.

OVX studies in rats

The rats used in the experiments were Sprague-Dawley, CrI:CD(SD)IGS.BR obtained from Charles River laboratories, Kisslegg, Germany. Experiments were approved by the Experimental Animal Committee, the Danish Ministry of Justice, Slotsholmsgade, Denmark (approval number: 2002/561-566) and performed according to the European standard for Good Clinical Practice.

Sixty 6-month-old female rats were included in the study. The rats were received 5 weeks before the experiment to allow complete acclimatization to the housing condition and to avoid influence of transportation-related stress on baseline measurements of bone and cartilage turnover. After acclimatization, 12 animals were subjected to sham operation, and the remaining 48 animals were ovariectomized. The OVX animals were divided into four equal groups to receive treatment either with vehicle, 17 α -ethinyl-estradiol (Sigma, E-4876, Lot #111K1611), or the SERM levormeloxi-

fene.¹⁸ All drugs were administered as oral suspension (in 50% propylene glycol, 0.075 M NaCl) by gavage on five weekdays (Monday- Friday). The daily dose of estradiol was 0.1 mg/kg. Levormeloxifene was administered either in a low dose (0.2 mg/kg/day) or in a high dose (5 mg/kg/day). The treatments were initiated the day after OVX/sham surgery. Rats were weighed and sampled for spot urine and serum at regular intervals. Urine samples were obtained by inducing urination by gently rubbing the belly or by placing the rats for a short time (20-30 min) in metabolic cages. Blood samples were obtained from the venous plexus of the orbita and were allowed to coagulate for 30 minutes at room temperature, followed by centrifugation for 10 minutes at 1500 rpm to obtain serum. Serum and urine samples were stored at -20°C until biomarker measurements were carried out. The rats were treated for 9 weeks after the OVX. At study termination, knee joints, uterus, liver, and spleen was excised and weighed. Knee joints were prepared for histology, as described below.

SERM intervention study in postmenopausal women

The levormeloxifene study consisted of 301 healthy, postmenopausal women aged 49 to 65 years.¹⁸ The study was designed as a phase two dose-finding study in which the effect of levormeloxifene on postmenopausal bone loss and changes in serum lipids was assessed. The study was performed at two Scandinavian clinical centers. The data presented here are based on measurements of frozen (-20°C) samples obtained from participants at our center (n = 92). All participants had been postmenopausal for at least 1 year and had concentrations of serum estradiol below 25 pg/mL. None of the participants had any clinically significant acute or chronic diseases, and none had received medications known to affect bone or cartilage metabolism 6 months before enrollment. Table 3 provides the physical demographics and relevant biomarker levels of the participants at baseline.

Random-numbered tables were used for allocating participants to double-blinded treatment either with placebo or various doses of levormeloxifene (1.25, 5, 10 or 20 mg/day, administered orally). All participants received a calcium supplement of 500 mg/day throughout the trial period. Women who had received levormeloxifene for 12 months were followed for an additional 12 months without treatment.

The study was approved by the Ethical Committee of Copenhagen County and performed according to the Helsinki Declaration II and the European standard for Good Clinical Practice. All persons gave a written informed consent to participate in the study.

Histology of rat knee articular cartilage

After careful dissection, the knees of the rats from the OVX study were decalcified in 10% formic acid, 2% formaldehyde. The decalcified knee joints were cleaved along the medial collateral ligament into two sections and embedded in paraffin. The embedded knees were then cut in three different depths (0, 250, and 500 µm) from the medial collateral ligament. Each section was subsequently stained in toluidine blue. The cartilage sections were scored blinded for the presence of surface erosion. The erosions were readily apparent as a loss of proteoglycan staining, fibrillation, loss of surface matrix, and disorganization and roughening of the surface. Severity of the erosion was calculated as the lengths of erosion in percent of the total cartilage surface on each section.¹⁹ The incidence of erosion in the different treatment groups was also calculated.

CartiLaps ELISA (CTX-II)

The CartiLaps ELISA measures CTX-II-derived fragments and provides an index of cartilage degradation. The assay and its technical performance have been described previously.¹⁷ Briefly, the assay was performed as follows: biotinylated CTX-II peptide (EKG-PDP) was coated on a streptavidin microtiter plate, and sample as well as primary antibody (MabF46) were added. After overnight incubation, the amount of bound antibody was quantified using a peroxidase labeled secondary antibody and a chromogenic peroxidase substrate. Concentration of CTX-II [ng/L] was corrected to the total urine creatinine [mmol/L]. Measurement precision of the assay was 7.1% and 8.4% for intra- and interassay variations, respectively. All samples were measured in duplicate, and samples from the same individual were included on the same microtiter plate. Three genuine control samples were included on each microtiter plate to verify performance. Samples were remeasured if the coefficient of variation for the double determination exceeded 15% or if any of the control samples were measured more than 20% off the predetermined value.

RatLaps ELISA (rCTX-I)

This assay measures collagen type I C-telopeptide degradation products (rCTX-I) using a specific monoclonal antibody in a competitive ELISA form.¹⁹ The assay provides an index of bone resorption and is applicable for measurement of both urine and serum samples from rodents. Only serum samples were assessed in this study. All serum samples were collected

ESTROGEN DEFICIENCY AND OSTEOARTHRITIS

TABLE 1. Characteristics of the treatment groups in the rat OVX study (mean $\pm$ SD)

Group	OVX, vehicle (n = 12)	OVX, estrogen (n = 11)	OVX, low Levo (n = 11)	OVX, high Levo (n = 12)	Sham, vehicle (n = 10)
Bodyweight Start (g)	307 $\pm$ 13	308 $\pm$ 21	308 $\pm$ 22	307 $\pm$ 23	308 $\pm$ 13
rCTX-I Start (μ g/l)	19.6 $\pm$ 4.7	19.5 $\pm$ 6.8	21.8 $\pm$ 7.5	21.4 $\pm$ 6.1	20.0 $\pm$ 5.5
CTX-II Start (μ g/mmol)	1.28 $\pm$ 0.54	1.50 $\pm$ 0.45	1.39 $\pm$ 0.42	1.43 $\pm$ 0.56	1.40 $\pm$ 0.51
Uterus weight End (g)	0.16 $\pm$ 0.05	0.49 $\pm$ 0.13	0.23 $\pm$ 0.03	0.20 $\pm$ 0.04	0.52 $\pm$ 0.19

rCTX-I is measured in serum and CTX-II is measured in urine and corrected for creatinine. Uterus weights represent wet weight of the tissue. OVX, ovariectomy; Levo, levormeloxifene; rCTX-I, collagen type I C-telopeptide degradation products; CTX-II, cartilage-specific collagen type II degradation products.

after at least 6 hours fasting. The assay was performed by incubating biotinylated synthetic rCTX-I peptide (EKSQDGGR) on a streptavidin microtiter plate. This was followed by addition of sample and primary antibody. After overnight incubation, the amount of bound antibody was visualized using a peroxidase-labeled secondary antibody and a chromogenic peroxidase substrate. The concentrations in the samples were determined from construction of a calibration curve based on measurement of synthetic peptide standards. Intra- and interassay variation was 6.9% and 10.4%, respectively. Assay performance and quality assurance was assured as described above for the CTX-II assay.

Serum CrossLaps ELISA (CTX-I)

Bone resorption in postmenopausal women treated with and without levormeloxifene was quantified using the serum CrossLaps ELISA. The ELISA is a sandwich assay using two monoclonal antibodies specific for the isomerized β -aspartate form of the epitope EKAHDGGR derived from the C-terminal telopeptide region of type I collagen α 1-chain.²⁰ Inter- and intra-assay imprecision are 6.2% and 5.4%, respectively. Serum CTX-I measurements were performed at baseline and at 6-month intervals thereafter. Assay performance and quality assurance was assured as described above for the CTX-II assay.

Statistical analyses

Results in text are provided as mean $\pm$ SD. Baseline characteristics of the different intervention groups were compared using independent *t* test (Mann-Whitney) or ANOVA, as appropriate. The association between CTX-I and CTX-II values was assessed by Spearman's correlation analysis. Statistical calculations were performed using SPSS for Windows, version 10.1 (SPSS Inc. Chicago, IL, USA). Differences were considered significant if *P* was less than 0.05.

RESULTS

Changes in cartilage turnover and structural integrity in ovariectomized rats

Baseline characteristics of the rats are shown in Table 1. There were no differences with regard to age, body weight and baseline levels of the bone and cartilage turnover markers. Sham-operated animals showed a $5.6 \pm 5.9\%$ increase in body weight during the 9-week study period. Compared with this group, OVX animals showed a more prominent ($17.6 \pm 11.0\%$) increase in body weight, which was inhibited by estrogen ($6.4 \pm 4.3\%$) and the two doses of levormeloxifene (low dose: $2.6 \pm 4.5\%$; high dose: $-0.7 \pm 1.9\%$) (mean $\pm$ SD). Estrogen replacement kept uterine weight comparable with that seen in sham-operated animals, whereas vehicle- and levormeloxifene-treated OVX rats had significantly reduced uterine weights (Table 1). The lack of proliferative stimulation of the endometrium by levormeloxifene was confirmed by immunohistology, using the proliferation marker Ki-67 (data not shown).²¹

Knee joints were excised at study termination and processed for histological analysis. A number of histological changes were observed when comparing vehicle-treated OVX rats with sham-operated animals. Most pronounced differences were observed with regard to surface erosions. These were apparent as fibrillation, proteoglycan loss, and loss of surface matrix. The vehicle-treated OVX group revealed significantly higher incidence and more severe surface erosions compared with the sham-operated group (Fig. 1). The estrogen- and levormeloxifene-treated groups showed lower incidence of erosion, comparable to the sham-treated rats. When erosive changes were calculated as a percentage of total cartilage surface, significant differences were observed for the medial and lateral femur as well as the medial tibia (Fig. 2). Interestingly, the lateral tibia was almost devoid of erosive changes in all groups (Fig. 2). A total score for the knee joint was calculated by taking the average score for each of the

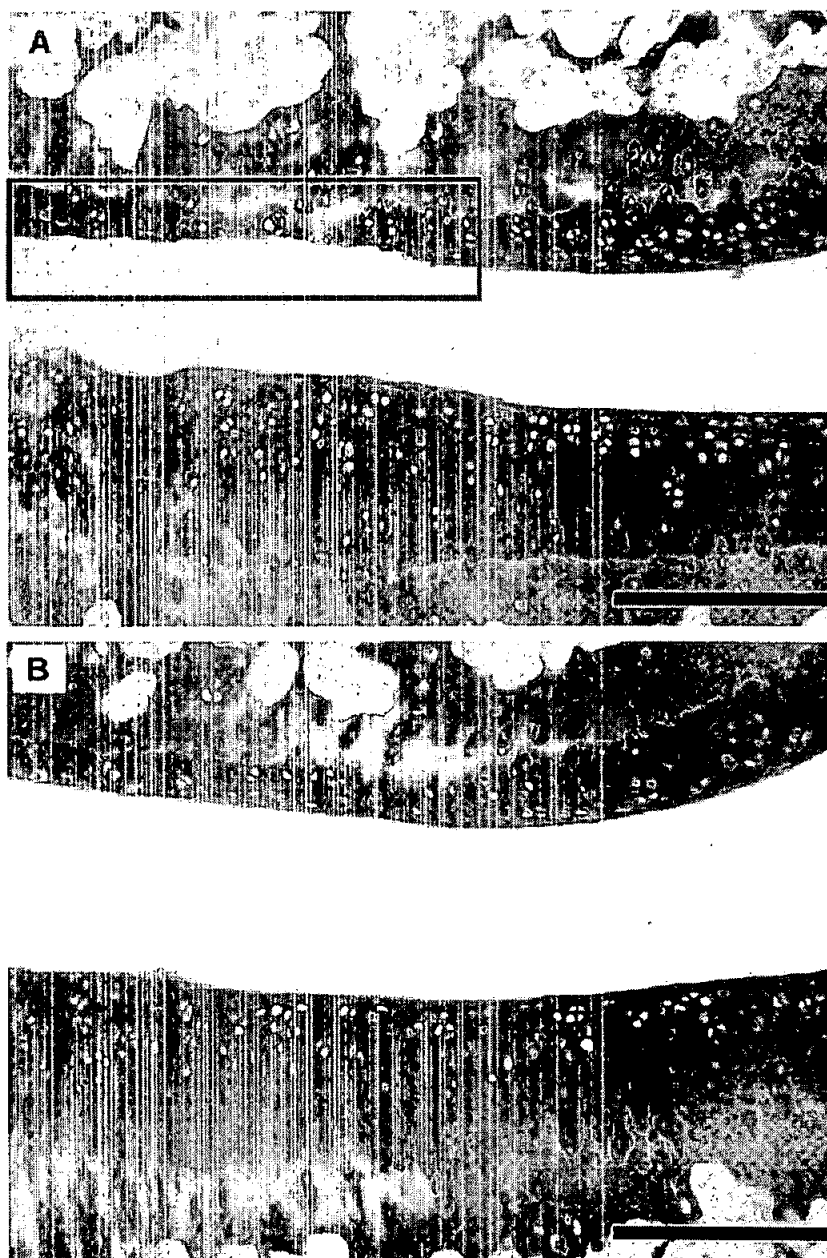
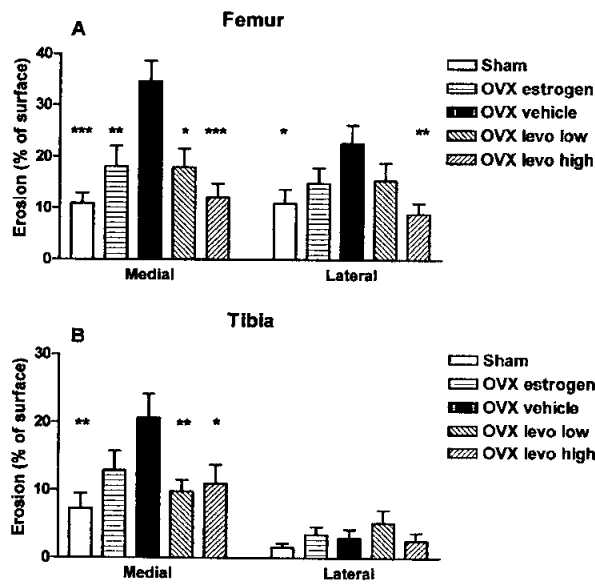


FIG. 1. Surface erosions on histological section of knee joints from a vehicle-treated, ovariectomized (A) and a sham-operated (B) rat. The boxed area in panel A represents an area with surface erosions of the articular cartilage. The length of the solid bars corresponds to 200 μ m.

four compartments, and this overall estimate of cartilage erosion was also significantly higher in the vehicle-treated OVX animals ($19.55 \pm 2.8\%$) compared with the treated groups (11.24 ± 1.9 , 11.68 ± 1.4 , and $8.15 \pm 1.7\%$ in estrogen, low-dose and high-dose levormeloxifene-treated rats, respectively; $P < 0.001$). The total erosion score in the sham-operated animals was $7.1 \pm 1.3\%$.

The levels of bone and cartilage degradation were assessed with biochemical markers of collagen type I

and type II degradation (rCTX-I and CTX-II). Samples were obtained at baseline and at biweekly intervals throughout the study. The responses for each marker were expressed in percent of individual baselines, and the results were compiled by Area Under the Curve (AUC) calculations. OVX induced a significant increase in both rCTX-I and CTX-II levels (Fig. 3) compared with the sham group. Estrogen treatment normalized both markers to sham levels. Interestingly, levormeloxifene seemed to have different potency in



reducing bone and cartilage turnover. Only the highest dose of levormeloxifene decreased rCTX-I levels significantly compared with vehicle treatments ($P = 0.0014$), whereas both the high-dose and the low-dose treatment of levormeloxifene were able to completely normalize CTX-II levels ($P < 0.0001$). The increased CTX-II levels in the vehicle-treated group were most pronounced at week 4 after OVX, with a decreasing tendency thereafter. rCTX-I levels were also highest 4 weeks after OVX but remained more persistently elevated throughout the study period (not shown).

The correlation between levels of the biomarkers as well as their changes and subsequent erosion were assessed (Table 2). The rCTX-I levels were not associated with cartilage erosion, regardless whether the change in this marker or absolute levels at 4 weeks were correlated with the corresponding erosion scores (Table 2). Only a weak borderline significant ($r = 0.26$, $P = 0.0495$) association was found between absolute rCTX-I levels week 4 and erosions scores of the medial femur. In contrast, a highly significant association was found between CTX-II and structural damage of the articular knee cartilage. The correlations of the 4-week changes in CTX-II and that of absolute levels of CTX-II at week 4 with subsequent erosive score are shown in

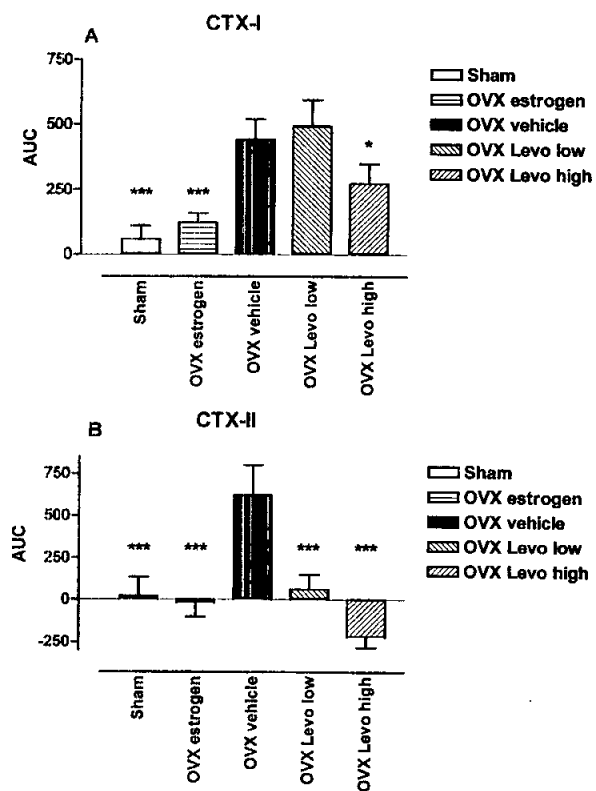


Table 2. This association between CTX-II levels and changes in the marker was observed both for the total erosion score and for scores from medial femur (Table 2), lateral femur, and medial tibia (not shown).

To further illustrate the association between changes in CTX-II and the severity of subsequent cartilage erosion, animals were stratified according to the 4-week change in CTX-II (Fig. 4). Thus the lowest quartile (Q1) includes animals with the most pronounced reductions in cartilage turnover (average Δ CTX-II, $-54.3 \pm 2.9\%$), whereas the highest quartile (Q4) includes those with the most pronounced increase (average Δ CTX-II, $+122.7 \pm 17.6\%$) comprising the majority (80%) of the vehicle-treated OVX rats. The rats in the lowest quartile have significantly lower erosion (both total as well

TABLE 2. Correlations between markers of bone and cartilage turnover and histologically assessed cartilage damage in the rat OVX study

	Total score	Medial femur
Δ rCTX-I, 0-4 weeks	0.13	0.11
rCTX-I, week 4	0.20	0.26 ^a
Δ CTX-II, 0-4 weeks	0.64 ^b	0.70 ^b
CTX-II, week 4	0.46 ^c	0.50 ^b

Correlations for the total histology score as well as for the medial femur are shown. The table lists Spearman's rho for each correlation. Δ denotes change from baseline in %. rCTX-I, collagen type I C-telopeptide degradation products; CTX-II, cartilage-specific collagen type II degradation products.

^a $P < 0.05$.

^b $P < 0.001$.

^c $P < 0.01$.

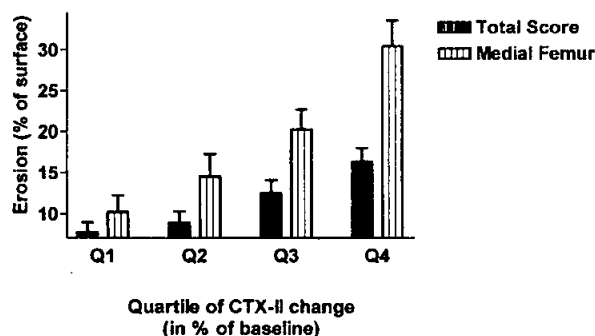


FIG. 4. Association between cartilage erosion and C-telopeptide fragments of collagen type II (CTX-II). Animals from the cohort of the estrogen-SERM (selective estrogen-receptor modulator) intervention experiment were stratified into quartiles of the 4-week change in CTX-II. The range of Δ CTX-II in each quartile was as follows. Q1: -78.8% to -39.5%; Q2: -36.8% to -6.0%; Q3: -5.8% to 40.1%; Q4: 41.0% to 256.4%. Average erosion score for the medial femur as well as total score for all four compartments of the knee are shown for each quartile. Error bars represent SEM. $P = 0.001$ by nonparametric ANOVA.

as medial femur, medial tibia, and lateral femur) compared with those in the highest quartile ($P < 0.001$).

Changes in cartilage turnover in levormeloxifene-treated postmenopausal women

To assess potential chondro-protective effects of levormeloxifene in humans, we measured the changes in the urinary excretion of CTX-II in samples from a phase II trial of levormeloxifene. Table 3 provides the baseline characteristics of the study population. There were no significant differences between placebo and the different intervention groups in terms of age, years since menopause (YSM), body mass index, or baseline value of bone and cartilage turnover. No statistically significant differences were found between the different dose groups (not shown).^{18,22}

The upper panel of Fig. 5 displays the results of the CTX-I measurements in the different treatment groups

TABLE 3. Demographics and biomarkers at baseline for postmenopausal women treated with either levormeloxifene or placebo

	Levormeloxifene	
	Placebo	1.25, 5, 10 and 20 mg/day
Randomized participants	21	71
Age (y)	57.4 $\pm$ 4.1	56.9 $\pm$ 3.8
BMI (kg/m ²)	25.4 $\pm$ 3.3	26.1 $\pm$ 3.7
YSM (y)	7.7 $\pm$ 4.0	6.3 $\pm$ 4.4
CTX-II/creatinine (ng/mmol)	232 $\pm$ 93	214 $\pm$ 104
S-CTX-I (pmol/L)	4412 $\pm$ 1350	3963 $\pm$ 1700

Results are mean $\pm$ SD. BMI, body mass index; YSM, years since menopause; CTX-II, cartilage-specific collagen type II degradation products; S-CTX-I, serum cartilage-specific collagen type I products.

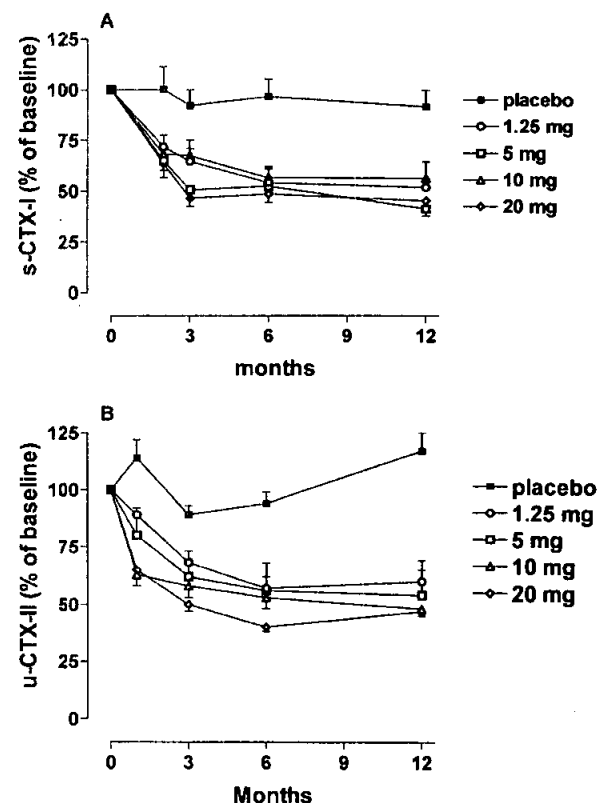


FIG. 5. Changes in bone and cartilage turnover during treatment with levormeloxifene. Participants received treatment either with placebo or with 1.25, 5, 10, or 20 mg of levormeloxifene daily. **A:** Changes in the bone resorption marker (s-CTX-I); **B:** Corresponding changes in the urinary excretion of the cartilage turnover marker (CTX-II). Results are expressed as average percent of individual means within the treatment groups. Error bars represent SEM.

during the first 12 months of the study. All four doses of levormeloxifene (1.25, 5, 10 and 20 mg/day) induced a significant and sustained decrease in CTX-I levels to approximately 50% of baseline levels. In contrast,

CTX-I levels in placebo-treated women were virtually stable throughout the intervention period. The changes in CTX-I in the treated groups already reached a nadir after 3 months. Maximal responses were obtained with all doses, and thus no apparent dose-response relationship could be demonstrated.

Results of CTX-II measurements from the levormeloxifene study are shown in the lower panel of Fig. 5. CTX-II levels showed similar changes, reaching a nadir at -50% from baseline at 3 to 6 months of the treatment. Though there were only small, nonsignificant differences between the responses of the four treatment groups, a trend toward dose-dependent effects was revealed. After cessation of the levormeloxifene treatment, all four treated groups reverted to baseline levels of CTX-II during the subsequent 12 months, indicating that the suppressive effect of levormeloxifene on cartilage turnover was reversible.

When changes in CTX-I were correlated with their corresponding CTX-II values, only a weak correlation was found ($r = 0.29$, $P < 0.05$).

DISCUSSION

The effect of estrogen and related compounds, such as SERMs, on estrogen-responsive tissues like the endometrium, bone, and breast has been extensively studied. Cartilage is not generally viewed as an estrogen-responsive tissue, and conflicting reports exist in the literature on whether estrogen exerts beneficial protective effects on cartilage.^{10,11} In this study, we show that the SERM levormeloxifene induces a significant decrease in urinary levels of collagen type II-derived fragments in both rodents and humans, indicating that this compound has a noteworthy chondro-protective effect.

Specific proteolytic degradation of collagen type II is a key event in cartilage degradation both *in vitro* and *in vivo*.²²⁻²⁴ Metabolites derived from this protein are thus biochemical markers suitable for the estimation of cartilage degradation.^{17,25} The CTX-II assay has been demonstrated to correlate with other known biochemical markers assessing cartilage turnover.^{26,27} More importantly, CTX-II levels and changes in this marker have consistently shown to be correlated with radiologically assessed cartilage damage in both OA and rheumatoid arthritis (RA) patient cohorts.²⁶⁻²⁹ In a longitudinal study of people with knee OA, CTX-II measurements were correlated with radiological estimates of cartilage degradation as well as standardized clinical scores of pain and joint function.^{26,28} Similar correlation between CTX-II and radiographically assessed cartilage damage has been demonstrated in early RA as well as in people with established disease.^{27,29} A recent

immunohistology study employing the collagen type II C-telopeptide-specific monoclonal antibody employed in the CTX-II assay has also revealed that the collagen type II fragments reactive with this antibody are generated in articular cartilage by the action of specific matrix metallo-proteases, and that production of these fragments is elevated in cartilage from people with OA or cartilage where catabolism is induced *in vitro*.³⁰ Thus, systemic CTX-II levels, as quantified in this study, are likely to represent a direct measure of articular cartilage turnover. Likewise a number of studies in humans as well as animals have assessed the association between the CTX-I marker and bone resorption, demonstrating a significant correlation between this marker and subsequent changes in BMD, as well as an ability of the marker to reflect the dynamic effects of antiresorptive therapies and increased bone turnover in arthritis.^{18-20,26,27,31-33} Also, the increased bone resorption after OVX is reflected as increased rCTX-I levels.

In rats, estrogen deficiency induced a significant increase in cartilage erosion, as evidenced by histological assessment of knee joints 9 weeks after surgical removal of the ovaries. Erosion was most prominent in the medial compartments, probably reflecting the additive effects of physical forces to the overall degree of erosion. The erosions were relatively mild and confined to the surface of the articular cartilage, indicating that they may be more representative of the early stages of arthritis pathology. These observations are in accordance with another study where ovariectomy induced similar erosion of the articular cartilage surface.¹⁹ Both estrogen and the estrogen-like SERM levormeloxifene were able to prevent this erosion. The higher dose levormeloxifene tended to provide greater benefits than those provided by estrogen. These observations indicate that estrogen replacement as well as selective estrogen-receptor modulation by levormeloxifene exhibits structurally notable chondro-protective effects in joints.

In accordance with previous studies, we also observed that levormeloxifene was able to decrease the OVX-induced elevation in bone resorption, as quantified by the rCTX-I marker.^{18,33} However, only the highest tested dose of the SERM showed any significant antiresorptive effects. In cynomolgus monkeys, levormeloxifene has also been shown to reduce OVX-induced elevated bone turnover. Yet even in these animals, the high dose of the compound (5 mg/kg/day) was unable to reduce bone resorption to the same extent as estrogen treatment, which seems to mimic the observations made in the study presented here.³³

In contrast to the relatively modest antiresorptive effect of levormeloxifene, a potent effect on cartilage turnover, as assessed with the CTX-II marker, was observed with both the low and the high dose of the SERM. When responses measured with rCTX-I and CTX-II markers reflecting bone and cartilage turnover, respectively, were compared, it seems that levormeloxifene has a more potent ability to suppress cartilage degradation relative to bone resorption in the OVX model. Both levormeloxifene-treated groups showed CTX-II levels similar to sham- or estrogen-treated OVX rats. Four-week responses, and in particular the 4-week change in urinary CTX-II excretion, showed a strong association with the degree of subsequent cartilage degradation. In other words, those animals whose cartilage turnover was effectively inhibited by estrogen or SERM also showed less progression and, therefore, absence or only mild cartilage erosion at the end of the intervention period. These observations are in line with clinical observations illustrating the utility of cartilage markers in clinical prognostics.²⁶⁻²⁹ Collectively, measurements of the relative changes in the urinary excretion of CTX-II after treatment initiation provide useful information regarding the clinical benefits of the therapy in terms of cartilage conservation.

Women experience an increased incidence of OA after menopause.^{3,4,8,34} In a recent study, we observed that urinary levels of CTX-II are elevated after menopause, and that subsequent HT results in restoration of the degradation marker to premenopausal levels.¹³ The dynamics of the changes in cartilage turnover at menopause, as assessed with the CTX-II marker, are similar to the well-established effects on bone resorption, where an elevation of approximately 100% is seen after menopause.³¹ This observation again emphasizes that reduced endogenous estrogen production accompanying menopause not only confers an increased bone turnover and subsequent risk of osteoporotic fractures, but also an increased risk of subsequent elevated cartilage turnover. It remains to be demonstrated whether anabolic and catabolic processes of cartilage metabolism are affected equally by estrogen deficiency; but, in a recent study on an OA cohort, an imbalance between collagen type II degradation and formation was demonstrated.²⁸ Based on these observations, it is plausible to assume that estrogen and estrogen-like substances could provide effective prevention of cartilage degradation in postmenopausal women.^{10,11}

Because the end stage of OA is an irreversible degradation of articular cartilage, prevention is at present a more feasible treatment aim to accomplish than curative therapy. To assess the potential clinical benefits of

levormeloxifene as suggested by the OVX study, we investigated the effect of this SERM on changes in cartilage degradation in a group of generally healthy postmenopausal women. These women were not selected based on the presence of clinically/radiological manifest OA. Rather, they may be considered as relevant high-risk population for developing OA based on their age, which corresponds to the period when cartilage turnover is expected to accelerate due to estrogen deficiency. Both estrogens in the form of HT and SERMs are among the medications clinicians frequently consider for the prevention of postmenopausal bone loss. In light of the results of the WHI study, which revealed that HT resulted in an unexpected increase in risks of breast cancer and cardiovascular disease, conventional HT is currently not recommended for primary prevention.¹⁴ Thus, it was particularly interesting to assess the potential chondro-protective effects of a SERM such as levormeloxifene, which has not been implicated to have adverse effects on the cardiovascular system or the breasts.²²

In the present study we investigated the effects of 12-month levormeloxifene treatment, after which the participants were followed for an additional 12 months. Levormeloxifene induced relatively rapid and marked decreases in the urinary excretion of CTX-II, suggesting an inhibition of cartilage degradation in analogy with the observations from the OVX study. Responses tended to show dose dependency in the first 3 to 6 months of the treatment period, with the 20-mg dose giving the most pronounced decrease in CTX-II excretion. At 12 months there was no significant difference between any of the doses. The suppression of cartilage degradation was reversible, as evidenced by the progressive restoration of CTX-II excretion to baseline levels during the 12 months of follow-up after treatment withdrawal.

The effects of levormeloxifene treatment on bone resorption as assessed with the CTX-I marker were of a similar magnitude as those on cartilage degradation assessed with the CTX-II assay (Fig. 5). Although the responses on average may seem similar, the two assays clearly mirror different processes. First, the correlation between CTX-II and CTX-I measurements was relatively weak ($r = 0.26$), and previous characterizations have revealed a high specificity of the antibodies employed in both assays.^{17,19} More importantly, there were notable differences in the dose-response relationships reflected by the two markers. Although there was a trend toward a dose-dependent change in CTX-II in the first 3 to 6 months of the study period, the responses in CTX-I were of the same magnitude without any

dose-dependency (Figure 5A).¹⁵ These observations also demonstrate the different dynamics of the effects exerted by levormeloxifene on bone and cartilage metabolism.

CONCLUSIONS

In summary, the data reported here are the first to suggest that a SERM may have a significant beneficial effect on cartilage degradation in humans. As no approved drugs are available today for preventing cartilage degradation and thus development of OA, the potential chondro-protective effect of levormeloxifene shown here enables the pursuit of new preventive and therapeutic strategies in the management of OA. As the incidence of OA is set to rise in the coming decades as a result of demographic changes, compounds and treatment strategies that can prevent or reduce the development of OA will clearly be of high importance. Our findings obtained in a novel animal model of OA provide promising preliminary results regarding the de facto cartilage-preserving effects of estrogen-like substances, which were further corroborated by assessment of cartilage turnover in postmenopausal women treated with levormeloxifene. However, further clinical trials confirming the translation of the observed changes in biomarkers to decreased cartilage erosion and incidence of clinically manifest OA are required to fully establish the potential role of SERMs such as levormeloxifene in clinical management and prevention of OA.

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Menopausal Symptoms and Treatment-Related Effects of Estrogen and Progestin in the Women's Health Initiative

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OBJECTIVE: To estimate the effects of estrogen plus progestin (E+P) therapy on menopausal symptoms, vaginal bleeding, gynecologic surgery rates, and treatment-related adverse effects in postmenopausal women.

METHODS: Randomized, double-blind, placebo-controlled trial of 16,608 postmenopausal women, ages 50–79 (mean $\pm$ standard deviation 63.3 $\pm$ 7.1) years, with intact uterus, randomized to one tablet per day containing 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate ($n = 8,506$) or placebo ($n = 8,102$), and followed for a mean of 5.6 years. Change in symptoms and treatment-related effects were analyzed at year 1 in all participants. Bleeding and gynecologic surgery rates were analyzed through study close-out.

RESULTS: Baseline symptoms did not differ between the treatment groups. More women assigned to E+P than placebo reported relief of hot flashes (85.7% versus 57.7%, respectively; odds ratio 4.40; 95% confidence interval 3.40–5.71), night sweats (77.6% versus 57.4%; 2.58; 2.04–3.26), vaginal or genital dryness (74.1% versus 54.6%; 2.40; 1.90–3.02), joint pain or stiffness (47.1% versus 38.4%; 1.43; 1.24–1.64), and general aches or pains (49.3% versus 43.7%; 1.25; 1.08–1.44). Women asymptomatic at baseline who were assigned to E+P more often developed breast tenderness (9.3% versus 2.4%, respectively; 4.26; 3.59–5.04), vaginal or genital discharge (4.1% versus 1.0%; 4.47; 3.44–5.81), vaginal or genital irritation (4.2% versus 2.8%; 1.52; 1.27–1.81), and headaches (5.8% versus 4.7%; 1.26; 1.08–1.46) than women on placebo. Estrogen plus progestin treatment prevented the onset of new musculoskeletal symptoms. Vaginal bleeding was reported by 51% of women on E+P

and 5% of women on placebo at 6 months; most bleeding was reported as spotting. Gynecologic surgeries (hysterectomy and dilation and curettage) were performed more frequently in women assigned to E+P (3.1% versus 2.5% for hysterectomy, hazard ratio = 1.23, $P = .026$; 5.4% versus 2.4% for dilation and curettage, hazard ratio = 2.23, $P < .001$).

CONCLUSION: Estrogen plus progestin relieved some menopausal symptoms, such as vasomotor symptoms and vaginal or genital dryness, but contributed to treatment-related effects, such as bleeding, breast tenderness, and an increased likelihood of gynecologic surgery. (Obstet Gynecol 2005;105:1063–73. © 2005 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: I

Vasomotor and vaginal symptoms typically attributed to menopause or the menopausal transition occur in approximately 70% of U.S. women and may be severe in up to 20%.^{1–3} Symptom relief remains the primary indication for hormone therapy, particularly in younger women when symptoms have a significant impact on quality of life.^{4–6}

The Women's Health Initiative (WHI), a large, long-term clinical trial and observational study initiated in 1993, was designed to study major causes of morbidity and mortality in postmenopausal women. The WHI clinical trial includes a trial of hormone therapy (separate trials of estrogen plus progestin and estrogen alone) for the prevention of coronary heart disease and hip fracture,⁷ plus a dietary trial and a calcium and vitamin D supplementation trial. Interested and eligible women

*For a list of other members of the Women's Health Initiative Investigators, see Appendix.

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could participate in 1, 2, or all 3 trials. The WHI estrogen plus progestin (E+P) trial intervention was stopped prematurely in July 2002 because the overall health risks of E+P exceeded the benefits⁸ in otherwise healthy women. In March 2004, the National Institutes of Health also ended early the estrogen-alone trial's intervention phase.⁹

Although the E+P trial was not designed to address the effects of E+P on the treatment of menopausal symptoms, symptom data were collected on E+P participants across all ages of menopause (50–79 years at baseline). Before the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial¹⁰ and the Heart and Estrogen/Progestin Replacement Study (HERS),¹¹ there were limited long-term clinical trial data on treatment-related and menopausal symptoms in older, postmenopausal women. Given the possible increased morbidity of women on E+P, a clear understanding of the impact of hormonal therapy on symptoms is essential. Quality-of-life data from the WHI E+P trial determined that combination therapy did not have a clinically meaningful impact on health-related quality of life.¹² However, comprehensive analyses regarding common menopausal complaints, such as hot flashes, and treatment-related symptoms were not presented and could provide an important elaboration of the quality-of-life findings.

The aims of these detailed data analyses from the 16,608 women enrolled in the WHI E+P trial were to better define the relationships among menopausal status, symptoms, and the effects of combined hormone therapy across the spectrum of postmenopausal women and to determine factors that influenced these outcomes. The impact of combined hormone therapy on the rate of selected gynecologic surgery procedures also was assessed.

SUBJECTS AND METHODS

Postmenopausal women between the ages of 50 and 79 years were recruited from 40 clinical centers across the United States to participate in the WHI. The clinical center institutional review boards reviewed and approved the project, and all participants provided written, informed consent. Ten clinical centers that were specifically designated as minority centers were to recruit and randomize 60% of their participants from minority groups to ensure that the racial/ethnic participation in the WHI was proportionate to the U.S. population.¹³

The WHI E+P trial was designed to evaluate the effects of estrogen plus progestin therapy on specific disease outcomes.⁷ Women in the E+P trial ($n = 16,608$) still had a uterus at baseline and were randomly assigned in a 1:1 ratio to either active treatment (0.625 mg/day conjugated equine estrogens plus 2.5 mg/day

medroxyprogesterone) or placebo. Details of the E+P trial design, recruitment, screening, randomization, and eligibility criteria are described elsewhere.^{7,8,13,14} Basically, women were considered postmenopausal if they had no vaginal bleeding for the previous 6 months (12 months for women aged 50–54), had a hysterectomy, or had ever used postmenopausal hormone therapy. Women were excluded if they had medical conditions associated with competing risk, safety concerns, or adherence and retention concerns. Relevant to this analysis is that menopausal symptoms (mild, moderate, or severe) were not an exclusion criterion for the trial except for those participants who were taking hormone therapy at baseline and had severe symptoms after a 3-month washout. Routine follow-up of all E+P trial participants consisted of semiannual contacts to collect self-reported outcome data and assess participant safety, as well as more extensive annual visits to obtain outcome and mammogram report data and carry out physical measurement and gynecologic examinations.

Reports of vaginal bleeding were collected at safety interviews, administered 6 weeks and 6 months after randomization, and semiannually thereafter while participants were still taking study pills. Reports of bleeding and other symptoms (eg, menopausal symptoms or hormonal adverse effects) were followed up by trained clinicians using specific algorithms. The algorithms were predicated on the fact that all participants had a negative endometrial assessment at baseline. Only study gynecologists were unblinded as necessary for the management of bleeding. A general algorithm was followed for the management of bleeding in the E+P trial as follows. Bleeding during the first 6 months that was equal to or lighter than a regular menstrual period was managed without intervention. After the first 6 months, the consulting gynecologist was unblinded for any bleeding. Further management was dependent on severity of bleeding, time since randomization, study arm assignment, and endometrial histology of past biopsy (if any). Bleeding management protocols were designed to ensure that participant safety remained the primary focus. In addition, blinding was preserved to the extent that was ethical and to minimize undue burden in the form of unnecessary work-up or treatment. After the first 6 months of the study, all women in the placebo group with bleeding had endometrial evaluation, either with aspiration biopsy or transvaginal ultrasonography. Women in the active E+P group had endometrial evaluation for heavy bleeding or increasing bleeding of any severity. Biopsy results of atrophy, secretory endometrium, proliferative endometrium, and insufficient tissue were considered negative. Based on histologic findings, women in the active E+P group were managed by using



specific protocols for additional estrogen or progestin, with re-evaluation after 6 months. Women in either group were referred to their personal health care providers for follow-up of abnormal findings (complex hyperplasia, hyperplasia with atypia, or cancer). An endometrial echo greater than 5 mm was considered an indication for histologic assessment.

A symptom checklist for WHI included items on menopausal symptoms based on the Postmenopausal Estrogen/Progestin Interventions (PEPI) symptom tool,¹⁰ as well as items from other national surveys and clinical trials,¹⁵ to capture symptoms commonly associated with hormone use and aging. For this discussion, 15 symptoms were analyzed: hot flushes, night sweats, breast tenderness, vaginal or genital irritation or itching, vaginal or genital dryness, vaginal or genital discharge, headaches or migraines, joint pain or stiffness, general aches or pains, lower back pain, neck pain, bloating or gas, swelling of hands or feet, mood swings, and difficulty concentrating. These symptoms represented those typically associated with menopause in previous research. Participants rated symptom severity on a 4-point scale, from symptom did not occur, to mild (did not interfere with usual activities), moderate (interfered somewhat with usual activities), or severe (so bothersome that usual activities could not be performed). The psychosocial forms containing these symptom items were reviewed for content validity by nationally recognized behavioral and clinical experts and were pretested extensively on age-appropriate women from diverse racial/ethnic groups. These forms were administered to all E+P participants at baseline and year 1 and to an 8.6% subsample of participants (oversampled for minorities) at year 3. This subsampling scheme maximized component- and racial/ethnic-specific information on intermediate effects of the intervention, including blood biomarkers, yet kept costs and clinic burden to a minimum.

Information was collected annually on health changes, hospital admissions, and surgery during the previous year, including gynecologic surgeries. The indication for hysterectomy, based on medical records review, was adjudicated in the majority of cases.

Primary analyses focused on symptom changes in all participants reported from baseline to year 1 in relation to E+P trial randomization assignment and in an 8.6% subsample at year 3. All analyses were based on the intention-to-treat principle using SAS 9.0 (SAS Institute Inc, Cary, NC). The Cochran-Armitage test¹⁶ was used to determine changes in prevalence with age for each symptom.

Logistic regression analyses were stratified by prevalence of baseline symptoms (moderate/severe versus

symptom did not occur/mild). For each symptom, treatment effect was determined based on the following:

- i. Relief of menopausal symptoms at year 1 among women symptomatic at baseline.
- ii. Onset of treatment-related symptoms at year 1 among women asymptomatic at baseline.

We controlled for type I error rates separately for (i) and (ii) by using a Bonferroni corrected α ($0.05/15 \sim 0.003$). Because symptoms are not statistically independent, multiple comparison corrections will be conservative.

Logistic regression models were used to examine whether there were subgroups of women for whom E+P had more substantial effects on relief of symptoms or occurrence of treatment-related effects, both adverse and beneficial. Each model included the randomization assignment, a baseline characteristic, and the corresponding interaction term. Baseline characteristics corresponding to these subgroups included age, years-since-menopause, body mass index (BMI), waist-to-hip ratio, prior postmenopausal hormone use, physical activity, smoking, and alcohol use. The type I error rates were controlled separately for the symptomatic and asymptomatic women, where the statistical significance of these interactions ($120 \text{ symptoms} \times \text{baseline characteristic combinations}$) were judged by a Bonferroni-corrected α ($0.05/15 \times 8 \sim 0.0004$).

For the gynecologic surgery data, Cox proportional hazards models¹⁷ were performed after stratification by age and randomization into the low-fat dietary trial. Time to event was defined as the numbers of days from randomization into the WHI trial to the date that the event was reported. Participants who did not self-report a surgery were censored by their last follow-up contact before July 8, 2002. Proportional hazards assumptions were verified by the interaction of time to event and treatment assignment and by inspecting parallelism of estimated survival functions. Nonsignificant, statistically significant interaction terms and parallel log-log survivor functions indicate that hazard functions are proportional.

RESULTS

Overall, 8,506 women were randomly assigned to the estrogen plus progestin group and 8,102 to the placebo group. At baseline, the mean age $\pm$ standard deviation (SD) of participants was 63.3 ± 7.1 years. All women had an intact uterus at baseline and were an average of 13.4 years postmenopausal. The women were largely white (83.9%) and well educated (73.8% had some school or college after high school). The mean length of follow-up in the E+P trial was 5.6 years. Detailed base-



Table 1. Baseline Symptoms Reported as Moderate/Severe by Participants in the WHI Estrogen Plus Progestin Trial by Age (N = 16,608)

Symptom	Age Group at Screening								Changing Prevalence With Age (P)
	50-54 y		55-59 y		60-69 y		70-79 y		
	(n = 2,029)		(n = 3,493)		(n = 7,510)		(n = 3,576)		
	n	%	n	%	n	%	n	%	
Hot flushes	476	23.5	522	14.9	451	6.0	95	2.7	Decreasing (< .001)
Night sweats	428	21.1	488	14	483	6.4	128	3.6	Decreasing (< .001)
Breast tenderness	54	2.7	67	1.9	109	1.4	45	1.3	Decreasing (< .001)
Vaginal or genital irritation or itching	80	3.9	110	3.2	231	3.1	128	3.6	.62
Vaginal or genital dryness	220	10.8	359	10.3	651	8.7	234	6.5	Decreasing (< .001)
Vaginal or genital discharge	34	1.7	40	1.1	54	0.7	30	0.8	Decreasing (< .001)
Headaches or migraines	284	14.0	409	11.7	629	8.4	213	6	Decreasing (< .001)
Joint pain or stiffness	405	20	729	20.9	1701	22.6	889	24.9	Increasing (< .001)
General aches or pains	410	20.2	712	20.4	1535	20.4	761	21.3	.30
Lower back pain	365	18	613	17.6	1290	17.2	709	19.8	.09
Neck pain	291	14.3	413	11.8	833	11.1	400	11.2	Decreasing (< .001)
Bloating or gas	289	14.2	490	14.0	1016	13.5	517	14.5	.80
Swelling of hands or feet	133	6.6	218	6.2	406	5.4	240	6.7	.86
Mood swings	245	12.1	264	7.6	367	4.9	123	3.4	Decreasing (< .001)
Difficulty concentrating	118	5.8	172	4.9	276	3.7	142	4	Decreasing (< .001)

line characteristics of the E+P trial participants are described elsewhere^{8,14} and did not differ between the 2 treatment groups.

There were no differences between the 2 treatment groups in any baseline symptom. Menopausal symptoms ranging from mild to severe were reported in all age groups. The prevalence of mild-to-severe hot flushes at baseline was 60.23% for women aged 50-54 years, 44.49% for ages 55-59, 23.37% for ages 60-69, and 11.38% for ages 70-79. The mean number $\pm$ SD of moderate or severe symptoms reported by each woman decreased with age, from 1.89 ± 2.31 in the 50-54 year age group to 1.60 ± 2.10 , 1.34 ± 1.84 , and 1.30 ± 1.77 in age groups 55-59, 60-69, and 70-79, respectively. Baseline symptoms were stratified by age instead of years-since-menopause because we had complete data on participants' ages; age is strongly correlated with years since menopause (Pearson $r = 0.82$; computed on continuous versions of both variables).

Rates of moderate-to-severe baseline symptoms for the entire cohort by age group at randomization, along with changing prevalence with age showed that 9 of the 15 symptoms decreased with age. Joint pain or stiffness was the only symptom that increased significantly with age (Table 1).

The prevalence of all symptoms, particularly vasomotor symptoms (hot flushes and night sweats), varied by ethnicity, with African-American (21.8% for moderate-severe hot flushes) and Hispanic women (19%) 2-3 times more likely to report moderate-to-severe vasomotor symptoms than white (7.9%) and Asian women (6.4%), $P < .001$.

At the time of the year 1 analysis, among active E+P women who reported moderate-to-severe hot flushes, night sweats, and vaginal or genital dryness at baseline, these symptoms had improved significantly, as had joint pain or stiffness and general aches or pains compared with women on placebo (Table 2). Of symptomatic women 50-54 years old, 82.5% on active treatment and 52.2% on placebo experienced relief of vasomotor symptoms.

Symptomatic women who were younger ($P = .013$ for hot flushes, $P < .001$ for night sweats), thinner ($P < .001$, $P = .01$ based on BMI; and $P = .15$, $P < .001$ based on waist/hip ratio), and closer to the menopause ($P = .04$, $P < .001$) experienced more relief from hot flushes and night sweats, respectively. The effectiveness of E+P on symptom relief did not vary for any other combination of symptom or participant baseline characteristic.

At year 1, the relative risk for breast tenderness and vaginal discharge in the E+P group compared with placebo more than quadrupled, yet only 9.3% and 4.1% of asymptomatic women in the E+P group developed breast tenderness and vaginal or genital discharge, respectively (Table 3). Treatment-related beneficial effects included prevention of vasomotor symptoms and vaginal or genital dryness in previously asymptomatic women. In addition, combined therapy reduced the incidence of new musculoskeletal symptoms, including joint pain or stiffness, general aches or pains, lower back pain, and neck pain.

In subgroup analyses, younger, asymptomatic women assigned to E+P and those closer to menopause were less likely to develop night sweats at year 1 ($P < .001$, $P < .001$, respectively) than those assigned to placebo.



Table 2. Relief/Improvement of Symptoms at Year 1 Among Women Symptomatic at Baseline in the WHI Estrogen Plus Progestin Trial by Treatment Assignment to Estrogen Plus Progestin or Placebo

Symptom	No. of Symptomatic Women* at Baseline (% Relieved at Year 1†)		Odds Ratio	95% CI	P
	E + P	Placebo			
Hot flushes	735 (85.7)	645 (57.7)	4.40	3.40–5.71	< .001
Night sweats	711 (77.6)	643 (57.4)	2.58	2.04–3.26	< .001
Breast tenderness	118 (58.5)	115 (72.2)	0.54	0.31–0.94	.03
Vaginal or genital irritation or itching	262 (61.8)	224 (64.7)	0.88	0.61–1.28	.51
Vaginal or genital dryness	711 (74.1)	606 (54.6)	2.40	1.90–3.02	< .001
Vaginal or genital discharge	72 (81.9)	67 (79.1)	1.20	0.52–2.78	.67
Headaches or migraines	727 (52.0)	654 (55.4)	0.87	0.71–1.08	.21
Joint pain or stiffness	1741 (47.1)	1639 (38.4)	1.43	1.24–1.64	< .001
General aches or pains	1623 (49.3)	1470 (43.8)	1.25	1.08–1.44	.002
Lower back pain	1359 (44.4)	1322 (42.3)	1.09	0.94–1.27	.26
Neck pain	916 (52.0)	847 (49.5)	1.11	0.92–1.33	.30
Bloating or gas	1046 (53.4)	1048 (52.5)	1.04	0.87–1.23	.69
Swelling of hands or feet	427 (60.9)	444 (63.5)	0.89	0.68–1.18	.42
Mood swings	447 (63.1)	412 (63.4)	0.99	0.75–1.31	.94
Difficulty concentrating	313 (59.7)	297 (58.6)	1.05	0.76–1.45	.77

E + P, estrogen plus progestin; CI, confidence interval.

* Reporting symptom severity as moderate or severe.

† Reporting symptom severity as mild or did not occur.

Younger women and those closer to menopause also were less likely to develop vaginal or genital discharge and vaginal or genital dryness at year 1 than those assigned to placebo ($P < .001$, $P < .001$, respectively). Women who were older ($P < .001$), further from menopause ($P < .001$), never/past hormone therapy users ($P < .001$), and thinner ($P < .001$) were more likely to develop breast tenderness. Treatment effects did not

vary for any other combination of symptoms or baseline characteristics. Missing data ranged from 7.9% to 8.5% per symptom and were handled via complete-case analysis.

Finally, there was a small, although statistically significant ($P < .001$), difference in weight change from baseline to year 1 (Table 4). A higher proportion of women on combined hormone therapy experienced weight loss than those on placebo. Results hold when stratifying by age.

Table 3. Incidence of Treatment Effects at Year 1 Among Women Asymptomatic at Baseline in the WHI Estrogen Plus Progestin Trial by Treatment Assignment to Estrogen Plus Progestin or Placebo

Symptom	No. of Asymptomatic Women* at Baseline (% Treatment Effect at Year 1†)		Odds Ratio	95% CI	P
	E + P	Placebo			
Hot flushes	7046 (1.3)	6765 (3.3)	0.39	0.31–0.50	< .001
Night sweats	7020 (3.2)	6746 (4.2)	0.76	0.64–0.91	.003
Breast tenderness	7645 (9.3)	7300 (2.4)	4.26	3.59–5.04	< .001
Vaginal or genital Irritation or itching	7484 (4.2)	7167 (2.8)	1.52	1.27–1.81	< .001
Vaginal or genital dryness	7020 (3.4)	6741 (5.2)	0.63	0.53–0.75	< .001
Vaginal or genital discharge	7663 (4.1)	7331 (1.0)	4.47	3.44–5.81	< .001
Headaches or migraines	7055 (5.8)	6771 (4.7)	1.26	1.08–1.46	.003
Joint pain or stiffness	6012 (10.1)	5743 (14.1)	0.68	0.61–0.76	< .001
General aches or Pains	6099 (11.0)	5894 (14.4)	0.73	0.66–0.82	< .001
Lower back pain	6369 (9.3)	6090 (11.6)	0.78	0.70–0.88	< .001
Neck pain	6835 (6.7)	6540 (7.9)	0.84	0.74–0.96	.01
Bloating or gas	6491 (12.1)	6237 (11.7)	1.04	0.94–1.16	.45
Swelling of hands Or feet	7319 (4.5)	6948 (5.0)	0.91	0.78–1.06	.21
Mood swings	7309 (4.0)	6973 (4.3)	0.95	0.80–1.12	.50
Difficulty Concentrating	7402 (3.0)	7074 (3.0)	0.99	0.81–1.20	.89

E + P, estrogen plus progestin; CI, confidence interval.

* Reporting symptom severity as moderate or severe.

† Reporting symptom severity as mild or did not occur.



Table 4. Weight Change at Year 1 Among the WHI Estrogen Plus Progestin Trial Participants by Treatment Assignment to Estrogen Plus Progestin or Placebo

Treatment	> -10 lb	-10 to -5 lb	-5 to 0 lb	0 to +5 lb	+5 to +10 lb	> +10 lb
E+P	1,093 (13.8)	1,170 (14.7)	2,273 (28.6)	2,008 (25.3)	829 (10.4)	566 (7.1)
Placebo	793 (10.5)	927 (12.2)	2,099 (27.7)	2,149 (28.3)	1,007 (13.3)	614 (8.1)

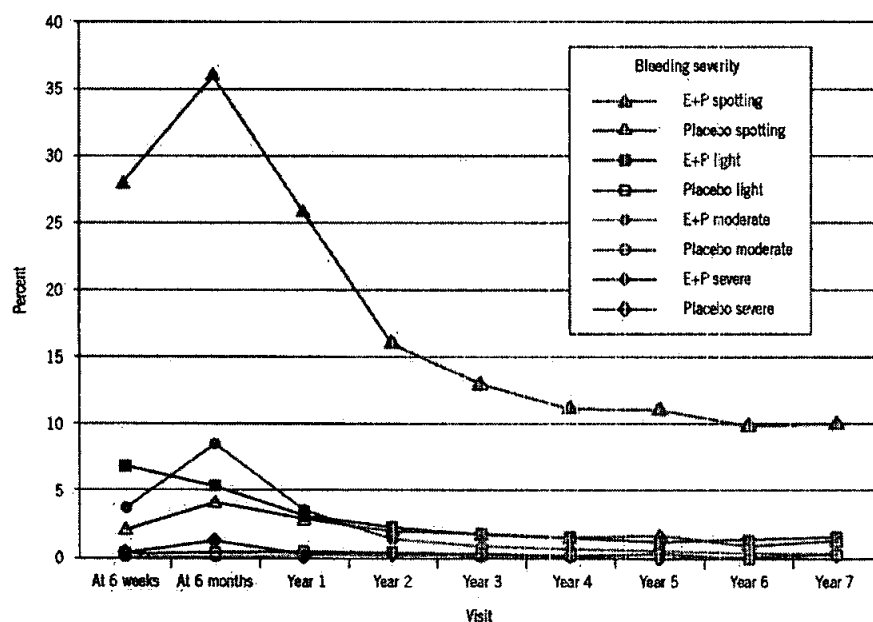
E+P, estrogen plus progestin.

Data are expressed as n (%).

Vaginal bleeding was the most frequently reported treatment effect for women in the active treatment group (Fig. 1), occurring in 42.5% and 51.0% of participants in the first 6 weeks and 6 months of the trial, respectively. Thereafter, reports of bleeding declined gradually but never fell below 11.6%. At year 5, 13.0% (544 of 4,184) of women in the E+P group reported bleeding, characterized as mostly spotting in both treatment groups. In the placebo group, 86.6% of women never reported bleeding, while only 33.3% of the active treatment group was amenorrheic throughout the trial. During year 1, 234 women on E+P and 8 women in the placebo group cited vaginal bleeding as one of the reasons for stopping intervention; multiple reasons could be cited by participants. Within the first 12 months of therapy, there were 875 endometrial aspiration procedures and 217 transvaginal ultrasound examinations performed for bleeding, with the majority of these (91.3% and 86.2%, respectively) performed in the E+P group. Complete data on the results of these procedures have been reported previously.¹⁸ At 6 months and year 1, women who were older ($P < .001$, $P < .001$, respectively), further from menopause ($P < .001$, $P < .001$), thinner ($P < .001$, $P < .001$) and never/past hormone therapy users ($P < .001$,

$P = .009$) were more likely to report bleeding. No subgroups were more likely to bleed at year 5 in the active treatment group relative to the placebo group (Bonferroni corrected $\alpha = 0.05/8 \times 3 = 0.002$).

Combined hormone therapy led to an increase in the occurrence of common gynecologic surgeries, although the absolute numbers were small. Annualized percentages for hysterectomy were 0.52% for women assigned to E+P (267 of 8,239 women, 3.14%) and 0.43% for placebo (204 of 7,898 women, 2.52%; hazard ratio [HR] 1.23, 95% confidence interval [CI] 1.03–1.48; $P = .026$). Medical records data on hysterectomies in E+P trial participants during follow-up were collected and evaluated by local clinical center adjudicators. In the adjudicated hysterectomy group ($n = 407$), the most common indication for the procedure was uterine descensus/prolapse (48.4% overall; 46.9% for the E+P group and 50.3% for the placebo group). Bleeding was the indication for hysterectomy in only 23 women in the E+P group and 8 women in the placebo group. The absolute excess risk of hysterectomy attributable to E+P is 9 events per 10,000 woman-years. Women assigned to E+P were more than twice as likely to undergo a dilation

**Fig. 1.** Bleeding frequency and severity in the Women's Health Initiative Estrogen Plus Progestin Trial participants by randomization assignment to estrogen plus progestin (E+P) or placebo.Barnabei. Treatment Effects of Estrogen Plus Progestin. *Obstet Gynecol* 2005.

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Table 5. Relief/Improvement of Symptoms At Year 3 Among Women Aged 50–59 in Subsample Symptomatic at Baseline in the WHI Estrogen Plus Progestin Trial by Treatment Assignment to Estrogen Plus Progestin or Placebo (N = 576)

Symptom	No. of Symptomatic Women* at Baseline (% Relieved at Year 3†)				Odds Ratio	95% CI	P
	E+P		Placebo				
Hot flushes	54	(83.3)	47	(72.3)	1.91	0.73–4.99	.19
Night sweats	51	(68.6)	38	(84.2)	0.41	0.14–1.18	.10
Breast tenderness	6	(66.7)	6	(83.3)	0.40	0.03–6.18	.51
Vaginal or genital irritation or itching	8	(62.5)	8	(87.5)	0.24	0.02–3.01	.27
Vaginal or genital dryness	24	(87.5)	30	(63.3)	4.05	0.98–16.76	.05
Vaginal or genital discharge	1	(100.0)	5	(100.0)	N/A		
Headaches or migraines	38	(57.9)	29	(51.7)	1.28	0.49–3.39	.62
Joint pain or stiffness	67	(41.8)	51	(27.5)	1.90	0.87–4.15	.11
General aches or pains	60	(50.0)	54	(42.6)	1.35	0.64–2.82	.43
Lower back pain	52	(40.4)	46	(52.2)	0.62	0.28–1.38	.24
Neck pain	36	(52.8)	29	(48.3)	1.20	0.45–3.19	.72
Bloating or gas	36	(44.4)	41	(61.0)	0.51	0.21–1.27	.15
Swelling of hands or feet	26	(73.1)	21	(76.2)	0.85	0.23–3.20	.81
Mood swings	12	(58.3)	19	(68.4)	0.65	0.14–2.90	.57
Difficulty concentrating	12	(58.3)	9	(22.2)	4.90	0.70–34.30	.11

E+P, estrogen plus progestin; CI, confidence interval; N/A, not applicable.

* Reporting symptom severity as moderate or severe.

† Reporting symptom severity as mild or did not occur.

and curettage (D&C) than those assigned to placebo, but information regarding specific indications for this procedure is not available in the database. Annualized percentages for D&C are 0.90% for E+P women (461 of 8,045 women, 5.42%) and 0.41% for placebo (198 of 7,904 women, 2.44%; HR 2.23, CI 1.88–2.63; $P < .001$). The

absolute excess risk of D&C attributable to E+P is 49 events per 10,000 woman-years.

Analyses of symptoms at year 3 on an 8.6% subsample of E+P trial participants (775 women assigned to E+P and 736 assigned to placebo, oversampled for minorities) showed that symptom relief and treatment effects from

Table 6. Incidence/Increase in Treatment Effects at Year 3 Among Women Aged 50–59 in Subsample Asymptomatic at Baseline in the WHI Estrogen Plus Progestin Trial by Treatment Assignment to Estrogen Plus Progestin or Placebo (N = 576)

Symptom	No. of Asymptomatic Women* at Baseline (% Treatment Effect at Year 3†)				Odds Ratio	95% CI	P
	E+P		Placebo				
Hot flushes	196	(3.6)	184	(6.5)	0.53	0.20–1.38	.19
Night sweats	199	(5.5)	190	(7.9)	0.68	0.31–1.53	.35
Breast tenderness	244	(6.6)	224	(2.7)	2.55	0.98–6.64	.06
Vaginal or genital irritation or itching	242	(3.7)	219	(6.9)	0.53	0.23–1.23	.14
Vaginal or genital dryness	223	(2.2)	197	(9.6)	0.22	0.08–0.59	.003
Vaginal or genital discharge	248	(1.6)	224	(2.7)	0.60	0.17–2.14	.43
Headaches or migraines	214	(7.5)	202	(10.4)	0.70	0.35–1.38	.30
Joint pain or stiffness	183	(10.9)	177	(18.6)	0.54	0.29–0.98	.04
General aches or pains	191	(11.0)	175	(17.1)	0.60	0.33–1.09	.09
Lower back pain	200	(9.5)	185	(11.4)	0.82	0.43–1.58	.55
Neck pain	215	(7.0)	200	(8.0)	0.86	0.42–1.79	.69
Bloating or gas	211	(13.7)	187	(15.0)	0.91	0.52–1.59	.73
Swelling of hands or feet	225	(5.8)	209	(4.8)	1.22	0.52–2.85	.65
Mood swings	235	(6.0)	211	(6.6)	0.89	0.42–1.92	.77
Difficulty concentrating	240	(4.6)	223	(4.5)	1.02	0.43–2.46	.96

E+P, estrogen plus progestin; CI, confidence interval.

* Reporting symptom severity as mild to did not occur.

† Reporting symptom severity as moderate to severe.



baseline to year 1 were similar to those seen in the full E+P cohort. By year 3, 83.3% of E+P participants who at baseline were aged 50–59 ($n = 576$) and had moderate or severe hot flushes were relieved of their symptoms (Table 5). However, 72.3% of placebo participants experienced similar relief. Of women in this same age group who were asymptomatic at baseline, those on E+P were less likely to report vaginal or genital dryness and joint pain or stiffness than women on placebo (Table 6).

DISCUSSION

The Women's Health Initiative is the largest, randomized intervention trial of postmenopausal hormone therapy ever conducted. The Estrogen Plus Progestin trial provided us the opportunity to study menopausal symptoms and the effects of hormone therapy on symptoms in women across the spectrum of postmenopausal ages.

Most previous reports of menopausal symptoms have been short-term studies limited to perimenopausal and younger menopausal women who are thought to be most likely to have these symptoms. In the Heart and Estrogen-Progestin Replacement Study (HERS) trial of older postmenopausal women, almost 20% of women aged 70–74 reported frequent or somewhat frequent hot flushes.¹¹ A large, population-based study of symptoms suggested that approximately 50% of women experience vasomotor symptoms at cessation of menses and 20% are symptomatic 4 years postmenopause.¹⁹ At baseline, more than 60% of WHI E+P trial participants aged 50–54 and more than 10% of those aged 70–79 still experienced hot flushes, ranging from mild to severe. However, these data might underestimate the prevalence in the general population slightly because women with more severe vasomotor symptoms were excluded from the trial if they were taking hormones at baseline and were unable or unwilling to be randomized to placebo. Estimates from other studies suggest that up to 70% of naturally menopausal women experience vasomotor symptoms, with severe symptoms in 15–20%.^{2,3} Our data are consistent with these estimates, although they cannot be generalized to women undergoing surgical menopause.

Black and Hispanic women reported a higher prevalence of vasomotor symptoms than white women, and Asian women reported the lowest rates. These data are similar to other reports of ethnic differences in symptom prevalence²⁰ although the reasons for these differences are not known.

At baseline, younger women more frequently reported hot flushes, night sweats, mood swings, and headaches or migraines than older women. Younger women

and those closer to menopause also were more likely to have relief of vasomotor symptoms. This suggests that vasomotor symptoms in older women may have causes other than menopausal status and may not respond as well to hormone therapy. Older women more frequently reported joint pain or stiffness. Other pain symptoms, including general aches or pains and low back pain, were very common among all age groups, with remarkable stability across the age distribution. This is somewhat surprising because the prevalence of musculoskeletal symptoms overall would be expected to increase with age. These data suggest that pain symptoms, such as general aches and pains and low back pain, are already well established by midlife. Among women asymptomatic at baseline, there was a prophylactic effect of E+P on these symptoms at years 1 and 3. The beneficial effect of hormone therapy on joint symptoms and other musculoskeletal complaints has long been suspected and women anecdotally have reported improvement, but this has not been well documented in the literature. This benefit of E+P was seen in all age groups of women and persisted at year 3, although the benefit in the subsample was not statistically significant. Hays and colleagues¹² reported a benefit in physical functioning and bodily pain in the E+P trial, consistent, in part, with the small, prophylactic effect of E+P on musculoskeletal symptoms seen among asymptomatic women in the current analysis. Smaller studies have demonstrated a beneficial effect of hormone therapy on quality of life in younger menopausal women.²¹

In WHI E+P trial participants, the rates of vaginal bleeding, a known treatment effect of combined hormone therapy, are similar to those reported in other studies of continuous, combined hormone therapy,^{22–25} although the range of bleeding reported in these studies is wide. Most prior studies reported short-term bleeding rates only. Our data suggest that bleeding persists in up to 12% of women at 5 or more years of use, which is important information for women considering combined hormone therapy for symptom relief. This is especially true for older women considering hormone therapy, because they were more likely to bleed than women closer to menopause. Most bleeding on combined hormone therapy in the E+P trial was classified as spotting and was associated with benign endometrial changes (ie, normal histology or atrophic/insufficient specimen).

Hysterectomy was slightly more common in women on active E+P, but the indications for the procedure did not differ between the groups. The most common indication, uterine prolapse or descensus, was not increased in women on active intervention.

Estrogen plus progestin improved vasomotor symptoms, vaginal or genital dryness, and all pain symptoms



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evaluated compared with placebo. In spite of a preponderance of mood swings in younger postmenopausal women, E+P did not have any effect on this symptom, bringing into question a direct relationship between hormonal status and mood. Other studies have shown that mood disorders are more common in symptomatic perimenopausal women, suggesting that some women have a heightened sensitivity to the effects of changing or declining estrogen levels than other women.²⁶ It is not known whether estrogen-alone therapy will have a different effect on mood swings in symptomatic women. The decrease in prevalence of other subjective symptoms, such as difficulty concentrating, could be due to difference in perception of these age groups. In addition, this analysis looked primarily at moderate-to-severe symptoms, which may be more apparent to younger women. Although weight gain has been a concern of women considering hormone therapy, recent data suggest that they are not at greater risk for weight gain.²⁷ The data from this study also confirm that combined hormone therapy has no adverse effect on weight in menopausal women.

Thinner women were more likely to experience relief from vasomotor symptoms, but were more prone to vaginal bleeding and breast tenderness. Older women and those further from menopause also were more likely to report breast tenderness, an anticipated adverse treatment effect of combined hormone therapy. Increases in mammographically defined breast density in response to hormone therapy are greater in women with lower breast density at the time hormone therapy is started.^{28,29} Although women remote from menopause might be expected to have lower breast density than younger women and be more susceptible to the effects of hormone therapy, a specific association between a change in breast density and breast tenderness has not been established.

Combined hormone therapy decreased the prevalence of vasomotor symptoms associated with menopause, especially in younger women. Estrogen plus progestin also decreased reports of vaginal or genital dryness and joint aches and pains. However, bleeding was common throughout therapy, especially in the first 6 months. Other treatment effects, such as vaginal discharge and irritation and breast tenderness, especially in older women, would limit the overall benefit on quality of life. Our results bridge earlier findings on the effect of E+P on health-related quality of life in this cohort, showing a beneficial effect for younger, symptomatic women only.¹² Long-term health benefits of E+P are outweighed by health risks, supporting short-term hormone therapy for the treatment of moderate-to-severe menopausal symptoms, primarily in younger women.

According to current prescribing guidelines, combined hormone therapy is indicated only for the treatment of moderate-to-severe vasomotor symptoms associated with menopause³⁰ when the benefits of short-term therapy may outweigh the risks.

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United States Patent**Plunkett et al.**

[19]

[11] E

Patent Number: Re. 36,247**[45] Reissued Date of Patent: Jul. 6, 1999**

[54] **METHOD OF HORMONAL TREATMENT FOR MENOPAUSAL OR POST-MENOPAUSAL DISORDERS INVOLVING CONTINUOUS ADMINISTRATION OF PROGESTOGENS AND ESTROGENS**

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[21] Appl. No.: **08/542,941**

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[51] Int. Cl.⁶ **A61K 31/56**

[52] U.S. Cl. **514/170**

[58] Field of Search **514/170**

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Attorney, Agent, or Firm—Pillsbury Madison & Sutro LLP

[57] ABSTRACT

A method of hormonally treating menopausal (including perimenopausal and post-menopausal) disorders in women, a composition, and a multi-preparation pack therefor. The administrative regimen to which the pack is particularly adapted comprises continuously and uninterruptedly administering a progestogen to a woman while cyclically administering an estrogen by using a repetitive dosage regimen. This regimen calls for administering the estrogen continuously for a period of time between about 20 and about 120 days, followed by terminating administering the estrogen for a period of time between about 3 and about 7 days. Alternatively, both the progestogen and estrogen may be administered for the full treatment period without interruption. The regimen avoids many of the problems associated with the administration of estrogen alone or with progestogen administered according to conventional regimens, and also avoids problems associated with such conventional regimens by maintaining the estrogen and progestogen at low daily dosage levels of between 0.005 mg and 2.5 mg estrogen and 0.25 mg and 30 mg progestogen.

46 Claims, 1 Drawing Sheet

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(21) International Application Number: PCT/EP95/00343 (22) International Filing Date: 31 January 1995 (31.01.95) (30) Priority Data: 9402203.5 4 February 1994 (04.02.94) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): EBBERS, Walter, F., W. [NL/CH]; Jago Pharma AG, Eptingerstrasse 51, CH-4132 MuttENZ (CH). ZIMMER, Robert, H. [FR/CH]; Jago Pharma AG, Eptingerstrasse 51, CH-4132 MuttENZ (CH). (74) Agent: WALKER, Ralph, Francis; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9EP (GB).		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: BILAYERED AMOXYCILLIN TABLETS (57) Abstract Tablet formulations for oral administration comprising a first layer which includes amoxycillin and/or clavulanate, and a second layer which includes amoxycillin and/or clavulanate. The overall tablet contains amoxycillin and the relative rate of release of amoxycillin and/or clavulanate from the first and second layers differs. The tablet formulations of the invention provide sustained release of amoxycillin and optionally also clavulanate.		

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
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WO 03/059327 A1

(54) Title: BILAYER PHARMACEUTICAL TABLET COMPRISING TELMISARTAN AND A DIURETIC AND PREPARATION THEREOF

(57) Abstract: A bilayer pharmaceutical tablet comprises a first layer formulated for immediate release of the angiotensin II receptor antagonist telmisartan from a dissolving tablet matrix which contains telmisartan in substantially amorphous form, and a second layer formulated for immediate release of a diuretic like hydrochlorothiazide from a fast disintegrating tablet matrix. A method of producing the bilayer tablet is also disclosed.



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(54) **BILAYER TABLET COMPRISING AN
ANTIHISTAMINE AND A DECONGESTANT**

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(57) **ABSTRACT**

A pharmaceutical composition in the form of a bilayer tablet comprising:

(a) a first discrete portion made with Formulation (A) which comprises a sympathomimetic drug, or a pharmaceutically acceptable salt thereof, and a first carrier base material which provides a sustained-release of the sympathomimetic drug or the pharmaceutically acceptable salt thereof, said first carrier base material comprising a mixture of: (i) a filler; (ii) a cellulose binder selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, and mixtures thereof, wherein the hydroxypropyl cellulose has a molecular weight of at least 80,000; (iii) ethylcellulose; (iv) a wax; and (v) a lubricant; and

(b) a second discrete portion made with Formulation (B) which comprises a piperidinoalkanol compound, or a pharmaceutically acceptable salt thereof, and a second carrier base material which provides an immediate-release of the piperidinoalkanol or the pharmaceutically acceptable salt thereof, said second carrier base comprising a mixture of: (i) a sugar; (ii) a disintegrant; and (iii) a lubricant. The bilayer tablets exhibit acceptable content uniformity under USP requirements, resist lamination and have acceptable physical strength during the self life.

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WO 03/077923 A1

(54) Title: **PROGESTERONE ORAL DRUG DELIVERY SYSTEM**

(57) Abstract: Provided is an oral dosage form suitable to deliver a combined dosage of progesterone and which upon delivery through the gastrointestinal tract provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml progesterone; said dosage form comprising a combination that includes (a) a first solid form comprising from about 25 mg to about 500 mg micronized progesterone in a solid polyethylene glycol carrier having an average molecular weight of from about 1000 to 10,000 and constituting at least about 30 % of said first solid form; and (b) a second solid form comprising an estrogen.

Other techniques known in the art may also be employed to prepare the solid dosage form, including, but not limited to, compression molding, tableting, and extrusion. See, for example, Remington, *supra*, Chapters 91-94.

5 **b) Combining Progesterone and Estrogen in One Dosage Form**

A combination dosage form comprising progesterone and estrogen dosage forms can be prepared by first preparing the progesterone and estrogen formulations or dosage forms separately and then combining them. In one aspect, progesterone and estrogen formulations can be compressed together to form one dosage form, for example, a multilayered tablet
10 wherein each layer represents a progesterone or an estrogen formulation. Alternatively, the progesterone dosage form and the estrogen dosage form can be encapsulated in one capsule. For example, one caplet of progesterone and one tablet of estradiol may be placed into a size # 1 hard shell gelatin capsule using an MG encapsulation machine fitted with custom built parts.

Methods of preparing estrogen formulations are well-known in the art. See,
15 Remington, *supra*, Chapters 91-93. For example, the estrogen formulation can be prepared by direct compression method. In this method, the required quantities of estrogen and a portion of anhydrous lactose are mixed together in a blender. The remaining anhydrous lactose, and, optionally, different types of color aluminum lake, are premixed by passing through a size 20 screen. Other ingredients such as microcrystalline cellulose and polacriline potassium may be
20 added to this mixture. The granulation may be lubricated with magnesium stearate. The granules are then made into tablets on a rotary tableting machine fitted with appropriate punches and dies to achieve the desired tablet size, thickness, and hardness.

Estrogen may constitute from about 0.5 % to about 5 % by weight of the tablet, depending on the type of estrogen and the therapeutically effective estrogen blood levels
25 needed for a given treatment. In one example, estradiol constitutes about 1.29 % of the weight of the mixture so that a tablet containing 1 mg of estradiol weighs about 80 mg and has a diameter of about 7/32 inch. The thickness of a tablet weighing 80 mg is about 0.107 inch.

We claim:

1. An oral dosage form suitable to deliver a combined dosage of progesterone and estradiol which upon delivery through the gastrointestinal tract provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml progesterone, said dosage form comprising a combination that includes (a) a first solid form comprising from about 25 mg to about 500 mg micronized progesterone in a solid polyethylene glycol carrier having an average molecular weight of from about 1000 to 10,000 and constituting at least about 30 % of said first solid form; and (b) a second solid form comprising an estrogen.
2. An oral dosage form of claim 1 wherein said polyethylene glycol carrier comprises from about 45 % to about 65 % weight of the component (a).
3. An oral dosage form of claim 1 wherein said second solid form (b) contains from about 0.25 mg to about 5 mg of estradiol.
4. An oral dosage form of claim 1 wherein said solid polyethylene glycol carrier comprises a mixture of polyethylene glycol 1450, polyethylene glycol 3350 or polyethylene glycol 8000.
5. An oral dosage form suitable to deliver a combined dosage of progesterone and an estrogen via the gastrointestinal tract which upon oral administration provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml progesterone; said dosage form comprising a combination that includes (a) a first solid form containing from about 25 mg to about 500 mg micronized progesterone, said first solid form having been derived from the extrusion of a polymer matrix extruded from a mixture comprising micronized progesterone in a solid polyethylene glycol carrier which is a mixture of polyethylene glycol 1450,

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polyethylene glycol 3350 or polyethylene glycol 8000, the micronized progesterone having first been dispersed in molten polyethylene glycol and, after cooling to a solid form, having been extruded, said mixture constituting from about 45 % to about 65 % weight of said first solid form; and (b) a second solid form which contains from about 0.25 mg to about 5 mg of estradiol.

6. An oral dosage form of claim 5 wherein said first solid form is a caplet and said second solid form is a tablet.

7. A method of providing an oral dosage of a combination therapy of progesterone and estradiol which comprises administering to a patient an oral dosage form suitable to deliver a combined dosage of progesterone and an estrogen via the gastrointestinal tract which upon oral administration provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml progesterone; said dosage form comprising a combination that includes (a) a first solid form containing from about 25 mg to about 500 mg micronized progesterone, said first solid form having been derived from the extrusion of a polymer matrix extruded from a mixture comprising micronized progesterone in a solid polyethylene glycol carrier which is a mixture of polyethylene glycol 1450, polyethylene glycol 3350 or polyethylene glycol 8000, the micronized progesterone having first been dispersed in molten polyethylene glycol and, after cooling to a solid form, having been extruded, said mixture constituting from about 45 % to about 65 % weight of said first solid form; and (b) a second solid form which contains from about 0.25 mg to about 5 mg of estradiol.

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(21) International Application Number: PCT/US94/14639 (22) International Filing Date: 20 December 1994 (20.12.94) (30) Priority Data: 93/9566 21 December 1993 (21.12.93) ZA (71) Applicant (for all designated States except US): APPLIED ANALYTICAL INDUSTRIES, INC. [US/US]; 1206 North 23rd Street, Wilmington, NC 28405 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GREAVES, Frank, C. [US/US]; 3108 Joe Wheeler Drive, Wilmington, NC 28409 (US). SWARBRICK, James [US/US]; 1260 Mallard Bay Road, Hampstead, NC 28443 (US). BEASLEY, Martin, W. [US/US]; 5808 Oak Bluff Lane, Wilmington, NC 28409 (US). (74) Agents: GARRETT, Arthur, S. et al.; Finnegan, Henderson, Farabow, Garrett & Dunner, 1300 I Street, N.W., Washington, DC 20005-3315 (US).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: METHOD FOR DRY BLEND COMPRESSION OF MEDICAMENTS (57) Abstract Disclosed is a method of dry blend compression of potent drugs with low solubility, such as steroidal medicaments using directly compressible agglomerated excipients that are not a conventional or spray dried polyalcohol or lactose. The agglomerated excipients include mannitol, maltodextrin or corn syrup solids which hold the medicament(s) in the crevices of the agglomerates. Also disclosed are the critical ratios of the agglomerated excipients to steroidal agent, specifically estradiol, that is distributed uniformly throughout the dry blend and then compressed into tablets.		

Claims

1. The method of making pharmaceutical tablets comprising blending a unit dosage quantity of one or more low dosage medicaments with an agglomerated excipient of the group comprising mannitol, maltodextrin or corn syrup solid adding optional tableting aids such as one or more tableting fillers, disintegrating agents or lubricants and drying and compression of said blend.
2. The method of claim of 1 in which the medicament is an estrogen.
3. The method of claim 1 in which the medicament is estradiol.
4. The method in claim 1 in which the excipient is mannitol.
5. The method of claim 1 in which the excipient is mannitol and the medicament is an estrogen.
6. The method of claim 1 in which the excipient is mannitol and the medicament is estradiol.
7. The method of claim 1 in which the excipient is a combination of mannitol and maltodextrin.
8. The method of claim 7 in which the medicament is an estrogen.
9. The method of claim 7 in which the medicament is a combination of an estrogen and a progestin.
10. The method of claim 7 in which the medicament is conjugated estrogens.
11. The method of claim 7 in which the medicament is a combination of conjugated estrogens and a progestin.

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

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(54) Title: HORMONE REPLACEMENT THERAPY

(57) Abstract: This invention relates to methods and pharmaceutical compositions for providing hormone replacement therapy in perimenopausal, menopausal, and postmenopausal women through the continuous administration of combinations of conjugated estrogens and medroxyprogesterone acetate.

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Both components can be incorporated in the compressed tablet core or in a tablet coating formulated to maintain drug stability and provide adequate oral bioavailability. For example, the progestin can be micronized.

5 Conjugated estrogens can be incorporated in granules, spheroids or other multiparticulate forms, and, if necessary, coated to provide adequate stability. These multiparticulates can be combined, in the appropriate proportions, with a powder blend, granulation or multiparticulates containing the progestin and incorporated into hard gelatin capsules.

10 This invention also provides a pharmaceutical does pack, containing any number of daily pharmaceutical dosage units. Preferably, and conventionally, the pack contains 28 tablets or multiples thereof. The pack should indicate that the dosage units are to be taken consecutively on a daily basis until the treatment period has ended, or until the pack has been completed. The next pack should be started on the next consecutive day. For combinations containing a unitary dosage tablet
15 containing both conjugated estrogens and MPA, it is preferable that the pack contain one tablet corresponding to each day of administration. For combinations containing separate dosage units of conjugated estrogens and MPA, it is preferable that each one tablet of each correspond to each given day's administration, as indicated on the pill pack.

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CLAIMS

1. Use of conjugated estrogens and medroxyprogesterone acetate in the manufacture of pharmaceutical packs comprising daily dosage units for the treatment or inhibition of menopausal or postmenopausal disorders in a perimenopausal, menopausal, or postmenopausal woman in need thereof, wherein each daily dosage unit comprises a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.
2. The use according to claim 1 which comprises treating or inhibiting vasomotor symptoms in a perimenopausal, menopausal, or postmenopausal woman in need thereof.
3. The use according to claim 2, wherein the vasomotor symptom is hot flushes.
4. The use according to claim 1 which comprises inhibiting or retarding bone demineralization or treating or inhibiting osteoporosis in a perimenopausal, menopausal, or postmenopausal woman in need thereof.
5. The use according to claim 1 which comprises treating or inhibiting vaginal or vulvar atrophy; atrophic vaginitis; vaginal dryness; pruritus; dyspareunia; dysuria; frequent urination; urinary incontinence; urinary tract infections in a perimenopausal, menopausal, or postmenopausal woman in need thereof.
6. The use according to claim 1 which comprises lowering cholesterol, triglycerides, Lp(a), or LDL levels; inhibiting or treating hypercholesterolemia; hyperlipidemia; cardiovascular disease; atherosclerosis; peripheral vascular disease; restenosis, vasospasm; or inhibiting vascular wall damage from cellular events leading toward immune mediated vascular damage, in a perimenopausal, menopausal, or postmenopausal woman in need thereof.
7. Use of conjugated estrogens and medroxyprogesterone acetate in the manufacture of pharmaceutical packs comprising daily dosage units for treating or inhibiting free radical involvement in the development of cancers, central nervous system disorders, Alzheimer's disease, bone disease, aging, inflammatory disorders, peripheral vascular disease, rheumatoid arthritis, autoimmune diseases, respiratory

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distress, emphysema, prevention of reperfusion injury, viral hepatitis, chronic active hepatitis, tuberculosis, psoriasis, systemic lupus erythematosus, amyotrophic lateral sclerosis, aging effects, adult respiratory distress syndrome, central nervous system trauma and stroke, or injury during reperfusion procedures in a perimenopausal, menopausal, or postmenopausal woman in need thereof, wherein each daily dosage unit comprises a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.

8. Use of conjugated estrogens and medroxyprogesterone acetate in the manufacture of pharmaceutical packs comprising daily dosage units for treating or inhibiting dementias, neurodegenerative disorders, and Alzheimer's disease; providing neuroprotection or cognition enhancement in a perimenopausal, menopausal, or postmenopausal woman in need thereof, wherein each daily dosage unit comprises a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.

9. Use of conjugated estrogens and medroxyprogesterone acetate in the manufacture of pharmaceutical packs comprising daily dosage units for increasing bone mineral density in a perimenopausal, menopausal, or postmenopausal woman in need thereof, wherein each daily dosage unit comprises a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.

10. Use of conjugated estrogens and medroxyprogesterone acetate in the manufacture of pharmaceutical packs comprising daily dosage units of minimizing or reducing levels of breast pain in a woman receiving hormone replacement therapy, wherein each daily dosage unit comprises a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.

11. Use of conjugated estrogens and medroxyprogesterone acetate in the manufacture of pharmaceutical packs comprising daily dosage units for minimizing spotting or breakthrough bleeding, or achieving amenorrhea in a woman receiving hormone replacement therapy, wherein each daily dosage unit comprises a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.

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12. The use according to claim 11, wherein the time for minimizing spotting or breakthrough bleeding or achieving the onset of amenorrhea is hastened.
13. The use according to any of claims 1 to 12, wherein the conjugated estrogens is synthetic conjugated estrogens, A.
14. The use according to any of claims 1 to 12, wherein the conjugated estrogens is conjugated equine estrogens, USP.
15. 15. The use according to any of the preceding claims, wherein the daily dosage of conjugated estrogens is between about 0.625 mg and about 0.3 mg.
16. The use according to any of the preceding claims, wherein the daily dosage of conjugated estrogens, is between about 0.45 mg and about 0.3 mg.
17. The use according to any of the preceding claims wherein the daily dosage of conjugated estrogens is about 0.45 mg.
18. The use according to any preceding claim wherein the daily dosage of conjugated estrogens, is about 0.3 mg.
19. The use according to any of the preceding claims wherein the pharmaceutical pack contains fixed daily dosage units.
20. 20. The use according to any of the preceding claims in which the pharmaceutical pack contains at least 28 daily dosage units.
21. The use according to any preceding claim in which the pharmaceutical pack comprises up to 180 daily dosage units.
22. The use according to any of the preceding claims in which the pharmaceutical pack contains at least 30 daily dosage units.
23. The use according to any preceding claim in which the pharmaceutical pack comprises up to 120 daily dosage units.

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24. The use according to any preceding claim in which the medroxyprogesterone acetate is micronized.
25. The use according to any preceding claim in which the daily dosage unit is
5 provided once a day.
26. The use according to any preceding claim in which the daily dosage unit is provided for oral administration.
- 10 27. The use according to any preceding claim in which the daily dosage unit contains 0.45 mg of conjugated equine estrogens and 1.5 mg of medroxyprogesterone acetate.
- 15 28. The use according to any preceding claim in which the daily dosage unit contains 0.3 mg of conjugated equine estrogens and 1.5 mg of medroxyprogesterone acetate.
- 20 29. A pharmaceutical composition for use in treating menopausal or postmenopausal disorders in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises conjugated estrogens, a dosage of about 1.5 mg medroxyprogesterone acetate, and a pharmaceutical carrier.
- 25 30. A pharmaceutical dosage unit which comprises conjugated estrogens, a dosage of about 1.5 mg of medroxyprogesterone acetate, and a pharmaceutical carrier.
31. A pharmaceutical pack comprising daily dosage units comprising a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate
- 30 32. The composition, unit or pack according to claim 29 or 30 or 31, wherein the conjugated estrogens is conjugated equine estrogens, USP.
33. The composition, unit or pack according to claim 29 or 30 or 31, wherein the conjugated estrogens is synthetic conjugated estrogens, A.

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- 34 The composition, unit or pack according to claim 32 or 33, wherein the dosage is between about 0.45 mg and about 0.30 mg.
- 35 The composition, unit or pack according to claim 32 or 33 wherein the dosage is about 0.45 mg or 0.30 mg.
- 36 The composition, unit or pack according to claim 29 or 30 or 31, wherein the medroxyprogesterone acetate is micronized.
- 37 The pharmaceutical pack according to claim 31 which comprises up to 180 fixed daily dosage units.
- 38 The pharmaceutical pack according to claim 37 containing at least 28 fixed daily dosage units.
- 39 The pharmaceutical pack according to claim 37 containing at least 30 fixed daily dosage units.
- 40 A method of treating or inhibiting menopausal or postmenopausal disorders in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises providing to said woman continuously and uninterruptedly over the treatment period, a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.
- 41 A method according to claim 40 which comprises treating or inhibiting vasomotor symptoms in a perimenopausal, menopausal, or postmenopausal woman in need thereof.
- 42 The method according to claim 41, wherein the vasomotor symptom is hot flushes.
- 43 A method according to claim 40 which comprises inhibiting or retarding bone demineralization or treating or inhibiting osteoporosis in a perimenopausal, menopausal, or postmenopausal woman in need thereof.

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44. A method according to claim 40 which comprises treating or inhibiting vaginal or vulvar atrophy; atrophic vaginitis; vaginal dryness; pruritus; dyspareunia; dysuria; frequent urination; urinary incontinence; urinary tract infections in a perimenopausal, menopausal, or postmenopausal woman in need thereof.
- 5
45. A method according to claim 40 which comprises lowering cholesterol, triglycerides, Lp(a), or LDL levels; inhibiting or treating hypercholesteremia; hyperlipidemia; cardiovascular disease; atherosclerosis; peripheral vascular disease; restenosis, vasospasm; or inhibiting vascular wall damage from cellular events
- 10 leading toward immune mediated vascular damage, in a perimenopausal, menopausal, or postmenopausal woman in need thereof.
46. A method of treating or inhibiting free radical involvement in the development of cancers, central nervous system disorders, Alzheimer's disease, bone disease,
- 15 aging, inflammatory disorders, peripheral vascular disease, rheumatoid arthritis, autoimmune diseases, respiratory distress, emphysema, prevention of reperfusion injury, viral hepatitis, chronic active hepatitis, tuberculosis, psoriasis, systemic lupus erythematosus, amyotrophic lateral sclerosis, aging effects, adult respiratory distress syndrome, central nervous system trauma and stroke, or injury during reperfusion
- 20 procedures in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises providing to said woman continuously and uninterruptedly over the treatment period, a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.
- 25 47. A method of treating or inhibiting dementias, neurodegenerative disorders, and Alzheimer's disease; providing neuroprotection or cognition enhancement in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises providing to said woman continuously and uninterruptedly over the treatment period, a combination of conjugated estrogens and a daily dosage of about
- 30 1.5 mg of medroxyprogesterone acetate.
48. A method of increasing bone mineral density in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises providing to said woman continuously and uninterruptedly over the treatment period, a
- 35 combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.

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49. A method of minimizing or reducing levels of breast pain in a woman receiving hormone replacement therapy, which comprises providing to said woman continuously and uninterruptedly over the treatment period, a combination of
5 conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.

50. A method of minimizing spotting or breakthrough bleeding; or achieving amenorrhea in a woman receiving hormone replacement therapy, which comprises
10 providing to said woman continuously and uninterruptedly over the treatment period, a combination of conjugated estrogens and a daily dosage of about 1.5 mg of medroxyprogesterone acetate.

51. The method according to claim 50, wherein the time for minimizing spotting
15 or breakthrough bleeding or achieving the onset of amenorrhea is hastened.

52. The method according to any of claims 40 to 51, wherein the conjugated estrogens is synthetic conjugated estrogens, A.

20 53. The method according to any of claims 40 to 51, wherein the conjugated estrogens is conjugated equine estrogens, USP.

54. The method according to any of claims 40 to 51, wherein the daily dosage of conjugated estrogens is between about 0.625 mg and about 0.3 mg.
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55. The method according any of claims 40 to 53, wherein the daily dosage of conjugated estrogens, is between about 0.45 mg and about 0.3 mg.

56. The method according any of claims 40 to 53 wherein the daily dosage of
30 conjugated estrogens, is about 0.45 mg or about 0.3 mg.

57. The method according to any of claims 40 to 53 in which the daily dosage unit contains 0.45 mg of conjugated equine estrogens and 1.5 mg of medroxyprogesterone acetate.
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(12) **EUROPEAN PATENT APPLICATION**

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(84) Designated Contracting States: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE	(72) Inventor: Barcomb, Reginald Joseph Mooers Forks, New York 12959 (US)
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(54) **Novel sugar coating composition for application to compressed medicinal tablets**

(57) A sugar coating composition for application to a compressed medicinal tablet comprising a sugar, a dose of a hormonal steroid and a steroid release rate controlling amount of microcrystalline cellulose.

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EXAMPLE 9

A sugar coating containing 5 mg of medrogestone in a matrix of sucrose with 0.4% microcrystalline cellulose and 0.5% polyvinyl pyrrolidone was applied to a sealed and sugar-coated tablet core. The *in vitro* dissolution profile of this dosage form was compared to that of a rapidly-disintegrating compressed tablet containing 5 mg of medrogestone using the dissolution test described in <711> of USP XX, p. 959 (1980) employing Apparatus 2 operating at 50 r.p.m., with 900 mL of 0.54% sodium lauryl sulfate at 37°C. The following data were obtained:

Mean Percentage Medrogestone Released (CV%)		
Time (Minutes)	Conventional Rapidly Disintegrating Tablet	Sugar Coated Tablet Containing Medrogestone in Sugar Coat
15	95 (2.0)	6 (11.2)
30	95 (2.9)	11 (6.9)
45	97 (1.6)	15 (6.4)
60	97 (1.9)	18 (6.6)
120	98 (1.9)	25 (6.2)

The dramatic effect of reduced dissolution of medrogestone when the hormone is incorporated in a sugar coat containing 0.4% microcrystalline cellulose is clearly demonstrated.

One preferred embodiment of this invention is a compressed tablet in which the tablet core contains a unit dose of an estrogenic compound or a mixture thereof in an amount of from about 0.1 to about 5.0 milligrams, or more preferably from about 0.3 to about 2.5 milligrams, in combination with standard excipient compression aids and fillers. Most desirably, the conjugated estrogens found in the tablet core comprises the naturally occurring conjugated estrogen product known as Premarin®. Over a sugar coat on the compressed tablet is applied an additional sugar coat containing about 1 to about 50 milligrams, and preferably about 1.5 to about 30 milligrams, of medroxyprogesterone acetate, a color coat, and finally, a polish coat.

Claims

1. A sugar coating composition for application to a compressed medicinal tablet comprising a sugar, a dose of a hormonal steroid and a steroid release rate controlling amount of microcrystalline cellulose.
2. A sugar coating composition according to claim 1 in which the sugar is sucrose.
3. A sugar coating composition according to claim 1 or claim 2 in which said hormonal steroid is medroxyprogesterone acetate, levonorgestrel, gestodene, medrogestone, estradiol, estriol, ethinylestradiol, mestranol, estrone, dienestrol, hexestrol, diethylstilbestrol, progesterone, desogestrel, norgestimate, hydroxyprogesterone, norethindrone, norethindrone acetate, norgestrel, megestrol acetate, methyltestosterone, ethylestrenol, methandienone, oxandrolone or trimegestone.
4. A sugar coating composition according to any one of claims 1 to 3 comprising from about 0.1% to about 3% microcrystalline cellulose, by weight, of the sugar coating.
5. A sugar coating composition according to any one of claims 1 to 4 further comprising polyvinylpyrrolidone in an amount of from 0 to about 5% by weight of the sugar coating.
6. A sugar coating composition according to any one of claims 1 to 5 comprising a hormonal steroid in an amount of from about 0.1 to about 20% by weight of the sugar coating.
7. A compressed tablet comprising a tablet core and a coating according to any one of claims 1 to 6.
8. A compressed tablet according to claim 7 wherein the tablet core comprises a medicinal agent which is conventionally administered in conjunction with a hormonal steroid.
9. A compressed tablet according to claim 8 wherein the tablet core comprises conjugated estrogens.

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EXAMPLE 9

A sugar coating containing 5 mg of medrogestone in a matrix of sucrose with 0.4% microcrystalline cellulose and 0.5% polyvinyl pyrrolidone was applied to a sealed and sugar-coated tablet core. The *in vitro* dissolution profile of this dosage form was compared to that of a rapidly-disintegrating compressed tablet containing 5 mg of medrogestone using the dissolution test described in <711> of USP XX, p. 959 (1980) employing Apparatus 2 operating at 50 r.p.m., with 900 mL of 0.54% sodium lauryl sulfate at 37°C. The following data were obtained:

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30	95 (2.9)	11 (6.9)
45	97 (1.6)	15 (6.4)
60	97 (1.9)	18 (6.6)
120	98 (1.9)	25 (6.2)

The dramatic effect of reduced dissolution of medrogestone when the hormone is incorporated in a sugar coat containing 0.4% microcrystalline cellulose is clearly demonstrated.

One preferred embodiment of this invention is a compressed tablet in which the tablet core contains a unit dose of an estrogenic compound or a mixture thereof in an amount of from about 0.1 to about 5.0 milligrams, or more preferably from about 0.3 to about 2.5 milligrams, in combination with standard excipient compression aids and fillers. Most desirably, the conjugated estrogens found in the tablet core comprises the naturally occurring conjugated estrogen product known as Premarin®. Over a sugar coat on the compressed tablet is applied an additional sugar coat containing about 1 to about 50 milligrams, and preferably about 1.5 to about 30 milligrams, of medroxyprogesterone acetate, a color coat, and finally, a polish coat.

Claims

1. A sugar coating composition for application to a compressed medicinal tablet comprising a sugar, a dose of a hormonal steroid and a steroid release rate controlling amount of microcrystalline cellulose.
2. A sugar coating composition according to claim 1 in which the sugar is sucrose.
3. A sugar coating composition according to claim 1 or claim 2 in which said hormonal steroid is medroxyprogesterone acetate, levonorgestrel, gestodene, medrogestone, estradiol, estriol, ethinylestradiol, mestranol, estrone, dienestrol, hexestrol, diethylstilbestrol, progesterone, desogestrel, norgestimate, hydroxyprogesterone, norethindrone, norethindrone acetate, norgestrel, megestrol acetate, methyltestosterone, ethylestrenol, methandienone, oxandrolone or trimegestone.
4. A sugar coating composition according to any one of claims 1 to 3 comprising from about 0.1% to about 3% microcrystalline cellulose, by weight, of the sugar coating.
5. A sugar coating composition according to any one of claims 1 to 4 further comprising polyvinylpyrrolidone in an amount of from 0 to about 5% by weight of the sugar coating.
6. A sugar coating composition according to any one of claims 1 to 5 comprising a hormonal steroid in an amount of from about 0.1 to about 20% by weight of the sugar coating.
7. A compressed tablet comprising a tablet core and a coating according to any one of claims 1 to 6.
8. A compressed tablet according to claim 7 wherein the tablet core comprises a medicinal agent which is conventionally administered in conjunction with a hormonal steroid.
9. A compressed tablet according to claim 8 wherein the tablet core comprises conjugated estrogens.

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10. A compressed tablet according to claim 9 in which said tablet core contains from about 0.1 to about 5.0 milligrams of conjugated estrogens and said sugar coating contains from about 1.0 to about 50 milligrams of said hormonal steroid.
- 5 11. A compressed tablet of claim 9 in which said tablet core contains from about 0.3 to about 2.5 milligrams of conjugated estrogens and said sugar coating contains about 1.5 to about 30 milligrams of medroxyprogesterone acetate.
12. A method of preparing a coating composition comprising bringing into association a sugar, a hormonal steroid and a steroid release rate controlling amount of microcrystalline cellulose.
- 10 13. A method of preparing a tablet which comprises coating a tablet core with a coating composition as claimed in any one of Claims 1 to 6.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/36, 31/56	A1	(11) International Publication Number: WO 97/04752 (43) International Publication Date: 13 February 1997 (13.02.97)
(21) International Application Number: PCT/US95/11797 (22) International Filing Date: 16 July 1996 (16.07.96) (30) Priority Data: 507,695 26 July 1995 (26.07.95) US (71) Applicant: DURAMED PHARMACEUTICALS, INC. [US/US]; 5040 Duramed Drive, Cincinnati, OH 45213 (US). (72) Inventors: HUBER, Harold, E.; 5021 Lord Alfred Court, Cincinnati, OH 45241 (US). RYAN, Mary, K.; 8220 Mariner Lane, Mainville, OH 45039 (US). (74) Agents: WEILD, David, III et al.; Pennie & Edmonds, 1155 Avenue of the Americas, New York, NY 10036 (US).		(81) Designated States: CA, CN, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL COMPOSITIONS OF CONJUGATED ESTROGENS AND METHODS FOR THEIR USE (57) Abstract This invention relates to novel pharmaceutical compositions containing conjugated estrogens for the treatment of peri-menopausal, menopausal and post-menopausal disorders in women. The novel pharmaceutical compositions comprise a carrier base material and conjugated estrogens formed into a solid unit dosage form possessing a regular incremental release of the medicament upon oral administration. Further, the invention comprises the combination of conjugated estrogens with progestogens in a solid, shaped dosage unit. Specifically, the invention comprises the use of an organic excipient such as high molecular weight hydroxyalkyl alkylcelluloses. The use of an organic excipient such as hydroxypropylmethylcellulose in a stable, solid dosage formulation containing either conjugated estrogens alone or in combination with a progestogen is described.		

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WE CLAIM:

1. A pharmaceutical composition in a solid, unit dosage form capable of oral administration for the hormonal treatment of peri-menopausal, menopausal and post-menopausal disorders in a woman comprising:
conjugated estrogens coated onto one or more organic excipients forming a powdered conjugated estrogen composition having less than about 2.5% free water by weight and greater than 2.5% total water wherein said solid unit dosage form is coated with a moisture barrier coating.
2. A pharmaceutical composition of claim 1 in which said organic excipients include a mixture of one or more gel-forming hydroxyalkylalkylcelluloses and a hydroxyalkyl cellulose wherein said organic excipients constitutes more than about one third by weight of the solid unit dosage form.
3. A pharmaceutical composition of claim 2 in which the gel-forming organic excipients are a mixture of one or more hydroxypropylmethylcelluloses and 0-33% of methyl cellulose or other cellulose ether.
4. A pharmaceutical composition of claim 1 wherein said powdered conjugated estrogen composition further includes at least about 40% by weight of a non-gel-forming organic excipient.
5. A pharmaceutical composition of claim 4 wherein said non-gel forming organic excipient is selected from the group consisting of lactose, mannitol, and cellulose derivatives.
6. A pharmaceutical composition of claim 1 wherein said conjugated estrogens is selected from the group consisting of the sodium sulfate esters of estrone, equilin, 17- α -dihydroequilin, 17- β -dihydroequilin and 17- α -estradiol.

7. A pharmaceutical composition of claim 1 wherein said moisture barrier coating comprises ethylcellulose.

8. A pharmaceutical composition of claim 7 wherein
5 said moisture barrier coating is 0.5-8.0% of the total weight of said solid unit dosage form.

9. A pharmaceutical composition of claim 1 further comprising about 30-70% gel-forming organic excipient and
10 about 30-70% non-gel forming organic excipient by weight.

10. A method for preparing an extended release pharmaceutical composition containing one or more conjugated estrogens and a carrier comprising:

- 15 (a) spraying a solution of said conjugated estrogens onto one or more organic excipients suspended in a fluidized bed in a closed system;
- (b) drying the mixture formed in (a) to where said mixture contains less than about 2.5% free water
20 and greater than about 2.5% total water by weight;
- (c) tableting the mixture formed in (b); and
- (d) coating said tablets with a film coating selected from the group including cellulose ethers, methacrylic acid and phthalates.

25 11. The method of claim 10 wherein said conjugated estrogens is selected from the group consisting of the sodium sulfate esters of estrone, equilin, 17- α -dihydroequilin, 17- β -dihydroequilin and 17- α -estradiol.

30 12. The method of claim 10 wherein said organic excipient mixture includes at least about 30% by weight of an aqueous gel-forming organic excipient.

35 13. The method of claim 12 wherein said gel-forming organic excipient is selected from the group consisting of

hydroxypropylmethylcellulose, sodium carboxymethylcellulose and hydroxypropylcellulose.

14. The method of claim 10 wherein said organic
5 excipient mixture contains about 30-70% by weight of a non-gel forming excipient.

15. The method of claim 14 wherein said non-gel forming
excipient is selected from the group consisting of lactose,
10 mannitol and cellulose derivatives.

16. A pharmaceutical composition of claim 1 wherein the solid unit dosage form is a tablet.

15 17. A pharmaceutical composition of claim 16 further comprising at least one additional hormone deposited on said tablet after the application of said moisture barrier coat.

18. A pharmaceutical composition of claim 17 wherein
20 said hormone is selected from the group consisting of progesterone, medroxyprogesterone, medroxyprogesterone acetate, testosterone, methyltestosterone and combinations thereof.

25 19. A pharmaceutical composition of claim 17 wherein said hormone is bonded to said tablet by a polymeric film.

20. A pharmaceutical composition of claim 19 wherein said polymeric film is selected from the group consisting of
30 hydroxypropylmethylcellulose and ethylcellulose aqueous dispersion.

21. A pharmaceutical composition of claim 17 further comprising two or more coatings with one outer coating
35 comprising a polymeric film and at least one additional hormone.

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22. A pharmaceutical composition of claim 21 wherein said hormone is selected from the group consisting of progesterone, medroxyprogesterone, medroxyprogesterone acetate, testosterone, methyltestosterone, and combinations thereof.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/36, 31/56	A1	(11) International Publication Number: WO 97/04753 (43) International Publication Date: 13 February 1997 (13.02.97)						
(21) International Application Number: PCT/US96/12295 (22) International Filing Date: 26 July 1996 (26.07.96) (30) Priority Data: <table border="0"><tr><td>507,695</td><td>26 July 1995 (26.07.95)</td><td>US</td></tr><tr><td>Not furnished</td><td>25 July 1996 (25.07.96)</td><td>US</td></tr></table> (71) Applicant: DURAMED PHARMACEUTICALS, INC. [US/US]; 5040 Duramed Drive, Cincinnati, OH 45213 (US). (72) Inventors: HUBER, Harold, E.; 5021 Lord Alfred Court, Cincinnati, OH 45241 (US). RYAN, Mary, K.; 8220 Mariner Lane, Mainville, OH 45039 (US). (74) Agents: WEILD, David, III et al.; Pennie & Edmonds, 1155 Avenue of the Americas, New York, NY 10036 (US).		507,695	26 July 1995 (26.07.95)	US	Not furnished	25 July 1996 (25.07.96)	US	(81) Designated States: CA, CN, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
507,695	26 July 1995 (26.07.95)	US						
Not furnished	25 July 1996 (25.07.96)	US						
(54) Title: PHARMACEUTICAL COMPOSITIONS OF CONJUGATED ESTROGENS AND METHODS FOR THEIR USE								
(57) Abstract This invention relates to novel pharmaceutical compositions and methods for their preparation containing conjugated estrogens for the treatment of peri-menopausal, menopausal and post-menopausal disorders in women. The novel pharmaceutical compositions comprise a carrier base material and conjugated estrogens formed into a solid unit dosage form possessing a regular incremental release of the medicament upon oral administration. Further, the invention comprises the combination of conjugated estrogens with progestogens in a solid, shaped dosage unit. Specifically, the invention comprises the use of an organic excipient such as high molecular weight hydroxyalkyl alkylcelluloses. The use of an organic excipient such as hydroxypropylmethylcellulose in a stable, solid dosage formulation containing either conjugated estrogens alone or in combination with a progestogen is described.								

is applied in a quantity of film coating to provide a tablet of Example 1 with, for example, 2.5 mg to 5.0 mg of medroxyprogesterone acetate per dose.

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Example 5

A combination tablet is made by applying a suspension of progesterone to a core tablet with the moisture barrier coat of Example 1. The suspension consists of small crystalline particles less than 50 microns, and preferably less than 10
10 microns. The progesterone is applied in a quantity of film coating to provide a tablet of Example 1 with, for example, 100 mg to 200 mg of progesterone per dose.

Example 6

15 A combination tablet containing conjugated estrogens and a progestogen is made by applying an aqueous based suspension of micronized progestogen in a commercially available coating formula such as an Opadry® Clear Coat. The resulting coating preparation contains approximately 10% solids by weight. In
20 this example, the progestogen is applied to the base coated conjugated estrogen tablet prior to application of the color coat and final clear coat.

Example 7

25 A combination tablet containing conjugated estrogens and a progestogen is made by applying an aqueous based suspension of micronized progestogen in a commercially available coating formula such as an Opadry® Color Coat. The resulting coating preparation contains approximately 22% by weight. In this
30 example, the progestogen is applied to the base coated conjugated estrogen tablet with the color coat and prior to application of the final clear coat.

Example 8

35 A combination tablet containing conjugated estrogens and a progestogen is made by applying an aqueous based suspension of micronized progestogen in a commercially available coating

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formula such as an Opadry® Color Coat. In this example there is also the addition of the surfactant, polysorbate 80, to facilitate drug dispersion in the coating preparation. The resulting coating preparation contains approximately 22% solids by weight. In this example, the progestogen is applied to the base coated conjugated estrogen tablet with the color coat and prior to the application of the final clear coat.

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Example 9

A combination tablet containing conjugated estrogens and medroxyprogesterone acetate is made by applying an aqueous based suspension of micronized medroxyprogesterone acetate containing an ethylcellulose dispersion, hydroxypropylmethylcellulose, and dibutylsebacate or triethyl citrate as the film coat. The film coat is applied to the subcoated tablets using an Accela Cota or Wurster apparatus.

The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of individual aspects of the invention. Indeed, various modifications for the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims. All publications cited herein are incorporated by reference in their entirety.

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WE CLAIM:

1. A pharmaceutical composition in a solid, unit dosage form capable of oral administration for the hormonal treatment of peri-menopausal, menopausal and post-menopausal disorders in a woman comprising:
conjugated estrogens coated onto one or more organic excipients forming a powdered conjugated estrogen composition having less than about 2.5% free water by weight and greater than 2.5% total water wherein said solid unit dosage form is coated with a moisture barrier coating.
2. A pharmaceutical composition of claim 1 in which said organic excipients include a mixture of one or more gel-forming hydroxyalkylalkylcelluloses and a hydroxyalkyl cellulose wherein said organic excipients constitutes more than about one third by weight of the solid unit dosage form.
3. A pharmaceutical composition of claim 2 in which the gel-forming organic excipients are a mixture of one or more hydroxypropylmethylcelluloses and 0-33% of methyl cellulose or other cellulose ether.
4. A pharmaceutical composition of claim 1 wherein said powdered conjugated estrogen composition further includes at least about 40% by weight of a non-gel forming organic excipient.
5. A pharmaceutical composition of claim 4 wherein said non-gel forming organic excipient is selected from the group consisting of lactose, mannitol, and cellulose derivatives.
6. A pharmaceutical composition of claim 1 wherein said conjugated estrogens is selected from the group consisting of the sodium sulfate esters of estrone, equilin, 17- α -dihydroequilin, 17- β -dihydroequilin and 17- α -estradiol.

7. A pharmaceutical composition of claim 1 wherein said moisture barrier coating comprises ethylcellulose.

8. A pharmaceutical composition of claim 7 wherein
5 said moisture barrier coating is 0.5-8.0% of the total weight of said solid unit dosage form.

9. A pharmaceutical composition of claim 1 further comprising about 30-70% gel-forming organic excipient and
10 about 30-70% non-gel forming organic excipient by weight.

10. A method for preparing an extended release pharmaceutical composition containing one or more conjugated estrogens and a carrier comprising:

- 15 (a) spraying a solution of said conjugated estrogens onto one or more organic excipients suspended in a fluidized bed in a closed system;
- (b) drying the mixture formed in (a) to where said mixture contains less than about 2.5% free water
20 and greater than about 2.5% total water by weight;
- (c) tableting the mixture formed in (b); and
- (d) coating said tablets with a film coating selected from the group including cellulose ethers, methacrylic acid and phthalates.

25 11. The method of claim 10 wherein said conjugated estrogens is selected from the group consisting of the sodium sulfate esters of estrone, equilin, 17- α -dihydroequilin, 17- β -dihydroequilin and 17- α -estradiol.

30 12. The method of claim 10 wherein said organic excipient mixture includes at least about 30% by weight of an aqueous gel-forming organic excipient.

35 13. The method of claim 12 wherein said gel-forming organic excipient is selected from the group consisting of

hydroxypropylmethylcellulose, sodium carboxymethylcellulose and hydroxypropylcellulose.

14. The method of claim 10 wherein said organic
5 excipient mixture contains about 30-70% by weight of a non-gel forming excipient.

15. The method of claim 14 wherein said non-gel forming
excipient is selected from the group consisting of lactose,
10 mannitol and cellulose derivatives.

16. A pharmaceutical composition of claim 1 wherein the solid unit dosage form is a tablet.

15 17. A pharmaceutical composition of claim 16 further comprising at least one additional hormone deposited on said tablet after the application of said moisture barrier coat.

18. A pharmaceutical composition of claim 17 wherein
20 said hormone is selected from the group consisting of progesterone, medroxyprogesterone, medroxyprogesterone acetate, testosterone, methyltestosterone and combinations thereof.

25 19. A pharmaceutical composition of claim 17 wherein said hormone is bonded to said tablet by a polymeric film.

20. A pharmaceutical composition of claim 19 wherein
said polymeric film is selected from the group consisting of
30 hydroxypropylmethylcellulose and ethylcellulose aqueous dispersion.

21. A pharmaceutical composition of claim 17 further
comprising two or more coatings with one outer coating
35 comprising a polymeric film and at least one additional hormone.

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22. A pharmaceutical composition of claim 21 wherein said hormone is selected from the group consisting of progesterone, medroxyprogesterone, medroxyprogesterone acetate, testosterone, methyltestosterone, and combinations thereof.

23. A pharmaceutical composition of claim 22 wherein said hormone is micronized.

24. A pharmaceutical composition of claim 21 wherein said polymeric film contains about 10-30% solids by weight.

25. A pharmaceutical composition of claim 24 wherein said polymeric film further comprises a surfactant.

26. A pharmaceutical composition of claim 25 wherein said surfactant is selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, and polyoxyethylene (20) sorbitan trioleate.

27. A pharmaceutical composition of claim 21 wherein said polymeric film further comprises a plasticizer.

28. A pharmaceutical composition of claim 27 wherein said plasticizer is selected from the group consisting of dibutyl sebacate or triethyl citrate.

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PROCESO 88-IP-2005

Interpretación prejudicial de los artículos 1 y 4 de la Decisión 344 de la Comisión del Acuerdo de Cartagena con fundamento en la consulta formulada por el Consejo de Estado de la República de Colombia, Sala de lo Contencioso Administrativo, Sección Primera. Expediente Interno N° 2001-00039 (6787). Actor: ELI LILLY AND COMPANY. Patente: "FORMULACIONES FARMACEUTICAS ADMINISTRABLES DE FORMA ORAL".

EL TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA, en Quito, a los veintisiete días del mes de julio del año dos mil cinco, procede a resolver la solicitud de Interpretación Prejudicial formulada por el Consejo de Estado de la República de Colombia, Sala de los Contencioso Administrativo, Sección Primera.

VISTOS:

Que de la solicitud de interpretación prejudicial y de sus anexos se desprende que los elementos exigidos por el artículo 33 del Tratado de Creación del Tribunal y 125 de su Estatuto fueron cumplidos, por lo que su admisión a trámite fue considerada procedente en el auto emitido el 22 de junio de 2005.

I. ANTECEDENTES.

El Tribunal, con fundamento en la documentación allegada estima procedente destacar como antecedentes del proceso interno que dio lugar a la presente solicitud, lo siguiente:

A. Las partes:

Demandante: ELI LILLY AND COMPANY.

Demandada: NACION COLOMBIANA - SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO.

B. Hechos Relevantes.**1. Los hechos.**

Entre los hechos principales relatados en la demanda, se encuentran los siguientes:

- a. El 27 de julio de 1994, la sociedad ELI LILLY AND COMPANY presentó ante la División de Nuevas Creaciones de la Superintendencia de Industria y Comercio solicitud de Patente de Invención para "FORMULACIONES FARMACÉUTICAS ADMINISTRABLES DE FORMA ORAL".
- b. El Superintendente de Industria y Comercio, mediante Resolución 04752 del 29 de febrero de 2000, negó el privilegio de patente de invención solicitado.
- c. Mediante la Resolución 18634 del 31 de julio de 2000, se resolvió el recurso de reposición presentado por la sociedad ELI LILLY AND COMPANY, confirmando la Resolución 04752 del 29 de febrero de 2000.

C. La demanda.

La Sociedad ELI LILLY AND COMPANY, en ejercicio de la acción de nulidad y restablecimiento del derecho, presentó demanda en relación con los actos administrativos mencionados

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anteriormente. Los argumentos en que se fundamentó son los siguientes:

Se violó el artículo 1 de la Decisión 344 de la Comisión del Acuerdo de Cartagena, por cuanto la demandada negó el privilegio de patente para el objeto de la solicitud 94-032.770, aún cuando se cumplió con el requisito de novedad, altura inventiva y aplicación industrial.

Igualmente se desconoció el artículo 4 de la Decisión 344 de la Comisión del Acuerdo de Cartagena, ya que no se reconoció el nivel inventivo de una creación que no resultaba obvia ni derivada de manera evidente del estado de la técnica para una persona versada en la materia.

Los conceptos técnicos que se tuvieron en cuenta para la expedición de los actos administrativos acusados no reflejan un correcto análisis del nivel inventivo y, además, no se tomó en consideración la posición de la persona versada en la materia en el momento de la creación de la invención, sino que se hicieron análisis posteriores a la misma; de esta manera se restó mérito a los efectos sorprendentes obtenidos con el invento, que superan los problemas técnicos observados en las formulaciones conocidas en el estado de la técnica.

Las formulaciones anteriores tenían un problema técnico que debía ser superado; consistía en que el principio activo de las mismas presentaba una biodisponibilidad limitada. Dicho problema fue superado por la solicitud denegada, por cuanto suministró *"una formulación sólida administrable que consiste de clorhidrato de raloxifeno en combinación con un tensoactivo, polivinilpirrolidona y un diluyente soluble en agua, en la cual: el tensoactivo es un éster de ácido graso de sorbitán o un éster de ácido graso de polioxietileno de sorbitán; y el diluyente soluble en agua es un poliol o azúcar"*.

En el objeto de la solicitud denegada queda claro que ni el clorhidrato de raloxifeno, ni el tensoactivo, ni el diluyente soluble en agua, ni el ligante hidrófilo son novedosos e inventivos por sí solos, sino que es la combinación de dichos elementos lo que le proporciona una formulación novedosa e inventiva. No obstante lo anterior, los examinadores hacen un análisis con criterios generales, de donde concluyen que como lo excipientes de la lista de la anterioridad son solamente algunos de los que se usan comúnmente y no importa cuál de ellos se elija, la composición formulada no tendría nivel inventivo.

La novedad y el nivel inventivo del objeto de la solicitud denegada ha sido reconocida por varias oficinas de patentes alrededor del mundo, tales como la Oficina de Patentes de los Estados Unidos de América y la Oficina de Patentes Europea.

D. La contestación a la demanda.

La Superintendencia de Industria y Comercio contestó de la demanda con los siguientes argumentos:

La característica principal de la tableta reivindicada es el raloxifeno, el cual carece de novedad como se demuestra en la patente US 44418068 en la cual se establece que este principio activo ya se había formulado en una tableta con los mismos aditivos.

Si se compara la composición reivindicada con las contenidas en los documentos encontrados como anterioridades, se concluye que si bien no son idénticas, en lo único que se diferencian es que la reivindicada contiene un éster ácido graso de sorbitán o un éster ácido graso de polioxietilensorbitán (pe), polisorbato 80 como tensoactivo.

Para una persona normalmente conocedora de la materia, sería obvio el cambiar los agentes

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tensoactivos de las anterioridades para obtener finalmente la composición reivindicada. En este sentido, las composiciones encontradas no tienen carácter inventivo porque la formulación no va más allá del progreso normal de la tecnología y no implica el ejercicio de una habilidad más allá de la esperada por personas conocedoras de la materia.

II. COMPETENCIA DEL TRIBUNAL:

El Tribunal de Justicia de la Comunidad Andina es competente para interpretar por la vía prejudicial las normas que conforman el Ordenamiento Jurídico de la Comunidad Andina, con el fin de asegurar su aplicación uniforme en el territorio de los Países Miembros.

III. NORMAS DEL ORDENAMIENTO JURIDICO COMUNITARIO A SER INTERPRETADAS:

Es procedente realizar la interpretación de los artículos solicitados por el consultante, estos son: 1 y 4 de la Decisión 344 de la Comisión del Acuerdo de Cartagena, vigente para la fecha de presentación de la solicitud de patente.

A continuación se inserta el texto de las normas a ser interpretadas:

DESICION 344

Artículo 1

"Los Países Miembros otorgarán patentes para las invenciones sean de productos o de procedimientos en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."

(...)

Artículo 4

"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."

IV. Consideraciones.

Procede el Tribunal a realizar la interpretación prejudicial solicitada, para lo cual analizará aspectos relacionados con: los requisitos de patentabilidad (La novedad, el nivel inventivo y la susceptibilidad de aplicación industrial), y con el examen del nivel inventivo en la combinación de elementos conocidos.

A. DE LOS REQUISITOS DE LA PATENTABILIDAD:

Los requisitos que deben ser cumplidos para la obtención de una patente de invención se encuentran fijados por el artículo 1 de la Decisión 344, y desarrollados por los artículos 2 al 5 de dicho cuerpo legislativo.

Según lo dispuesto por el artículo 1 de esa Decisión, son tres los requisitos para que un invento sea considerado patentable: ser novedoso, tener nivel inventivo y ser susceptible de

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aplicación industrial.

1. De la novedad de la invención:

El artículo 2 de la Decisión 344 dice: *"Una invención es nueva cuando no se encuentra comprendida en el estado de la técnica"*; en el ordenamiento andino, la novedad que se predica de los inventos debe ser absoluta o universal, esto es, que comprende el estado de la técnica a nivel mundial.

A la pregunta qué se entiende por invención, el Tribunal de Justicia de la Comunidad Andina ha sostenido lo siguiente:

"el concepto de invención, a efectos de ser objeto de una concesión de patentes, comprende todos aquellos nuevos productos o procedimientos que, como consecuencia de la actividad creativa del hombre, impliquen un avance tecnológico -y por tanto no se deriven de manera evidente del 'estado de la técnica'- y, además, sean susceptibles de ser producidos o utilizados en cualquier tipo de industria"^[1]; lo mismo que se simplifica en la conceptualización recogida por el artículo 1 de la Decisión 344, la que la define como aquellos productos o procedimientos en todos los campos de la tecnología, que posean novedad, nivel inventivo, y sean susceptibles de aplicación industrial.^[2]

Ahora, para que una invención sea novedosa se requiere que no esté comprendida en el estado de la técnica; es decir, que antes de la fecha de presentación de la solicitud de patente o de la prioridad reconocida, tanto la innovación como los conocimientos técnicos que de ella se desprenden no hayan sido accesibles al público, entendiendo que la difusión de la información que se menciona debe ser minuciosa, detallada y suficiente para que una persona versada en la materia pueda utilizar esa información para explotar la invención.

En este punto resulta menester precisar que la información debe resultar útil no para el común de la población sino para destinatarios calificados en un preciso campo, el relacionado con la materia objeto de la información.

Sobre el requisito de la novedad ha señalado la doctrina:

"Un invento es novedoso cuando la relación causa efecto entre el medio empleado y el resultado obtenido no era conocido." ^[3]

El Tribunal de Justicia de la Comunidad Andina, recogiendo los siguientes criterios expuestos por la doctrina, con la finalidad de delimitar el concepto de novedad ha concluido:

"Guillermo Cabanellas indica que las características del concepto de novedad son las siguientes:

a) "Objetividad. La novedad de la tecnología a ser patentada no se determina en relación con personas determinadas ni con el pretendido inventor, sino en relación con el estado objetivo de la técnica en un momento determinado."

b) "Irreversibilidad de la pérdida de novedad." "...una vez que una tecnología pierde su carácter novedoso, por haber pasado a integrar el estado de la técnica, esa pérdida de novedad se hace irreversible."

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c) "Carácter Universal de la Novedad" "... la novedad de la invención se determina en relación con los conocimientos existentes en el país o en el extranjero."

"... no puede pretenderse una patente respecto de una tecnología ya conocida en el extranjero, aunque fuera novedosa en el país."

d) "Carácter público de la novedad." "...la invención patentada pasará a ser conocida a partir de su publicación implícita en su patentamiento, y posteriormente entrará en el dominio público al expirar la patente.^[4]" (Proceso 07-IP-2004. Interpretación prejudicial del 17 de marzo de 2004).

Concretando aún más el concepto de novedad como requisito de las invenciones, este Tribunal ha precisado el concepto de novedad absoluta como requisito esencial para la concesión de una patente, de la siguiente manera:

"El concepto de novedad absoluta respecto de una invención implica que para que un invento sea nuevo y no se encuentre en el estado de la técnica, no puede haber sido conocido ni dentro del territorio en el que se solicita la patente, ni en ningún otro país. Es lo que se conoce como el alcance universal de la novedad, pues no basta que un invento sea nuevo y no esté en el estado de la técnica de un territorio dado, sino que tampoco lo esté en el resto del mundo, salvo el año de prioridad a que se refiere el artículo 12 de la Decisión 344. La novedad absoluta, como criterio para determinar la patentabilidad de una invención, se ha venido abriendo camino en el ámbito internacional. Así en el Reino Unido a partir de 1977 (Patents Act inglesa). En la República Federal Alemana se empezó a exigir la novedad absoluta a partir de la Ley de 16 de diciembre de 1980. En la actualidad, en los Estados Miembros de las Comunidades Europeas se ha impuesto la exigencia de la novedad absoluta como una de las consecuencias de las patentes europeas, según Tratado de Munich de 5 de Octubre de 1963. (Bercovitz, Alberto, "PROTECCIÓN DE LA TECNOLOGÍA", en Revista del Derecho Industrial N° 35, Depalma 1990, pág. 321)." (Proceso N° 1-AI-1996. Sentencia de 30 de octubre de 1996, publicada en Gaceta Oficial del Acuerdo de Cartagena N° 234 de 21 de abril de 1997).

Una vez delimitado el concepto de novedad, es pertinente destacar que el Tribunal ha definido algunas reglas con el objetivo de determinar la novedad del invento:

- "a) Concretar cual es la regla técnica aplicable a la solicitud de la patente, para lo cual el examinador técnico deberá valerse de las reivindicaciones, que en últimas determinarán este aspecto.
- b) Precisar la fecha con base en la cual deba efectuarse la comparación entre la invención y el Estado de la Técnica, la cual puede consistir en la fecha de la solicitud o la de la prioridad reconocida.
- c) Determinar cuál es el contenido del Estado de la Técnica (anterioridades) en la fecha de prioridad.
- d) Finalmente deberá compararse la invención con la regla técnica.^[5]

2. Del nivel inventivo:

El artículo 4 de la Decisión 344 desarrolla el requisito de nivel inventivo al establecer que la

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invención goza de dicho nivel al no derivar de manera evidente del estado de la técnica, ni que hubiese resultado obvia para una persona entendida o versada en la materia. Este requisito ofrece al examinador la posibilidad de determinar si con los conocimientos técnicos que existían al momento de la invención, se hubiese podido llegar de manera evidente a la misma, o si el resultado hubiese sido obvio para un experto medio en la materia de que se trate, es decir, para una persona del oficio y normalmente versada en la materia técnica correspondiente.

Con respecto a lo anterior, el Tribunal de Justicia de la Comunidad Andina ha manifestado lo siguiente:

"Con el requisito del nivel inventivo, lo que se pretende es dotar al examinador técnico de un elemento que le permita afirmar o no si a la invención objeto de estudio no se habría podido llegar a partir de los conocimientos técnicos que existían en ese momento dentro del estado de la técnica... En este punto conviene advertir que uno es el examen que realiza el técnico medio respecto de la novedad y otro el que se efectúa con respecto al nivel inventivo; si bien en uno y otro se utiliza como parámetro de referencia el 'estado de la técnica', en el primero, se coteja la invención con las 'anterioridades' existentes dentro de aquella, cada uno (sic) por separado, mientras que en el segundo (nivel inventivo) se exige que el técnico medio que realiza el examen debe partir del conocimiento general que él tiene sobre el estado de la técnica y realizar el cotejo comparativo con su apreciación de conjunto, determinando si con tales conocimientos técnicos existentes ha podido o no producirse tal invención". [6]

Ahora bien, a los efectos del artículo 4 de la Decisión 344 resulta pertinente definir que se entiende por "obvio" y por "evidente" a fin de, consecuentemente, determinar qué se debe entender por nivel inventivo.

Lo obvio es "aquello que salta a la vista de manera clara y directa; lo que se encuentra o pone delante de los ojos o que no tiene dificultad". Mientras que lo evidente "es algo tan cierto y claro que nadie puede dudar racionalmente de ello; se presenta de manera tan perceptible y manifiesta que muestra certeza y claridad"^[7]. Como se podrá ver, la diferencia radica en lo "tan", de forma que algo que resulte obvio no es necesariamente evidente; empero lo que es evidente, es también obvio.

En este orden de ideas, se puede concluir que una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no sea consecuencia clara y directa de dicho estado.

3. De la susceptibilidad de aplicación industrial:

Igualmente, para que un invento pueda ser protegido a través de una patente debe ser susceptible de aplicación industrial, es decir, que pueda ser producido o utilizado en cualquier actividad productiva o de servicios, como lo manifiesta el artículo 5 de la norma comunitaria que se interpreta.

Este requisito de la invención encuentra su justificación en el hecho de que la concesión de una patente estimula el desarrollo y crecimiento industrial, procurando beneficios económicos a quienes la exploten, por esto sólo son susceptibles de patentabilidad las

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invenciones que puedan ser llevadas a la práctica.

B. COMBINACION O MEZCLA DE ELEMENTOS CONOCIDOS.

En relación con los requisitos atinentes al nivel inventivo y a la novedad de la invención se presentan algunos casos dudosos que merecen un análisis especial, ya que al aplicar las reglas arriba citadas no es tan fácil determinar su novedad y su altura inventiva.

Uno de esos casos es el que se presenta en relación con la combinación o mezcla de medios o elementos conocidos, que impone que, en primer lugar, el examinador establezca si lo que se trata de patentar es una combinación o una simple agregación de elementos. Al efecto, vale la pena citar que: *"Se podría diferenciar la combinación de elementos de la simple agregación. La primera es la sinergia de los elementos de forma tal que se genera uno nuevo con propiedades distintas, de tal manera que el nuevo elemento sólo es resultado de dicha combinación sin que puedan determinarse los elementos por separado; la segunda se da cuando los elementos se mantienen intactos en cuanto a su efecto fundamental y, por lo tanto, son claramente distinguibles unos de otros, es decir, no hay una sinergia o combinación intrínseca de los elementos"*.^[8]

Pero dicha distinción no puede llevar a priori una conclusión ya que no se puede predicar instantáneamente falta de nivel inventivo de uno o de otro, ya que en ambos cabe analizar siempre el caso concreto; es el primero el que ofrece una mayor importancia en cuanto al presente asunto y el que podría presentar mayor discusión en cuanto al nivel inventivo.

Daniel R. Zucherino, en su libro "PATENTES DE INVENCION", trata el tema y reconoce la complejidad en determinar un nuevo resultado:

"Se reconoce que hay invento cuando se utilizan medios ya conocidos, pero combinados por primera vez en forma tal, que de su combinación deriva un resultado distinto del dado por cada uno de los medios, o por otras combinaciones conocidas.

Claro está que en la práctica, resulta a veces difícil determinar si existe un "nuevo resultado", porque éste puede consistir incluso en un resultado mejor que el conocido (por ejemplo, la calidad sonora de un disco compacto con un disco de vinilo). Si el aporte implica un adelanto y se ha hecho alguna contribución novedosa y útil, se considera que hay invento."^[9]

En consideración al tema tratado, no le es dable a las oficinas de patentes de los Países Miembros hacer un análisis apriorístico en contra del invento. Lo que debe hacer la oficina de patentes respectiva, al realizar un análisis del nivel inventivo de agregaciones o de combinaciones o mezclas de elementos, es establecer si con el estado de la técnica actual, dicho producto, así sea por combinación de elementos conocidos, no es obvio ni evidente para un técnico medio en la materia. Es decir, no es acorde con el espíritu de la normativa sobre patentes, que de un simple análisis consistente en que si el producto se genera de elementos conocidos, se concluya per se que no tiene nivel inventivo.

Una combinación de elementos conocidos, dependiendo del caso particular debe ser novedosa, con actividad inventiva y susceptible de aplicación industrial, es decir, debe cumplir los tres requisitos que establece la norma comunitaria, sin que quepa necesariamente hacer dicho análisis en relación con cada componente cuando se trata de patentar este tipo de mezclas o combinaciones.

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El Tribunal de Justicia de la Comunidad Andina sobre el tema, ha sostenido lo siguiente:

"La novedad no es un requisito que deban cumplir todos y cada uno de los componentes que conforman la invención, pudiendo incluso ser conocidos individualmente la totalidad de tales elementos, si combinados entre ellos dan lugar a un objeto o a un procedimiento desconocido anteriormente. En efecto, ninguna invención aparece de la nada; por el contrario, toda innovación requiere aplicar conocimientos y objetos previamente creados o descubiertos por la humanidad, los cuales constituirán la «materia prima» para desarrollar un nuevo producto o procedimiento.

En este sentido, el invento constituye una derivación del estado de la técnica, pero, para calificar su carácter de patentable, es preciso determinar si dicha derivación no resulta evidente para una persona normalmente versada en la materia técnica. Surge, por consiguiente, un requisito adicional al de la novedad: el nivel inventivo, del cual se desprende que la invención, además de no ser obvia para un experto medio, debe ser siempre el resultado de una actividad creativa del hombre, sin que ello signifique que para alcanzar la regla técnica propuesta, no se puedan utilizar procedimientos o métodos comunes o ya conocidos en el área técnica correspondiente. Específicamente en el área de los inventos químicos y biotecnológicos sucede con frecuencia que aplicando procedimientos conocidos pueden obtenerse resultados inesperados para una persona normalmente versada en la materia. Por ello, el juicio del nivel inventivo no puede ser elaborado con criterios generales, sino que dependerá de las especiales circunstancias de cada caso." (Proceso 21-IP-2000. Interpretación Prejudicial de 27 de octubre de 2000).

Es conveniente señalar que la normativa andina sobre patentes no estipula nada sobre el tema, como si lo hacen otras legislaciones como la Ley de patentes argentina, artículo 6, inciso f), pero de ello no surge que con base en las normas que regulan la materia, las oficinas de patentes puedan hacer un examen apriorístico de la altura inventiva en casos como el de combinación de elementos conocidos para denegar la patente de invención.

Aún bajo consagraciones legales sobre el tema, lejos de sus problemas sintácticos y de técnica legislativa, es importante tener presente que respecto de los casos dudosos se previene al operador jurídico del supuesto de hecho, es decir, de hacer un análisis simple y apriorístico de la situación presentada y dudosa.

En virtud de lo anteriormente expuesto,

EL TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA,

CONCLUYE:

PRIMERO: La novedad, el nivel inventivo y la aplicación industrial constituyen requisitos absolutamente necesarios, insoslayables y de obligatoria observancia para el otorgamiento de una patente de invención, sea de producto o de procedimiento, en todos los campos de la tecnología.

SEGUNDO: La invención, además de no ser obvia para un experto medio, debe ser siempre el resultado de una actividad creativa del hombre, descartando, en efecto, como invención la acción propia de la naturaleza.

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TERCERO: Dentro del Ordenamiento Jurídico Andino no hay norma especial para resolver sobre el nivel inventivo de mezclas y / o combinaciones de elementos conocidos. Sin embargo, lo anterior no implica que el examen de patentabilidad en los casos de combinación de elementos conocidos para generar uno nuevo pueda hacerse a la ligera; por el contrario, se debe partir de que sí pueden llegar a constituir una invención patentable las combinaciones si son novedosas, tienen altura inventiva y aplicación industrial.

De conformidad con el artículo 35 del Tratado de Creación del Tribunal de Justicia de la Comunidad Andina, el Juez Nacional consultante, al emitir el fallo en el proceso interno N° 2001-00039 (6787), deberá adoptar la presente interpretación. Así mismo deberá dar cumplimiento a las prescripciones contenidas en el párrafo tercero del artículo 128 del Estatuto vigente.

Notifíquese al Juez consultante mediante copia certificada y remítase copia a la Secretaría General de la Comunidad Andina, para su publicación en la Gaceta Oficial del Acuerdo de Cartagena.

Walter Kaune Arteaga
PRESIDENTE (e)

Rubén Herdoíza Mera
MAGISTRADO

Ricardo Vigil Toledo
MAGISTRADO

Olga Inés Navarrete Barrero
MAGISTRADA

Mónica Rosell Medina
SECRETARIA

TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA.- La sentencia que antecede es fiel copia del original que reposa en el expediente de esta Secretaría. CERTIFICO.-

Mónica Rosell
SECRETARIA

[1] **TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA.** Sentencia de 21 de octubre de 2000. **Proceso N° 21-IP-2000.** Caso: "DERIVADOS DE BILIS HUMANA". Publicada en Gaceta Oficial del Acuerdo de Cartagena N° 631, de 10 de enero de 2001

[2] **TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA.** Sentencia de 14 de abril de 2005. **Proceso N° 07-IP-2005.** Patente de invención; "PROTECTOR DERMATOLOGICO. GEL PARA QUEMADURAS." Publicada en Gaceta Oficial del Acuerdo de Cartagena N° 1203 de 31 de mayo de 2005.

[3] ZUCCHERINO, Daniel R. "MARCAS Y PATENTES EN EL GATT. REGIMEN LEGAL". Editado por Abeledo Perrot. 1997. Pág. 150.

[4] CABANELLAS, Guillermo. "DERECHO DE LAS PATENTES DE INVENCION". Tomo 1.

105

Editorial Heliasta. Buenos Aires 2001. Págs. 702 a 704.

[5] **TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA.** Sentencia de 20 de mayo de 1998. **Proceso 12-IP-1998.** Patente: "COMPOSICIONES DETERGENTES COMPACTAS CON ALTA ACTIVIDAD CELULOSA". Publicada en Gaceta Oficial del Acuerdo de Cartagena N° 428 de 16 de abril de 1999.

[6] **TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA. Proceso N° 12-IP-98.**
Doc. Cit.

[7] **DICCIONARIO DE LA LENGUA ESPAÑOLA.** Vigésima Primera Edición. Madrid - España. 1992. "DEFINICIONES DE EVIDENTE, EVIDENCIA Y OBVIO". Págs. 655 y 1036.

[8] Esta distinción la podemos encontrar en los cursos sobre patentes dictados por la Dra. ZAMUDIO, Teodora, profesora de la Universidad de Buenos Aires. Publicado en la página www.dpi.bioetica.org/patfondo.htm.

[9] ZUCCHERINO, Daniel R. "PATENTES DE INVENCION", Gráfica laf s.r.l, Buenos Aires, 1998, Pág. 72.

AA 3286377
NOTARIA TERCERA
ENCUENTRO



ESCRITURA NUMERO CUATRO MIL QUINIENTOS -
TREINTA Y NUEVE (No.4.539) -----
En la ciudad de Cali, Capital del Depar-
tamento del Valle del Cauca, República de
Colombia, a los VEINTITRES (23) días -
del mes de OCTUBRE del año DOS MIL UNO --

(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario
T E R C E R O (3o.) del Círculo de Cali, - - - - -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: -----

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y
representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida
mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
junio de 1957, reformada en distintas oportunidades, según consta en el certificado
expedido por la Cámara de Comercio, de Cali -----

SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial
pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de
Bogotá, identificado con C.C. # 79.152.473 de Bogotá, abogado en ejercicio, portador
de la T.P 44655 del C.S. de la J., domiciliado en Bogotá, D.C., República de Colombia
con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante
con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad
industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos
represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente
ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo
concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y
oposición a patentes de invención, modelos y dibujos industriales y el registro de
licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad,
medidas cautelares, concesión de licencias y en general los procesos civiles, penales,
administrativos o contencioso-administrativos relacionados con estos derechos y otros de
diferente naturaleza; acciones y procesos que promovamos o seamos promovidos para

Como Notario Venitres de este Círculo
hago constar que esta fotocopia coincide
con su fotocopia auténtica que he tenido
a la vista.
13 AGO 2007
WILLY VALERIO
NOTARIO VENITRES
Bogotá D.C. - Colombia

4539
05-23

LUZ MERY CORREA
ELABORACION DE ESCRITURAS
Notaría 3ª de Cali

29 DIC 2009
ESTE DOCUMENTO
ES COPIA DE LA ORIGINAL
CÓPIA REPRESENTADA PARA ESTA
DILIGENCIA DE AUTENTICACIÓN

que en todos los asuntos arriba determinados, , tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.

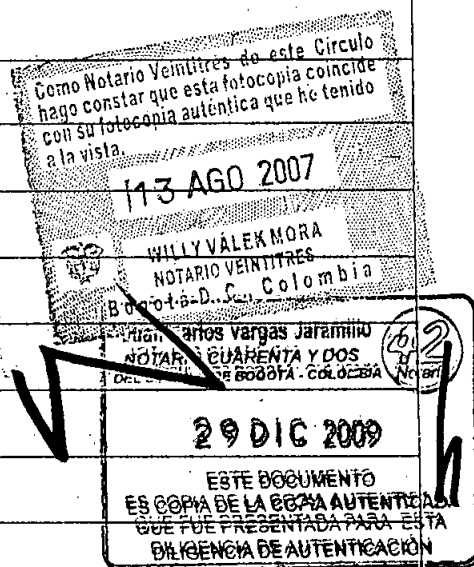
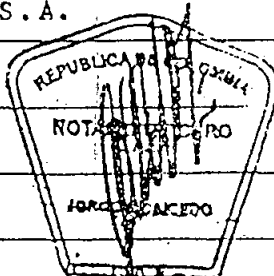
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.

Se agregan comprobantes. Derechos \$30.000.00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrigió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

Juan m. Barberi

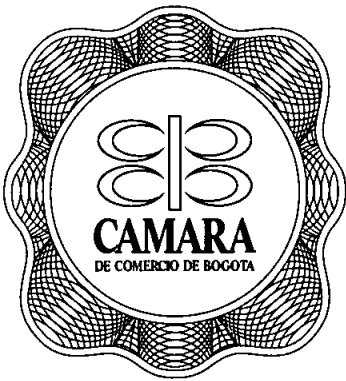
JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/12/28

HORA: 17:17:44

OPERACION: 02XMA1228173

PAGINA: 1

CERTIFICA:

NOMBRE: TECNOQUIMICAS S.A.

SIGLA : TQ S.A.

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL : CL. 23 NRO. 7 39

DIRECCION NOTIFICACION JUDICIAL: CL. 23 NRO. 7 39

CIUDAD: CALI

MATRICULA MERCANTIL NRO. 7049-4 FECHA MATRICULA : 01 DE JULY DE 1957
AFILIADO

CERTIFICA:

NIT : 890300466-5

CERTIFICA:

QUE POR ESCRITURA NRO. 2670 DEL 12 DE JUNE DE 1957 NOTARIA SEGUNDA DE CALI ,
INSCRITA EN LA CAMARA DE COMERCIO EL 01 DE JULY DE 1957 BAJO EL NRO. 16627 DEL
LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA COMPANIAS TECNOQUIMICAS
LIMITADA

CERTIFICA:

QUE POR ESCRITURA NRO. 8438 DEL 30 DE DECEMBER DE 1970 NOTARIA SEGUNDA DE
CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 07 DE JANUARY DE 1971 BAJO EL NRO.
42260 DEL LIBRO IX , LA SOCIEDAD SE TRANSFORMO DE SOCIEDAD LIMITADA EN SOCIEDAD
EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA
COMANDITA POR ACCIONES (SIC) .

CERTIFICA:

QUE POR ESCRITURA NRO. 2139 DEL 21 DE APRIL DE 1972 NOTARIA SEGUNDA DE CALI ,
INSCRITA EN LA CAMARA DE COMERCIO EL 26 DE APRIL DE 1972 BAJO EL NRO. 794 DEL
LIBRO IX , LA SOCIEDAD CAMBIO SU NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA
COMANDITA POR ACCIONES (SIC) . POR EL DE TECNOQUIMICAS LIMITADA & CIA S.C.
A. .

CERTIFICA:

QUE POR ESCRITURA NRO. 3255 DEL 30 DE AUGUST DE 1983 NOTARIA DECIMA DE CALI ,
INSCRITA EN LA CAMARA DE COMERCIO EL 31 DE AUGUST DE 1983 BAJO EL NRO. 62343
DEL LIBRO IX , LA SOCIEDAD SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES
EN SOCIEDAD ANÓNIMA BAJO EL NOMBRE DE TECNOQUIMICAS S A .

CERTIFICA:

QUE POR ESCRITURA NRO. 5664 DEL 12 DE DECEMBER DE 2005 NOTARIA TERCERA DE

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CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 19 DE DECEMBER DE 2005 BAJO EL NRO. 14102 DEL LIBRO IX , SE APROBO LA FUSION POR ABSORCION ENTRE (ABSORBENTE) TECNOQUIMICAS S.A. Y (ABSORBIDA (S)) DISTRIBUIDORA FARMACEUTICA CALOX COLOMBIANA S.A. - EN LIQUIDACION-, ORGANIZACION FARMACEUTICA AMERICANA S.A. OFA - EN LIQUIDACION- .

CERTIFICA:

QUE POR ESCRITURA NRO. 1675 DEL 08 DE MAY DE 2008 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 16 DE MAY DE 2008 BAJO EL NRO. 5362 DEL LIBRO IX , LA SOCIEDAD CAMBIO SU NOMBRE DE TECNOQUIMICAS S A . POR EL DE TECNOQUIMICAS S.A. . SIGLA: TQ S.A.

CERTIFICA:

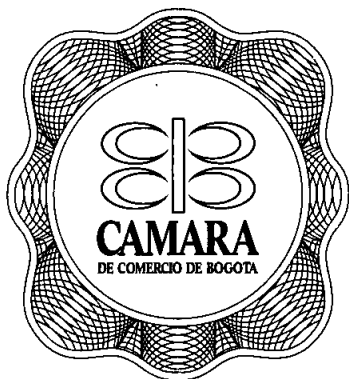
QUE POR ESCRITURA NRO. 4551 DEL 23 DE OCTOBER DE 2008 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE NOVEMBER DE 2008 BAJO EL NRO. 12416 DEL LIBRO IX ,SE APROBO LA ESCISION PARCIAL DEL PATRIMONIO SOCIAL ENTRE (ESCINDENTE) TECNOQUIMICAS S.A. Y (BENEFICIARIA(S)) INVERSIONES TQTS S.A. .

CERTIFICA:

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
INS LIBRO				
E.P. 4075 16922	05/09/1957	NOTARIA SEGUNDA DE CALI	27/09/1957	
E.P. 5718 17242	28/11/1957	NOTARIA SEGUNDA DE CALI	30/12/1957	
E.P. 5507 17529	31/12/1957	NOTARIA PRIMERA DE CALI	13/03/1958	
E.P. 3124 18365	16/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	
E.P. 3325 18366	29/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	
E.P. 5726 19258	17/12/1958	NOTARIA PRIMERA DE CALI	12/05/1959	
E.P. 2374 19368	12/05/1959	NOTARIA PRIMERA DE CALI	03/06/1959	
E.P. 2793 22616	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961	

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E.P. 2794 22617	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961
E.P. 6365 23489	30/12/1961	NOTARIA PRIMERA DE CALI	23/01/1962
E.P. 1383 23850	21/03/1962	NOTARIA PRIMERA DE CALI	28/03/1962
E.P. 3396 26016	28/05/1963	NOTARIA PRIMERA DE CALI	11/06/1963
E.P. 8853 27107	30/12/1963	NOTARIA PRIMERA DE CALI	23/01/1964
E.P. 5718 27181	28/11/1957	NOTARIA SEGUNDA DE CALI	10/02/1964
E.P. 2743 27681	29/04/1964	NOTARIA PRIMERA DE CALI	06/05/1964
E.P. 2744 27682	29/04/1964	NOTARIA PRIMERA DE CALI	06/05/1964
E.P. 7057 28591	21/10/1964	NOTARIA PRIMERA DE CALI	22/10/1964
E.P. 1693 29569	26/04/1965	NOTARIA PRIMERA DE CALI	28/04/1965
E.P. 1799 31623	10/05/1966	NOTARIA PRIMERA DE CALI	11/05/1966
E.P. 2498 32757	18/11/1966	NOTARIA CUARTA DE CALI	25/11/1966
E.P. 2792 33009	27/12/1966	NOTARIA CUARTA DE CALI	05/01/1967
E.P. 2209 34591	25/09/1967	NOTARIA CUARTA DE CALI	04/10/1967
E.P. 6933 35082	20/12/1967	NOTARIA SEGUNDA DE CALI	28/12/1967
E.P. 6363 37141	14/11/1968	NOTARIA SEGUNDA DE CALI	26/11/1968
E.P. 7711 37615	31/12/1968	NOTARIA SEGUNDA DE CALI	04/02/1969
E.P. 5597	30/09/1969	NOTARIA SEGUNDA DE CALI	18/10/1969

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PAGINA: 4

39341

E.P. 5211 27/08/1970 NOTARIA SEGUNDA DE CALI 04/09/1970

41379

E.P. 6576 07/10/1971 NOTARIA SEGUNDA DE CALI 14/10/1971

44154

E.P. 7286 08/11/1971 NOTARIA SEGUNDA DE CALI 10/11/1971

44367

E.P. 8042 03/12/1971 NOTARIA SEGUNDA DE CALI 21/12/1971

44716

E.P. 6209 05/10/1973 NOTARIA SEGUNDA DE CALI 15/10/1973

5505 IX

E.P. 8741 31/12/1973 NOTARIA SEGUNDA DE CALI 08/03/1974

7636 IX

E.P. 9270 31/12/1974 NOTARIA SEGUNDA DE CALI 31/01/1975

11772 IX

E.P. 9504 31/12/1974 NOTARIA SEGUNDA DE CALI 04/04/1975

12441 IX

E.P. 7566 05/12/1975 NOTARIA SEGUNDA DE CALI 09/01/1976

15581 IX

E.P. 2671 09/05/1980 NOTARIA SEGUNDA DE CALI 22/10/1980

41529 IX

E.P. 779 10/03/1982 NOTARIA DECIMA DE CALI 03/08/1982

54655 IX

E.P. 4324 10/11/1982 NOTARIA DECIMA DE CALI 30/06/1983

61172 IX

E.P. 1269 18/03/1986 NOTARIA DECIMA DE CALI 01/04/1986

83730 IX

E.P. 5089 24/09/1986 NOTARIA DECIMA DE CALI 29/09/1986

87933 IX

E.P. 7064 04/11/1987 NOTARIA DECIMA DE CALI 19/11/1987

2552 IX

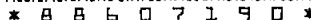
E.P. 7065 04/11/1987 NOTARIA DECIMA DE CALI 19/11/1987

2553 IX

E.P. 5929 14/07/1989 NOTARIA DECIMA DE CALI 26/07/1989

20225 IX

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ESPECIE DE LA SOCIEDAD MERCANTIL, NACIONAL O EXTRANJERA, QUE TENGAN COMO ACTIVIDAD O NEGOCIO PROPIO DE SU OBJETO LA FABRICACION, DISTRIBUCION Y COMERCIO EN GENERAL DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS, ALIMENTOS NATURALES Y/O PROCESADOS, PRODUCTOS DE CONSUMO POPULAR, SERVICIOS EN GENERAL O LA EXPLOTACION DE ESTABLECIMIENTOS DE COMERCIO DEDICADOS A DICHO GIRO. C) ADQUIRIR ACCIONES, CUOTAS SOCIALES, BONOS CEDULAS, TITULOS U OTROS VALORES EN COMPANIAS DE CUALQUIER NATURALEZA O TIPO LEGAL, DEDICADAS A LA EXPLOTACION DE CUALQUIER ACTIVIDAD ECONOMICA LICITA Y ENAJENARLAS.D) LA EXPLOTACION DEL NEGOCIO DE LA PUBLICIDAD Y EL ESTABLECIMIENTO DE OFICINAS DEDICADAS A ESTE NEGOCIO O A LA CREACION DE ORGANOS DE PUBLICIDAD HABLADOS O ESCRITOS. E) GARANTIZAR LAS OBLIGACIONES PROPIAS DE LOS ACCIONISTAS O DE TERCEROS. F) LA ADQUISICION DE BIENES MUEBLES, INMUEBLES Y DE TODA CLASE DE EQUIPO Y MAQUINARIA PARA SU ARRENDAMIENTO O PARA LA COMERCIALIZACION DE ELLOS. EN DESARROLLO DEL OBJETO SOCIAL PODRA OBTENER PRIVILEGIOS INDUSTRIALES, CONCESIONES, PATENTES DE INVENCION, DE MEJORAS O PROCEDIMIENTOS, MARCAS DE FABRICA O DE COMERCIO, YA SEA EN NOMBRE PROPIO O DE TERCEROS, OTORGAR A TERCEROS, DENTRO O FUERA DEL PAIS CONCESIONES O USOS DE EXPLOTACION SOBRE ESTOS DERECHOS, EJECUTAR TODA CLASE DE CONTRATOS DE COMPRAVENTA, DISTRIBUCION DE MATERIAS PRIMAS, DE PRODUCTOS SEMIELABORADOS O ELABORADOS EN EL MERCADO INTERNO O EN EL EXTERIOR Y EN GENERAL, LA CELEBRACION DE TODO ACTO O CONTRATO SOBRE BIENES MUEBLES O INMUEBLES DE COMERCIO, INDUSTRIALES O DE OTRA INDOLE QUE SE REFIERAN DIRECTAMENTE A LAS ACTIVIDADES QUE PERSIGUE LA SOCIEDAD.

QUE EN LA ESCRITURA PUBLICA NRO. 5409 DE REFORMA CITADA, SE ADICIONA AL ARTICULO 4 DE LOS ESTATUTOS SOCIALES EL LITERAL G) EN LOS SIGUIENTES TERMINOS:

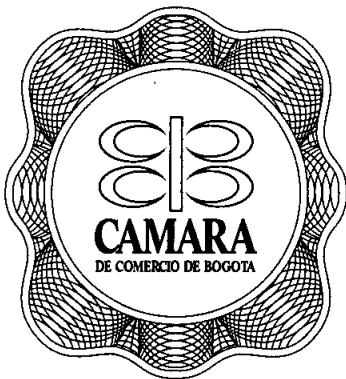
i) LA PRESTACION DE SERVICIOS RELACIONADOS CON EL CUIDADO DE BEBES, INCLUIDOS SERVICIOS DE GUARDERIA, SALA CUNA Y SIMILARES.

ii) LA PRESTACION DE SERVICIOS RELACIONADOS CON LA INVESTIGACION DE MERCADOS EN BENEFICIO DE NEGOCIOS PROPIOS O DISTRIBUIDOS.

CERTIFICA:

ÓRGANOS DE DIRECCIÓN Y ADMINISTRACIÓN. PARA LOS FINES DE SU DIRECCIÓN, ADMINISTRACIÓN Y REPRESENTACIÓN, LA SOCIEDAD TIENE LOS SIGUIENTES ÓRGANOS: A) ASAMBLEA GENERAL DE ACCIONISTAS. B) JUNTA DIRECTIVA. C) PRESIDENTE EJECUTIVO. D) DOS VICEPRESIDENTES EJECUTIVOS. E) VICEPRESIDENCIAS ADMINISTRATIVAS.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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LA DIRECCIÓN DE LA SOCIEDAD CORRESPONDE, EN PRIMER TERMINO A LA ASAMBLEA GENERAL DE ACCIONISTAS Y EN SEGUNDO LUGAR, A LA JUNTA DIRECTIVA COMO DELEGADA DE AQUELLA.

LA REPRESENTACIÓN LEGAL DE LA SOCIEDAD Y LA GESTIÓN DE LOS NEGOCIOS SOCIALES, ESTARÁN A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS DOS VICEPRESIDENTES EJECUTIVOS. LAS VICEPRESIDENCIAS ADMINISTRATIVAS SON ORGANOS ESPECIALES CREADOS POR LA ASAMBLEA EN BENEFICIO DE LA COMPAÑIA Y EL NOMBRAMIENTO DE QUIENES SEAN DESIGNADOS, SU NUMERO, FACULTADES Y ATRIBUCIONES QUE EJERCERAN SE CONFIEREN EN SU REGLAMENTACION Y EJECUCION, COMO NORMA ESPECIAL, A LA JUNTA DIRECTIVA QUE LAS DETERMINARÁ DE CONFORMIDAD ESTOS ESTATUTOS, A LA ORGANIZACIÓN ADMINISTRATIVA QUE POR ORIENTACIÓN SE LE QUIERE DAR A LA SOCIEDAD Y POR LA LEY.

FUNCIONES DE LA ASAMBLEA DE ACCIONISTAS. ENTRE OTRAS LAS SIGUIENTES: 1) ACORDAR LA FUSIÓN DE LA SOCIEDAD, SU TRANSFORMACIÓN, LA ENAJENACIÓN O EL ARRENDAMIENTO DE LA EMPRESA SOCIAL, LA DISOLUCIÓN O LA PRORROGA Y CUALQUIER REFORMA, AMPLIACIÓN MODIFICACIÓN DEL CONTRATO SOCIAL. 9) AUTORIZAR LA ADQUISICIÓN DE ACCIONES PROPIAS, CON SUJECCIÓN A LOS REQUISITOS ESTABLECIDOS POR LA LEY. 10) ADOPTAR EN GENERAL, TODAS LAS MEDIDAS QUE RECLAMEN EL CUMPLIMIENTO DE LOS ESTATUTOS O EL INTERÉS DE LA SOCIEDAD.

LA JUNTA DIRECTIVA SE COMPONE DE SIETE (7) MIEMBROS PRINCIPALES O DIRECTORES, ELEGIDOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS PARA PERÍODOS DE DOS AÑOS, SIN PERJUICIO DE QUE PUEDAN SER REMOVIDOS LIBREMENTE POR LA ASAMBLEA O REELEGIDOS INDEFINIDAMENTE.

SIMULTÁNEAMENTE CON LA ELECCIÓN DE LOS PRINCIPALES LA ASAMBLEA ELEGIRÁ SIETE (7) SUPLENTE PERSONALES LOS CUALES REEMPLAZARÁN A LOS RESPECTIVOS PRINCIPALES EN SUS FALTAS ABSOLUTAS, ACCIDENTALES O TEMPORALES.

EN LA JUNTA DIRECTIVA SE ENTIENDE DELEGADO EL MAS AMPLIO MANDATO PARA ADMINISTRAR LA SOCIEDAD Y POR CONSIGUIENTE, TENDRÁ ATRIBUCIONES SUFICIENTES PARA ORDENAR QUE SE EJECUTE O CELEBRE CUALQUIER ACTO O CONTRATO COMPRENDIDO DENTRO DEL OBJETO SOCIAL Y PARA ADOPTAR LAS DETERMINACIONES NECESARIAS EN ORDEN A QUE LA SOCIEDAD CUMPLA SUS FINES Y DE MANERA ESPECIAL, TENDRÁ LAS SIGUIENTES FUNCIONES ENTRE OTRAS:

C) NOMBRAR Y REMOVER LIBREMENTE AL PRESIDENTE EJECUTIVO, A LOS VICEPRESIDENTES EJECUTIVOS Y A LOS VICEPRESIDENTES ADMINISTRATIVOS.

E) DISPONER EL ESTABLECIMIENTO O LA CLAUSURA DE SUCURSALES O AGENCIAS, DENTRO

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CERTIFICADO NACIONAL

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O FUERA DEL DOMICILIO SOCIAL.

F) FIJAR LAS POLÍTICAS DE LA SOCIEDAD EN LOS DIFERENTES ORDENES DE SU ACTIVIDAD, ESPECIALMENTE EN MATERIA FINANCIERA, ECONÓMICA Y LABORAL; APROBAR PLANES DE INVERSIÓN Y DE PRODUCCIÓN; DECIDIR SOBRE NUEVAS LINEAS DE PRODUCCIÓN Y VENTA, ESTABLECER NORMAS GENERALES EN MATERIA DE PRECIOS Y DE VENTAS DE LOS PRODUCTOS ELABORADOS POR LA SOCIEDAD O DE LOS MATERIALES Y DEMÁS ELEMENTOS EN QUE ELLA NEGOCIE Y DICTAR NORMAS Y REGLAMENTOS PARA LA ORGANIZACIÓN Y EL FUNCIONAMIENTO DE TODAS LAS DEPENDENCIAS DE LA SOCIEDAD.

G) DETERMINAR LA APLICACIÓN QUE DEBA DARSE A LAS UTILIDADES QUE, CON EL CARÁCTER DE RESERVAS DE INVERSIÓN, HAYAN SIDO APROPIADAS POR LA ASAMBLEA DE ACCIONISTAS.

H) AUTORIZAR PREVIAMENTE LAS OPERACIONES QUE TENGAN POR OBJETO:

1) ADQUIRIR, HIPOTECAR Y EN CUALQUIER OTRA FORMA GRAVAR O LIMITAR EL DOMINIO DE BIENES RAÍCES, CUALQUIERA QUE SEA SU CUANTÍA.

2) CONSTITUIR PRENDA SOBRE BIENES SOCIALES O DARLOS EN ANTICRESIS PARA ACTOS O CONTRATOS CUYA CUANTÍA SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE.

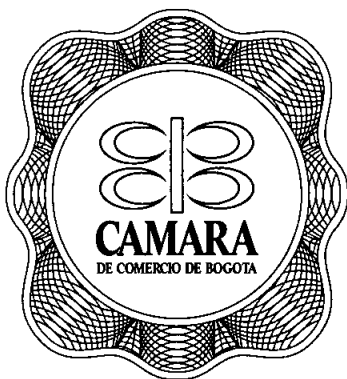
3) AUTORIZAR INVERSIONES EN BIENES DE CAPITAL O EFECTUAR REPARACIONES O MEJORAS DE LOS MISMOS, CUANDO UNAS U OTRAS IMPLIQUEN, EN CADA CASO, COSTOS O DESEMBOLSOS EN CUANTÍA IGUAL O SUPERIOR A CIEN MIL DÓLARES DE USA (\$US100.000.00).

4) AUTORIZAR LOS CONTRATOS DE MUTUO QUE PUEDAN CELEBRAR LA SOCIEDAD, LOS REPRESENTANTES LEGALES CUANDO SU CUANTÍA SEA SUPERIOR A \$100.000.000.00 MONEDA LEGAL COLOMBIANA O A TRESCIENTOS MIL DÓLARES DE USA (\$US300.000.00).

PARAGRAFO: NO OBSTANTE LO ANTERIOR, LOS REPRESENTANTES LEGALES PODRÁN CELEBRAR ILIMITADAMENTE, SIN NECESIDAD DE APROBACIÓN PREVIA DE LA JUNTA DIRECTIVA, CONTRATOS RELACIONADOS CON LICENCIAS, AGENCIA COMERCIAL, SUMINISTRO, ADQUISICIÓN, VENTA O DISTRIBUCIÓN DE PRODUCTOS FABRICADOS O DISTRIBUIDOS POR LA COMPAÑÍA; LA ADQUISICIÓN DE MATERIAS PRIMAS O MATERIALES Y EL DESCUENTO DE TÍTULOS- VALORES O DE CRÉDITOS ORIGINADOS DE LAS OPERACIONES SOCIALES; CREAR LOS EMPLEOS, FIJAR SUS ASIGNACIONES O LA FORMA DE RETRIBUCIÓN, NOMBRAR Y REMOVER LIBREMENTE A LOS EMPLEADOS.

(5) CELEBRAR CUALQUIER ACUERDO, ARREGLO O TRANSACCIÓN CON CUALQUIER PERSONA NATURAL O JURÍDICA RELACIONADA CON LA COMPAÑÍA, INCLUYENDO A CUALQUIER ACCIONISTA, MIEMBRO DE JUNTA DIRECTIVA, ADMINISTRADOR, EMPLEADO, FUNCIONARIO, AFILIADO, O A CUALQUIER COMPAÑÍA CONTROLADA POR CUALQUIERA DE LOS ACCIONISTAS

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MAYORITARIOS DE LA COMPAÑÍA; SIEMPRE Y CUANDO TALES CONTRATOS O ACUERDOS:

(i) INVOLUCREN PAGOS DE LA COMPAÑÍA SUPERIORES A UN MONTO EQUIVALENTE A SETENTA Y CINCO MIL DÓLARES DE USA (US\$75.000.00).

(ii) TENGAN UN PLAZO SUPERIOR A UN AÑO.

(iii) NO HAYAN SIDO NEGOCIADOS EN IGUALDAD DE CONDICIONES QUE TRANSACCIONES CON PERSONAS NO RELACIONADAS, O NO SE CONSIDEREN DENTRO DEL GIRO ORDINARIO DE LOS NEGOCIOS.

PARÁGRAFO I.- PARA EFECTOS DEL NUMERAL (5) SE CONSIDERA "PERSONA RELACIONADA" A CUALQUIER PERSONA: (i) QUE ES AFILIADA DE LA OTRA PERSONA ESPECIFICADA.

(ii) QUE ACTÚA COMO MIEMBRO DE JUNTA DIRECTIVA, ADMINISTRADOR, SOCIO, ALBACEA, O FIDUCIARIO DE LA OTRA PERSONA ESPECIFICADA.

(iii) EN LA CUAL LA OTRA PERSONA ESPECIFICADA POSEE UN INTERÉS MATERIAL.

(iv) QUE TIENE UN INTERÉS MATERIAL EN LA OTRA PERSONA ESPECIFICADA. EN RELACIÓN CON UN INDIVIDUO, EL TÉRMINO "PARTE RELACIONADA" INCLUYE A UN INDIVIDUO QUE SEA MIEMBRO DE LA FAMILIA DEL INDIVIDUO EN CUESTIÓN HASTA EL CUARTO GRADO DE CONSANGUINIDAD, Y CUALQUIER PERSONA QUE ES UNA PARTE RELACIONADA DE DICHO MIEMBRO DE FAMILIA.

PARA ESTOS EFECTOS, "INTERÉS MATERIAL" SIGNIFICA PROPIEDAD, DIRECTA O INDIRECTA, DE ACCIONES CON DERECHO A VOTO QUE REPRESENTEN POR LOS MENOS EL 10% DEL CAPITAL O DE LOS DERECHOS DE VOTO DE LA PERSONA EN CUESTIÓN.

PARÁGRAFO II. IGUALMENTE, PARA EFECTOS DEL NUMERAL (5), EN RELACIÓN CON CUALQUIER PERSONA SE CONSIDERA "AFILIADA" A CUALQUIERA OTRA PERSONA QUE:

(i) DIRECTA O INDIRECTAMENTE LA CONTROLE.

(ii) QUE SEA CONTROLADA POR DICHA PERSONA O QUE SE ENCUENTRAN COMÚNMENTE CONTROLADAS POR OTRA PERSONA. PARA ESTOS EFECTOS, "CONTROL" CONSISTE EN LA FACULTAD DE DIRIGIR O DE HACER DIRIGIR, DIRECTA O INDIRECTAMENTE, LA ADMINISTRACIÓN Y LAS POLÍTICAS DE ESA PERSONA, BIEN SEA A TRAVÉS DE LA PROPIEDAD DE LAS ACCIONES CON DERECHO A VOTO, O A TRAVÉS DE UN CONTRATO U OTRA FORMA, EN EL ENTENDIDO QUE LA PROPIEDAD DIRECTA O INDIRECTA DEL 25% O MÁS DEL LAS ACCIONES CON DERECHO A VOTO DE LA PERSONA EN CUESTIÓN SE CONSIDERA COMO EVENTO CONSTITUTIVO DE CONTROL SOBRE DICHA PERSONA.

(6) APROBAR O MODIFICAR O MODIFICAR EL PLAN ANUAL DE NEGOCIOS O EL PRESUPUESTO ANUAL DE LA COMPAÑÍA.

(7) REALIZAR ADQUISICIONES O INVERSIONES EN UNA O MAS CORPORACIONES, SOCIEDADES, ASOCIACIONES O CUALQUIER OTRA ORGANIZACIÓN O PERSONA JURÍDICA.

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SIMILAR, POR UNA SUMA O SUMAS QUE, CONJUNTAMENTE, SUPEREN UN MONTO EQUIVALENTE A DOS MILLONES QUINIENTOS MIL DÓLARES (US\$2.500.000.00) DURANTE UN AÑO FISCAL.

L) AUTORIZAR AL REPRESENTANTE LEGAL PARA QUE SOLICITE, LLEGADO EL CASO, QUE SE ADMITA A LA COMPAÑÍA A LA CELEBRACIÓN DE CONCORDATO PREVENTIVO CON SUS ACREEDORES.

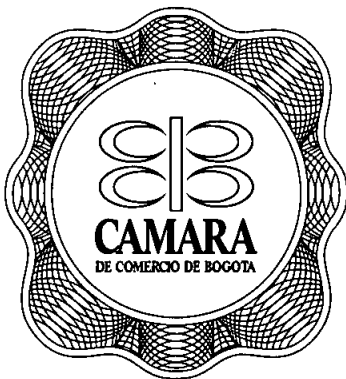
M) SERVIR DE ÓRGANO CONSULTIVO Y ASESOR DE LOS REPRESENTANTES DE LA COMPAÑÍA.

LA ADMINISTRACIÓN INMEDIATA DE LA COMPAÑÍA, SU REPRESENTACIÓN LEGAL Y LA GESTIÓN DE LOS NEGOCIOS SOCIALES ESTARÁN A CARGO DEL PRESIDENTE EJECUTIVO Y DE DOS (2) VICEPRESIDENTES EJECUTIVOS, DESIGNADOS POR LA JUNTA DIRECTIVA PARA PERIODOS DE UN AÑO, REELEGIBLES INDEFINIDAMENTE Y REMOVIBLES LIBREMENTE POR ELLA EN CUALQUIER TIEMPO, QUIENES COMO REPRESENTANTES LEGALES PODRÁN ACTUAR CONJUNTA O SEPARADAMENTE. TODOS LOS EMPLEADOS DE LA COMPAÑÍA CON EXCEPCIÓN DE LOS DESIGNADOS POR LA ASAMBLEA DE ACCIONISTAS Y LOS DEPENDIENTES DEL REVISOR FISCAL, SI LOS HUBIERE, ESTARÁN SOMETIDOS EN EL DESEMPEÑO DE SUS CARGOS A LOS REPRESENTANTES LEGALES.

LOS REPRESENTANTES LEGALES SON MANDATARIOS CON REPRESENTACIÓN INVESTIDOS DE FUNCIONES EJECUTIVAS Y ADMINISTRATIVAS Y COMO TALES TIENEN A SU CARGO LA REPRESENTACIÓN LEGAL DE LA COMPAÑÍA, LA GESTIÓN COMERCIAL Y FINANCIERA, LA RESPONSABILIDAD DE LA ACCIÓN ADMINISTRATIVA, LA COORDINACIÓN Y LA SUPERVISIÓN GENERAL DE LA EMPRESA, LAS CUALES CUMPLIRÁN CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS Y A LAS DISPOSICIONES LEGALES Y CON SUJECCIÓN A LAS ORDENES E INSTRUCCIONES DE LA JUNTA DIRECTIVA.

COMO REPRESENTANTES LEGALES DE LA COMPAÑÍA EN JUICIO Y FUERA DE JUICIO, LOS REPRESENTANTES TIENEN FACULTADES PARA EJECUTAR O CELEBRAR SIN OTRAS LIMITACIONES QUE LAS ESTABLECIDAS EN LOS ESTATUTOS EN CUANTO SE TRATE DE OPERACIONES QUE DEBAN SER PREVIAMENTE AUTORIZADAS POR LA JUNTA DIRECTIVA O POR LA ASAMBLEA DE ACCIONISTAS, TODOS LOS ACTOS O CONTRATOS COMPRENDIDOS DENTRO DEL OBJETO SOCIAL O QUE TENGAN CARÁCTER SIMPLEMENTE PREPARATORIO, ACCESORIO O COMPLEMENTARIO PARA LA REALIZACIÓN DE LOS FINES QUE PERSIGUE LA SOCIEDAD Y LOS QUE SE RELACIONAN DIRECTAMENTE CON LA EXISTENCIA Y EL FUNCIONAMIENTO DE LA MISMA. LOS REPRESENTANTES QUEDAN INVESTIDOS DE PODERES ESPECIALES PARA TRANSIGIR, ARBITRAR Y COMPROMETER LOS NEGOCIOS SOCIALES; PROMOVER O COADYUVAR ACCIONES JUDICIALES, ADMINISTRATIVAS O CONTENCIOSAS ADMINISTRATIVAS EN QUE LA COMPAÑÍA TENGA INTERÉS E INTERPONER TODOS LOS RECURSOS QUE SEAN PROCEDENTES CONFORME A LA LEY; DESISTIR DE LAS ACCIONES O RECURSOS QUE INTERPONGAN; NOVAR

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OBLIGACIONES O CRÉDITOS; DAR O RECIBIR BIENES EN PAGO; CONSTITUIR APODERADOS JUDICIALES O EXTRAJUDICIALES, DELEGARLES FACULTADES REVOCAR MANDATOS Y SUSTITUCIONES.

PARÁGRAFO: LOS REPRESENTANTES LEGALES DE LA SOCIEDAD TIENEN AMPLIAS FACULTADES, SIN NINGUNA LIMITACIÓN Y SIN REQUERIR AUTORIZACIÓN PREVIA DE LA JUNTA DIRECTIVA, PARA ACTUAR EN NOMBRE DE LA SOCIEDAD EN LICITACIONES PUBLICAS, PRIVADAS O CUALQUIER OTRA MODALIDAD DE CONTRATACIÓN, PRESENTAR PROPUESTAS, ACEPTAR ADJUDICACIONES Y CONTRATAR SIN LIMITACIÓN DE CUANTÍA ALGUNA ANTE LAS ENTIDADES PUBLICAS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMÍA MIXTA, BIEN SEAN ELLAS DEL ORDEN NACIONAL, DISTRITAL, DEPARTAMENTAL O MUNICIPAL.

CERTIFICA:

DOCUMENTO: ACTA No. 393 DEL 20 DE JANUARY DE 1993

ORIGEN: JUNTA DIRECTIVA

INSCRIPCION: 26 DE JANUARY DE 1993 No. 62203 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

PRESIDENTE EJECUTIVO

FRANCISCO JOSE BARBERI OSPINA

C.C.14445880

VICEPRESIDENTE EJECUTIVO

JUAN MANUEL BARBERI OSPINA

C.C.14949561

VICEPRESIDENTE EJECUTIVO

EMILIO SARDI APARICIO

C.C.14434582

CERTIFICA:

DOCUMENTO: ACTA No. 70 DEL 22 DE JANUARY DE 2009

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 13 DE MARCH DE 2009 No. 2979 DEL LIBRO IX

FUE (RON) NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

FRANCISCO JOSE BARBERI OSPINA

C.C.14445880

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SEGUNDO RENGLON

JUAN MANUEL BARBERI OSPINA

C.C.14949561

TERCER RENGLON

MAURICIO BARBERI BLUM

C.C.16749545

CUARTO RENGLON

SANTIAGO BARBERI GONZALEZ

C.C.94384742

QUINTO RENGLON

FRANCISCO PIEDRAHITA PLATA

C.C.14934246

SEXTO RENGLON

ISAAC YANOVICH FARBAIARZ

C.C.8243355

SEPTIMO RENGLON

DIEGO HUMBERTO QUIJANO REISSNER

C.C.16615708

SUPLENTE

PRIMER RENGLON

EMILIO SARDI APARICIO

C.C.14434582

SEGUNDO RENGLON

JORGE ENRIQUE ARIZA BERNAL

C.C.19494493

TERCER RENGLON

ANA MARIA ALVAREZ ROBLEDO

C.C.31170896

CUARTO RENGLON

MARIA TERESA CAÑON DE GUZMAN

C.C.31238104

QUINTO RENGLON

ANTONIO JAIRO RAMIREZ ECHAVE

C.C.16741040

SEXTO RENGLON

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ALONSO BOTERO PARDO
C.C.16830282
SEPTIMO RENGLON
MARTHA LUZ GONZALEZ TORRES
C.C.31854671

CERTIFICA:

DOCUMENTO: ACTA No. 59 DEL 31 DE MARCH DE 2003
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 23 DE APRIL DE 2003 No. 2845 DEL LIBRO IX
FUE(RON) NOMBRADO(S):
REVISOR FISCAL
DELOITTE & TOUCHE LTDA D & T LTDA
NIT.860005813-4

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 26 DE AUGUST DE 2004
ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA
INSCRIPCION: 30 DE AUGUST DE 2004 No. 9417 DEL LIBRO IX
FUE(RON) NOMBRADO(S):
REVISOR FISCAL PRINCIPAL
LUIS FERNANDO QUICENO BENAVIDES
C.C.6106227

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 08 DE JUNE DE 2009
ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA
INSCRIPCION: 11 DE JUNE DE 2009 No. 6757 DEL LIBRO IX
FUE(RON) NOMBRADO(S):
REVISOR FISCAL SUPLENTE
KENELMA JUDITH PALENCIA CABANA
C.C.29181230

CERTIFICA:

QUE POR ESCRITURA NRO. 5235 DEL 19 DE JULY DE 1996 NOTARIA DECIMA DE CALI ,
INSCRITA EN LA CAMARA DE COMERCIO EL 25 DE JULY DE 1996 BAJO EL NRO. 144 DEL
LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A
CARLOS ALBERTO QUINTERO, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO
CON LA CEDULA DE CIUDADANIA NRO.

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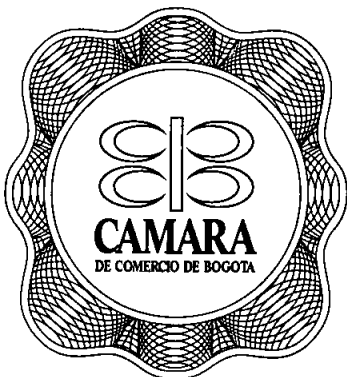
PAGINA: 14

14.440.778 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA, EL REPRESENTANTE EN LOS SIGUIENTES ACTOS: A) PRESENTAR EN LA ADMINISTRACION DE IMPUESTOS Y ADUANAS NACIONALES O DEL ORGANISMO QUE HAGA SUS VECES Y FIRMAR EN REPRESENTACION DE LA SOCIEDAD, LAS DECLARACIONES DEL IMPUESTO SOBRE LA RENTA Y COMPLEMENTARIOS QUE CORRESPONDA A LA SOCIEDAD, Y TODAS LAS DEMAS DECLARACIONES QUE LA SOCIEDAD DEBA PRESENTAR ANTE DICHA ENTIDAD, TALES COMO LA DE VENTAS, RETENCION EN LA FUENTE, TIMBRE Y CUALESQUIER OTRA DECLARACION QUE POR LEY LA SOCIEDAD ESTE OBLIGADA A PRESENTAR. B) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A TECNOQUIMICAS S.A., COMO DECLARANTE DEL IMPUESTO DE INDUSTRIA Y COMERCIO Y EL COMPLEMENTARIO DE AVISOS Y TABLEROS EN LOS MUNICIPIOS EN QUE LA SOCIEDAD ESTE OBLIGADA AL PAGO DE LOS CITADOS IMPUESTOS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE LOS MENCIONADOS TRIBUTOS. C) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A TECNOQUIMICAS S.A. COMO DECLARANTE DEL IMPUESTO PREDIAL Y COMPLEMENTARIOS EN LOS MUNICIPIOS DONDE TENGA BIENES INMUEBLES, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DEL CITADO IMPUESTO. D) PARA DAR RESPUESTA A LOS REQUERIMIENTOS ORDINARIOS Y A LAS SOLICITUDES DE INFORMACION EN RELACION CON LOS IMPUESTOS ADMINISTRADOS POR LA DIRECCION DE IMPUESTOS Y ADUANAS NACIONALES Y POR LAS DEPENDENCIAS MUNICIPALES QUE ADMINISTREN LOS IMPUESTOS DE CARACTER TERRITORIAL. E) Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO LA SOCIEDAD QUEDE SIN REPRESENTACION EN LOS ASUNTOS RELACIONADOS CON LAS FACULTADES OTORGADAS.

CERTIFICA:

QUE POR ESCRITURA NRO. 307 DEL 31 DE JANUARY DE 2002 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRUARY DE 2002 BAJO EL NRO. 298 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A JORGE ROBERTO OBANDO RODRIGUEZ, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 14.960.183 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA: lo.) PROMUEVA O DESISTA DE ACCIONES ANTE CORPORACIONES, ENTIDADES O FUNCIONARIOS DEL ORDEN JUDICIAL O GUBERNATIVO, YA SEA EN PROCESOS, ACTUACIONES O ACTOS SIMPLES, DILIGENCIAS O GESTIONES EN QUE TECNOQUIMICAS S.A. TENGA INTERES COMO ACTOR,

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DEMANDANDO O TERCERO INTERVINIENTE EN RELACION CON LOS ASUNTOS DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA, EN QUE LA EMPRESA SEA PARTE ACTIVA O PASIVA, CON CAPACIDAD PARA NOTIFICARSE Y CONTESTAR Y HACERSE PARTE DE ELLOS EN NOMBRE DE TECNOQUIMICAS S.A. 2o.) SUSCRIBA Y DE POR TERMINADO LOS CONTRATOS DE TRABAJO DEL PERSONAL VINCULADO A LA EMPRESA. 3o.) CONSTITUYA APODERADOS EN DESARROLLO DE ESTA REPRESENTACION LABORAL, REVOQUE Y SUSTITUYA DICHOS PODERES CUANDO LO ESTIME PROCEDENTE. 4o.) TRANSIGA, CONCILIE, DESISTA Y COMPROMETA A LA EMPRESA EN TODOS LOS TRAMITES ADMINISTRATIVOS Y PROCESOS JUDICIALES, DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA EN LOS QUE LA EMPRESA SEA PARTE DEMANDANTE, DEMANDADA O TERCERO INTERVINIENTE. PARAGRAFO. LA FACULTAD PARA TRANSIGIR O CONCILIAR SE LIMITA A LA SUMA DE QUINIENTOS (500) SALARIOS LEGALES MENSUALES. 5o.) OTORQUE PODERES Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES JUDICIALES DE CARACTER CIVIL, COMERCIAL Y PENAL TENDIENTES A LA RECUPERACION DE LOS CREDITOS A FAVOR DE LA SOCIEDAD, BIEN SEA REPRESENTADOS EN FACTURAS, CHEQUES, TITULOS VALORES O CUALQUIER OTRO DOCUMENTO REPRESENTATIVO DE CREDITO, HASTA POR SUMA EQUIVALENTE A QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE TECNOQUIMICAS S.A. A LAS AUDIENCIAS DE CONCILIACION QUE PROGRAMEN LOS JUZGADOS CIVILES MUNICIPALES Y DEL CIRCUITO, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD HASTA POR LA CUANTIA INDICADA. 6o. REPRESENTA A TECNOQUIMICAS S.A. DENTRO DE LOS TRAMITES DE CONCORDATOS, PROCESOS DE REESTRUCTURACION ECONOMICA PREVISTO EN LA LEY 550 DE 1999 Y LAS NORMAS QUE LA ADICIONEN O MODIFIQUEN Y LIQUIDACIONES OBLIGATORIAS QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE ACREEDORES O ANTE LOS JUZGADOS CIVILES, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER, NOMBRAR APODERADOS, PRESENTAR LOS CREDITOS, APORTAR LAS PRUEBAS QUE ESTIME NECESARIAS, ASISTIR A LAS AUDIENCIAS PRELIMINARES Y DEFINITIVAS, ACORDAR FORMULAS DE PAGO, RECIBIR Y EN GENERAL PARA EJERCER TODAS AQUELLAS GESTIONES NECESARIAS PARA OBTENER EL RECONOCIMIENTO Y PAGO DE LOS CREDITOS PRESENTADOS. LAS FACULTADES AQUI ESTABLECIDAS ESTAN LIMITADAS PARA LOS CREDITOS HASTA POR CUANTIA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. PARAGRAFO. IGUALMENTE QUEDA FACULTADO PARA ACEPTAR Y REPRESENTAR A TECNOQUIMICAS CUANDO LA EMPRESA SEA NOMBRADA EN JUNTA DE ACREEDORES O EN ORGANOS EQUIVALENTES O SIMILARES, EN LOS PROCESOS QUE TRAMITEN ANTE LA

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SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES. 7o.) REPRESENTA A TECNOQUIMICAS S.A. EN LOS PROCEDIMIENTOS DE CONCILIACION QUE LOS DEUDORES DE LA SOCIEDAD CONVOQUEN ANTE LAS ENTIDADES FACULTADAS PARA ELLO CON EL FIN OBTENER UN ACUERDO EN EL PAGO DE LAS ACREENCIAS, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER Y RECIBIR, FACULTADES QUE SE LIMITAN HASTA POR LA SUMA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. 8o.) REVISE LOS EXPEDIENTES DE LOS PROCESOS JUDICIALES DE CARACTER EJECUTIVO EN QUE LA SOCIEDAD SEA PARTE DEMANDANTE, EN TODO EL TERRITORIO NACIONAL, PARA LA RECUPERACION DE SUS ACREENCIAS. 9o.) APRUEBE Y SUSCRIBA ACUERDOS PRIVADOS DE PAGO Y CONCILIACIONES DE OBLIGACIONES A FAVOR DE TECNOQUIMICAS POR LA VENTA DE SUS PRODUCTOS HASTA POR LA SUMA DE (500) SALARIOS MINIMOS LEGALES MENSUALES.

CERTIFICA:

QUE POR ESCRITURA NRO. 6224 DEL 15 DE DECEMBER DE 2004 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 17 DE JANUARY DE 2005 BAJO EL NRO. 3 DEL LIBRO V MEDIANTE LA CUAL CONCEDE PODER ESPECIAL PERO AMPLIO Y SUFICIENTE A DIEGO PEREZ MENDOZA MAYOR DE EDAD, VECINO DE BOGOTA, IDENTIFICADO CON CEDULA DE CIUDADANIA NUMERO 16.820.530 DE CALI, COMO SU REPRESENTANTE CON PODER ESPECIAL, AMPLIO Y SUFICIENTE, PARA REALIZAR TODOS LOS TRAMITES RELACIONADOS CON EL PROCEDIMIENTO DE OTORGAMIENTO DE LICENCIA DE VENTA DE LOS PRODUCTOS AGRICOLAS DE LA SOCIEDAD, CON FACULTAD PARA FIRMAR TODO TIPO DE DOCUMENTOS, SOLICITUDES, REQUERIMIENTOS, MEMORIALES RESPUESTAS, ACLARACIONES BIEN SEA ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO ICA, MINISTERIO DEL MEDIO AMBIENTE, MINISTERIO DE PROTECCION SOCIAL O ANTE LAS AUTORIDADES GUBERNAMENTALES COMPETENTES EN LO RELACIONADO CON LOS TRAMITES QUE PERMITAN LA COMERCIALIZACION DE ESE TIPO DE PRODUCTOS. LA FACULTAD TAMBIEN COMPRENDERA LA DE NOTIFICARSE, RESPONDER E INTERPONER RECURSOS DE TODO TIPO DE ACTO ADMINISTRATIVO. EL APODERADO SUSCRIBIRA TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A LA SOCIEDAD ANTE LAS AUTORIDADES MENCIONADAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA A NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE

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QUE TRATA ESTE PODER. EL APODERADO SE CEÑIRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA:

QUE POR ESCRITURA NRO. 4265 DEL 16 DE SEPTEMBER DE 2005 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE OCTOBER DE 2005 BAJO EL NRO. 168 DEL LIBRO V EL SEÑOR JUAN BAUTISTA DE LOS RIOS GUTIERREZ MAYOR DE EDAD, DOMICILIADO EN CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 17108621 DE BOGOTA, QUIEN ACTUA EN SU CALIDAD DE REPRESENTANTE LEGAL DE TECNOQUIMICAS S. A. SOCIEDAD COMERCIAL ORGANIZADA Y EXISTENTE CONFORME A LAS LEYES COLOMBIANAS, CON DOMICILIO Y SEDE PRINCIPAL EN CALI. EN DICHA CONDICION CONFIERE PODER AMPLIO Y SUFICIENTE A LAS SIGUIENTES PERSONAS: CLAUDETTE VERNOT HERNANDEZ ABOGADA TITULADA Y EN EJERCICIO, IDENTIFICADA CON LA CEDULA DE CIUDADANIA No. 51722517 DE BOGOTA, PORTADORA DE LA TARJETA PROFESIONAL DE ABOGADO No. 57111 DEL C.S. DE LA J., ANDRES FELIPE ZAPATA OCAMPO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79598546 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 107240 DEL C.S. DE LA J. Y JUAN MANUEL SERRANO CASTILLO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79875670 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 124953 DE C.S. DE LA J., TODOS CON DOMICILIO EN LA CIUDAD DE BOGOTA, D.C., PARA QUE EN NOMBRE DE MI REPRESENTADA ACTUEN EN TODOS LOS ASUNTOS DE PROPIEDAD INTELECTUAL Y LOS DERIVADOS DE ELLA, CON FACULTAD PARA RECIBIR NOTIFICACIONES, NOMBRAR APODERADOS JUDICIALES O EXTRAJUDICIALES EN ESTOS ASUNTOS.

EL PRESENTE PODER SE CONFIERE PARA QUE LOS APODERADOS ACTUEN ANTE CUALQUIER PERSONA O AUTORIDAD ADMINISTRATIVA DEL ORDEN NACIONAL, DEPARTAMENTAL, DISTRITAL Y LOCAL; ANTE LAS AUTORIDADES CONTENCIOSO ADMINISTRATIVAS Y JUDICIALES, PARA OBTENER LA PROTECCION DE NUESTRA PROPIEDAD INTELECTUAL Y CONTRA LAS PRACTICAS RESTRICTIVAS DE LA COMPETENCIA Y LOS ASUNTOS DE COMPETENCIA DESLEAL, A CUYO EFECTO LA AUTORIZO, EN TODO LO CONCERNIENTE A LOS SIGUIENTES ASUNTOS: A) OBTENCION DE PATENTES DE INVENCION, DE MODELO DE UTILIDAD, ESQUEMAS DE TRAZADOS DE CIRCUITOS INTEGRADOS, DISEÑOS INDUSTRIALES, EL REGISTRO DE MARCAS DE PRODUCTOS O SERVICIOS; LEMAS COMERCIALES; DEPOSITO DE NOMBRES Y ENSEÑAS COMERCIALES, INDICACIONES GEOGRAFICAS; RENOVACION DE SIGNOS DISTINTIVOS, RENOVACIONES, AFECTACIONES AL REGISTRO, INSCRIPCION DE CONTRATOS, SOLICITUD Y RENOVACION DE NOMBRES DE DOMINIO; B) PRESENTACION DE OPOSICIONES

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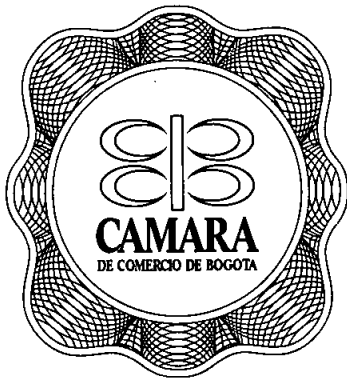
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AL REGISTRO DE MARCAS DE TERCERO, PRESENTACION DE ALEGATOS EN DEFENSA DE OPOSICIONES AL REGISTRO, ACCION DE CANCELACION, ACCION POR INFRACCION DE DERECHOS, REVOCATORIA DIRECTA, ACCION DE NULIDAD, ACCION DE NULIDAD Y RESTABLECIMIENTO DEL DERECHO, ACCION REIVINDICATORIA, ACCIONES DE TUTELA, POPULARES, DE GRUPO, DE CLASE; ACCIONES Y PROCESOS QUE PROMOVAMOS O SE NOS PROMUEVAN; C) AGOTAMIENTO DE LA VIA GUBERNATIVA, EJERCICIO DEL DERECHO DE PETICION ANTE CUALQUIER PERSONA O AUTORIDAD; D) SOLICITUD DE MEDIDAS CAUTELARES, PRESENTACION DE ACCIONES MEDIANTE PROCESOS CIVILES, PENALES, ADMINISTRATIVOS O CONTENCIOSO ADMINISTRATIVOS RELACIONADOS CON ESTOS DERECHOS U OTROS DE DIFERENTE NATURALEZA, MEDIDAS EN FRONTERA, ACCIONES Y PROCESOS QUE PROMOVAMOS O SE NOS PROMUEVAN; E) OBTENER Y TRAMITAR TODO LO RELACIONADO CON EL RECONOCIMIENTO DE DERECHOS DE AUTOR, DERECHOS CONEXOS Y NUEVAS TECNOLOGIAS Y SU PROTECCION LEGAL; F) SOLICITUD DE REGISTRO Y RENOVACION DE CONTRATOS DE TRANSFERENCIA DE TECNOLOGIA; G) OBTENER Y TRAMITAR TODO LO RELACIONADO CON LICENCIAS DE FUNCIONAMIENTO, REGISTROS SANITARIOS, AUTORIZACION DE CERTIFICADOS DE LIBRE VENTA, AUTORIZACION DE PUBLICIDAD ANTE EL MINISTERIO DE PROTECCION SOCIAL O EL INVIMA O ANTE CUALQUIER AUTORIDAD SANITARIA; H) OBTENCION DE CERTIFICADOS DE CARENCIA DE INFORMES POR TRAFICO DE ESTUPEFACIENTES.RENOVACIONES, AUTORIZACIONES EXTRAORDINARIAS ANTE LA DIRECCION NACIONAL DE ESTUPEFACIENTES O EL CONSEJO NACIONAL DE ESTUPEFACIENTES; I) SOLICITUD DE AUTORIZACIONES PARA PROMOCIONES, RIFAS Y JUEGOS ANTE ETESA O ANTE LAS AUTORIDADES COMPETENTES DEL ORDEN LOCAL, DISTRITAL O DEPARTAMENTAL; Y EN GENERAL CUALQUIERA OTRA PETICION ANTE LAS AUTORIDADES ADMINISTRATIVA, ASI COMO PARA NOTIFICARSE DE CUALQUIER PROVIDENCIA Y RENUNCIAR A TERMINOS. EN TODOS LOS ASUNTOS ARRIBA DETERMINADOS LA APODERADA QUEDA FACULTADA PARA SUSTITUIR TOTAL O PARCIALMENTE ESTE MANDATO, TRANSIGIR, CONCILIAR EXTRAJUDICIAL O JUDICIALMENTE, ADMITIR LOS HECHOS DEL PROCESO PERO NO PARA CONFESAR, DESISTIR, CANCELAR, RECIBIR, RENUNCIAR Y RATIFICAR LOS ACTOS DE AGENTES OFICIOSOS.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 22 DE MAY DE 2008 DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE JUNE DE 2008 BAJO EL NRO. 90 DEL LIBRO V Y MODIFICADO POR DOCUMENTO PRIVADO DE FECHA 18 DE JULIO DE 2008, INSCRITA EN LA CAMARA DE COMERCIO EL 08 DE AGOSTO DE 2008 BAJO EL NRO. 151 DEL LIBRO V, SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A LOS SIGUIENTES FUNCIONARIOS DE LA EMPRESA:

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1. ANA MARÍA ÁLVAREZ R., CON C.C. 31.170.896 DE CALI Y JORGE ENRIQUE GIRALDO, CON C.C. 16.784.794 DE CALI, OBRARAN COMO APODERADOS ESPECIALES PARA EL DESARROLLO DE LAS SIGUIENTES FACULTADES:

A. SUSCRIBIR LOS CONTRATOS DE TRABAJO, SUS MODIFICACIONES Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE A TECNOQUÍMICAS S.A.

B. SUSCRIBIR CONTRATOS DE APRENDIZAJE Y PASANTIAS ASI COMO SUS MODIFICACIONES Y ADICIONES.

C. SUSCRIBIR ACUERDOS CON LOS EMPLEADOS DE LA SOCIEDAD.

D. COMPARECER DIRECTAMENTE U OTORGAR PODER PARA ATENDER RECLAMACIONES Y PROCESOS DE ORDEN LABORAL BIEN SEA DE CARÁCTER ADMINISTRATIVO O JUDICIAL ANTE LAS OFICINAS REGIONALES DE TRABAJO, MINISTERIO DE LA PROTECCIÓN SOCIAL Y ANTE CUALQUIER OTRA AUTORIDAD O ENTIDAD ANTE LA QUE SE INICIE Y TRAMITE PROCEDIMIENTOS DE CARÁCTER LABORAL O RELACIONADOS CON TEMAS DE LA SEGURIDAD SOCIAL.

E. FIRMAR TODOS LOS DOCUMENTOS Y ATENDER TODOS LOS TRÁMITES ANTE LAS CAJAS DE COMPENSACIÓN FAMILIAR, EMPRESAS PRESTADORAS DE SERVICIOS DE SALUD (EPS), FONDOS DE PENSIONES Y CESANTÍAS, ADMINISTRADORA DE RIESGOS PROFESIONALES (ARP), INSTITUTO DE LOS SEGUROS SOCIALES (ISS). ESTA FACULTAD TAMBIÉN COMPRENDE LA DESIGNACIÓN DE APODERADOS.

F. ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACIÓN, DECLARACIONES DE PARTE Y RENDICIÓN DE TESTIMONIOS DENTRO DE LOS PROCESOS DE LA JURISDICCIÓN LABORAL Y TRÁMITES ADMINISTRATIVOS, CUANDO ELLO SEA REQUERIDO.

G. RESPONDER LAS DEMANDAS DE TUTELA DIRECTAMENTE O A TRAVÉS DE APODERADO ESPECIAL.

H. SUSCRIBIR LOS CONTRATOS DE TODO TIPO CON ENTIDADES EDUCATIVAS DE TODO ORDEN, SIN LIMITACIÓN DE CUANTÍA.

I. SUSCRIBIR LOS DOCUMENTOS Y ESCRITURAS DE DONACIÓN QUE SEAN AUTORIZADAS POR LA JUNTA DIRECTIVA, SIN LIMITACIÓN ALGUNA.

J. SUSCRIBIR TODOS LOS CONTRATOS DE CONSTRUCCIÓN, INSTALACIÓN, SERVICIOS, REPARACIONES Y ADECUACIONES QUE SE REALICEN Y PRESTEN EN LA PLANTA Y SEDE ADMINISTRATIVA DE TECNOQUÍMICAS S.A. LOCALIZADAS EN CALI, HASTA POR LA SUMA EQUIVALENTE A TRESCIENTOS (300) SALARIOS MÍNIMOS LEGALES MENSUALES, DARLOS POR TERMINADO POR CUALQUIER CAUSA, PRESENTAR RECLAMOS ANTE LAS COMPAÑÍAS ASEGURADORAS, EXIGIR EL PAGO DE MULTAS E INDEMNIZACIONES DE CUALQUIER TIPO QUE ESTÉN PACTADAS EN LOS RESPECTIVOS CONTRATOS Y EL CUMPLIMIENTO DE ELLOS.

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K. ANTE EL MINISTERIO DEL MEDIO AMBIENTE Y ORGANISMOS DE CONTROL AMBIENTAL DEL ORDEN NACIONAL, DEPARTAMENTAL Y MUNICIPAL O DISTRITAL: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TRÁMITES QUE LA SOCIEDAD TECNOQUIMICAS S.A. REQUIERA ADELANTAR ANTE LA ENTIDAD, ASÍ COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CARÁCTER JUDICIAL O GUBERNATIVO.

L. SUSCRIBIR LOS CONTRATOS DE PRENDA SOBRE VEHICULOS DE PROPIEDAD DE TERCEROS PARA RESPALDAR LOS PRESTAMOS QUE LA EMPRESA OTORQUE Y TODO LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA SU FORMALIZACIÓN ANTE LAS SECRETARIAS DE TRANSITO Y/O MOVILIDAD DE LOS RESPECTIVOS MUNICIPIOS. ESTE PODER TAMBIEN COMPRENDE LA CANCELACION DE LAS PRENDAS Y LA FIRMA DE TODOS LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA TAL FIN.

M. FORMULAR PETICIONES RELACIONADAS CON LAS FACULTADES OTORGADAS ANTE CUALQUIER AUTORIDAD.

PARÁGRAFO I. EN LA ATENCIÓN DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL, GUBERNATIVO, TRIBUNALES DE ARBITRAMIENTO Y RECLAMOS ANTE LAS COMPAÑÍAS ASEGURADORAS.

PARÁGRAFO II. LOS APODERADOS EJERCERÁN SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACIÓN.

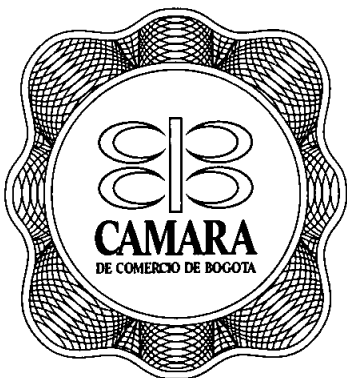
2. JORGE ENRIQUE ARIZA BERNAL, IDENTIFICADO CON LA CÉDULA DE CIUDADANÍA NO. 19.494.493 DE BOGOTÁ, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES:

A. ANTE EL MINISTERIO DEL MEDIO AMBIENTE: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TRÁMITES QUE LA SOCIEDAD TECNOQUÍMICAS S.A. REQUIERA ADELANTAR ANTE LA ENTIDAD, ASÍ COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CARÁCTER JUDICIAL O GUBERNATIVO.

B. ANTE LA SUPERINTENDENCIA DE VIGILANCIA: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, OTORGAR PODERES, RENDIR DECLARACIONES, ATENDER VISITAS, FIRMAR LAS ACTAS CORRESPONDIENTES Y NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TRÁMITES QUE LA SOCIEDAD TECNOQUÍMICAS S.A. REQUIERA

ADELANTAR ANTE LA ENTIDAD, ASÍ COMO DESIGNAR APODERADOS PARA INICIAR O

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RESPONDER PROCESOS DE CARÁCTER JUDICIAL O GUBERNATIVO.

C. ANTE EL FONDO NACIONAL DE ESTUPEFACIENTES Y DIRECCIÓN NACIONAL DE ESTUPEFACIENTES FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TRÁMITES QUE LA SOCIEDAD TECNOQUÍMICAS S.A. REQUIERA ADELANTAR ANTE LAS CITADAS ENTIDADES, SUSCRIBIR LAS ACTAS DE VISITA, Y DESIGNAR APODERADOS PARA NOTIFICARSE DE ACTOS ADMINISTRATIVOS, INICIAR O RESPONDER PROCESOS DE CARÁCTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

D. EN TODO LO RELACIONADO CON LOS TRÁMITES DE IMPORTACIONES Y EXPORTACIONES, SEGÚN SE INDICA:

I. OTORGAR PODERES Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS ADMINISTRACIONES DE ADUANAS DE LA DIRECCIÓN DE IMPUESTOS Y ADUANAS - DIAN - ASÍ COMO RENDIR DECLARACIONES, ATENDER VISITAS E INSPECCIONES Y FIRMAS LAS CORRESPONDIENTES ACTAS ATENDER DIRECTAMENTE, CUANDO ELLO SEA REQUERIDO Y EN GENERAL OBRAR COMO APODERADO ESPECIAL ANTE LAS AUTORIDADES ADUANERAS EN TODAS LAS OPERACIONES RELACIONADAS CON EL COMERCIO EXTERIOR.

II. OTORGAR PODERES Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS SOCIEDADES PORTUARIAS DE BUENAVENTURA, CARTAGENA Y BARRANQUILLA, ASÍ COMO RESPONDER Y ATENDER LOS TRÁMITES DIRECTAMENTE O A TRAVÉS DE APODERADOS.

III- OTORGAR PODERES ESPECIALES Y GENERALES, OTORGAR GARANTÍAS Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS NAVIERAS Y EMPRESAS ADMINISTRADORAS DE CONTENEDORES PARA EL MANEJO Y RETIRO DE ELLOS.

IV. OTORGAR PODERES ESPECIALES Y GENERALES A LAS SOCIEDADES DE INTERMEDIACIÓN ADUANERA - SIA- Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN DE ACUERDA CON LA NORMATIVIDAD LEGAL SOBRE LA MATERIA.

V. SUSCRIBIR LAS CARTAS DE ANTINARCÓTICOS QUE SE PRESENTAN ANTE LA POLICÍA AEROPORTUARIA BIEN DIRECTAMENTE O AUTORIZANDO A LOS JEFES DE BODEGA DE YUMBO Y JAMUNDÍ PARA ESE TRÁMITE DOCUMENTOS DENTRO DE LOS TRÁMITES DE EXPORTACIONES O REEMBARQUES DE MERCANCÍAS, Y EN GENERAL ATENDER TODAS LAS DILIGENCIAS DIRECTAMENTE U OTORGAR PODER AUN TERCERO.

D. SUSCRIBIR CONTRATOS DE CONSTRUCCIÓN Y DE OBRA QUE SE REALICEN Y PRESTEN EN LAS PLANTAS DE TECNOQUÍMICAS S.A. LOCALIZADAS EN JAMUNDÍ, YUMBO Y VILLA RICA (DEPARTAMENTO DEL CAUCA EN EL CONJUNTO INDUSTRIAL PARQUESUR) HASTA POR LA SUMA EQUIVALENTE A TRESCIENTOS (300) SALARIOS MÍNIMOS LEGALES MENSUALES.

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E. SUSCRIBIR CONTRATOS, SIN LIMITACIÓN DE CUANTÍA QUE TENGA QUE VER CON LA ADQUISICIÓN DE EQUIPO Y MAQUINARIA, REPARACIÓN, ADECUACIÓN, INSTALACIÓN, SERVICIOS TÉCNICOS Y DE ASESORÍA.

E. SUSCRIBIR CONTRATOS DE FABRICACIÓN CON TERCEROS BIEN SEA QUE TECNOQUÍMICAS OBRE COMO FABRICANTE O COMO PROPIETARIO.

PARAGRAFO. EN LA ATENCIÓN DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

3. MARÍA TERESA CAÑON DE GUZMAN, IDENTIFICADA CON LA CÉDULA DE CIUDADANÍA NO. 31.238.104 DE CALI, CARLOS ARTURO PEÑA NIETO IDENTIFICADO CON LA CÉDULA DE CIUDADANÍA NO. 19.483.439 DE BOGOTÁ Y ÁNGELA MARÍA CORREA CARDONA IDENTIFICADA CON LA CÉDULA DE CIUDADANÍA NO. 66.835.555 DE CALI, LA PRIMERA COMO PRINCIPAL, EL SEGUNDO COMO PRIMER SUPLENTE Y LA TERCERA COMO SEGUNDA SUPLENTE, PARA QUE REPRESENTEN A TECNOQUÍMICAS S.A. EN:

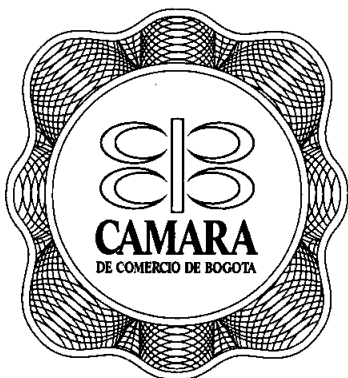
A. EN TODOS LOS ASUNTOS CAMBIARIOS, CON FACULTAD PARA FIRMAR DECLARACIONES DE CAMBIOS SEA POR CRÉDITOS EN MONEDA EXTRANJERA, POR MOVIMIENTOS DE LA CUENTAS CORRIENTES DE COMPENSACIÓN, IMPORTACIONES DE BIENES Y SERVICIOS, TRANSFERENCIAS Y OTROS CONCEPTOS, REGISTRO DE PRÉSTAMOS EN MONEDA EXTRANJERA OTORGADOS A LA EMPRESA EN SU CONDICIÓN DE RESIDENTE Y TODOS AQUELLOS DOCUMENTOS, DECLARACIONES O RESPUESTAS A REQUERIMIENTOS QUE DEBAN HACERSE ANTE EL BANCO DE LA REPÚBLICA U OTRAS ENTIDADES GUBERNAMENTALES RESPECTO DE OPERACIONES EN EL MERCADO CAMBIARIO.

LOS APODERADOS SUSCRIBIRÁN TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A LA SOCIEDAD ANTE LAS AUTORIDADES CAMBIARIAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL, PARA QUE ASUMAN LA PERSONERÍA A NOMBRE DE TECNOQUÍMICAS S.A., BIEN SEA DIRECTAMENTE O A TRAVÉS DE APODERADO, SIEMPRE QUE LO ESTIMEN CONVENIENTE, DE MANERA QUE EN NINGÚN CASO QUEDE SIN LA DEBIDA REPRESENTACIÓN EN LA SALVAGUARDIA DE SUS DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES DE CARÁCTER CAMBIARIO Y EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER.

B. EN RELACIÓN CON SECTOR FINANCIERO:

I. SUSCRIBIR LOS CONTRATOS DE CRÉDITO Y LEASING CON LOS BANCOS, ENTIDADES FINANCIERAS, COMPAÑÍAS DE FINANCIAMIENTO COMERCIAL, DE ACUERDO CON LOS CUPOS

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FIJADOS POR LA JUNTA DIRECTIVA, ASÍ COMO LOS PAGARÉS, LOS CONTRATOS DE GARANTÍA PRENDARIA E HIPOTECARIA, LA CONFIRMACIÓN DE FORWARDS Y TODOS LOS DEMÁS DOCUMENTOS QUE SEAN REQUERIDOS PARA LA CULMINACIÓN Y FORMALIZACIÓN DE ESTOS TRÁMITES.

ESTAS FACULTADES IGUALMENTE APLICAN PARA TODOS LOS CRÉDITOS QUE OTORQUE EL BANCO DE COMERCIO EXTERIOR DE COLOMBIA - BANCOLDEX.

II. SUSCRIBIR LOS FORMATOS Y CONTRATOS DE APERTURAS DE CUENTAS CORRIENTES, AHORROS, SERVICIOS DE BANCA VIRTUAL, LOS FORMATOS DE PROVEEDORES PARA PAGOS POR TRANSFERENCIA ELECTRÓNICA Y LOS FORMULADOS ÚNICOS DE CONOCIMIENTO DE PERSONA JURÍDICA QUE EXIGE EL SECTOR FINANCIERO.

III. SUSCRIBIR LAS LETRAS DE COBRANZA Y LAS CARTAS DE CRÉDITO.

C. SOLICITAR TIDIS Y FIRMAR TODOS LOS DOCUMENTOS RELACIONADOS CON ESTE TRÁMITE.

D. EN RELACIÓN CON LA COMPAÑÍAS ASEGURADORAS:

I. SUSCRIBIR DOCUMENTOS DE RECLAMACIÓN Y OTORGAR PODERES PARA QUE COMPAREZCAN A LAS AUDIENCIAS DE RECLAMACIONES, ASÍ COMO LOS DOCUMENTOS DE TRANSACCIÓN. ESTAS FACULTADES SE OTORGAN SIN LIMITACIÓN DE CUANTÍA.

II. SUSCRIBIR LAS CARTAS DE NO RECLAMACIÓN A LAS COMPAÑÍAS ASEGURADORAS POR OCURRENCIA DE SINIESTROS Y LAS RESPECTIVAS CONSTANCIAS.

III. SUSCRIBIR LOS DOCUMENTOS REQUERIDOS POR EL SISTEMA DE INFORMACIÓN PARA LA PREVENCIÓN DE LAVADO DE ACTIVOS (SIPLA).

E. FORMULAR PETICIONES RELACIONADAS CON LAS FACULTADES OTORGADAS.

PARÁGRAFO 1. EN LA ATENCIÓN DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL O GUBERNATIVO.

PARÁGRAFO II. LOS APODERADOS EJERCERÁN SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACIÓN.

4. ADRIANA JIMÉNEZ MERA, IDENTIFICADA CON LA C.C. 31.174.077 DE PALMIRA, PARA EL DESARROLLO DE LAS SIGUIENTES FUNCIONES:

A. OTORGAR PODER Y CONSTITUIR MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACIÓN DE LA CARTERA, SIN LIMITACION DE CUANTÍA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACIÓN, CON AUTORIZACIÓN PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE

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INTERVENGA EN ASUNTOS RELACIONADOS CON LAS DEUDAS A FAVOR DE TECNOQUÍMICAS S.

A.

B. SUSCRIBIR LOS CONTRATOS DE ARRENDAMIENTO DE INMUEBLES, SU MODIFICACIÓN Y O TERMINACIÓN, INVENTARIOS Y ANEXOS PERTINENTES, BIEN SEA QUE LA SOCIEDAD OBRE COMO ARRENDADOR O ARRENDATARIO, SIN LIMITACIÓN DE CUANTÍA. ESTA FUNCIÓN LA PODRÁ EJERCER DIRECTAMENTE O MEDIANTE LA DESIGNACIÓN DE APODERADOS.

C. SUSCRIBIR LOS FORMATOS DE AUTORIZACIÓN DE CREACIÓN DE CLIENTES Y PROVEEDORES DE LA EMPRESA.

D. EN RELACIÓN CON LOS VEHÍCULOS DE TODO TIPO QUE FIGUREN A NOMBRE DE TECNOQUÍMICAS, TIENE LA FACULTAD DE SUSCRIBIR LOS FORMULARIOS OFICIALES PARA TODO TIPO DE TRAMITE, ENTRE ELLOS EL TRASPASO, QUE SE REQUIERA REALIZAR, ANTE LAS SECRETARIAS DE TRANSITO Y ANTE LAS AUTORIDADES DE TRANSITO Y TRANSPORTE DE CUALQUIER ORDEN, ASÍ COMO FIRMAR TODO TIPO DE CONTRATOS RELACIONADOS CON LOS VEHÍCULOS.

PARÁGRAFO. EN LA ATENCIÓN DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

ESTOS PODERES ESTARÁN VIGENTES HASTA TANTO SEAN REVOCADOS O MODIFICADOS
EXPRESAMENTE POR DOCUMENTO PRIVADO.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 10 DE JULY DE 2008 DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 29 DE JULY DE 2008 BAJO EL NRO. 141 DEL LIBRO V , SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A LOS SIGUIENTES FUNCIONARIOS DE LA EMPRESA:

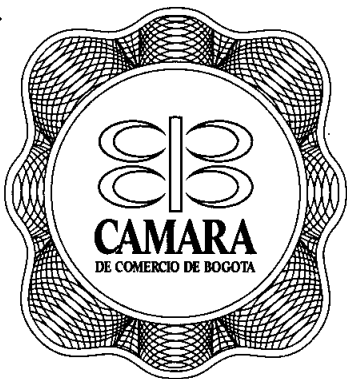
- GERMAN ALBERTO SUAREZ HINCAPIE, C.C. 16.722.521 DE CALI, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL CENTRO PACIFICO DE LA SOCIEDAD, CON SEDE EN CALI.

- MARIA VICTORIA VARGAS PORRAS, C.C. 39.638.185 DE BOGOTA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA D.C.

- ESPERANZA GRANADOS JAIMES, C.C. 63.392.189 DE MALAGA (SANTANDER), SUBGERENTE ADMINISTRATIVO DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA D.C.

- DIEGO FERNANDO MUÑOZ QUINTERO, C.C. 94.282.452 DE CALI, SUBGERENTE

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FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ANTIOQUIA DE LA SOCIEDAD, CON SEDE EN MEDELLIN.

- CARLOS ORLANDO MUTIS PICON, C.C. 91.200.418 DE BUCARAMANGA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ORIENTE DE LA SOCIEDAD, CON SEDE EN BUCARAMANGA.

- DANIEL AMEZQUITA LIZARAZO, C.C. 8.681.962 DE BARRANQUILLA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ATLANTICO DE LA SOCIEDAD, CON SEDE EN BARRANQUILLA.

LOS MENCIONADOS FUNCIONARIOS EJERCERAN, EN SUS RESPECTIVAS REGIONALES, LAS SIGUIENTES FACULTADES:

1.PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A., Y EN ASUNTOS QUE TENGA QUE VER CON SUS RESPECTIVOS DISTRITOS DE VENTAS SE NOTIFIQUEN Y PROMUEVAN ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES, DISTRITALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE.

PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES.

2.PARA QUE OTORGUEN PODERES Y CONSTITUYAN MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION E INTERROGATORIOS DE PARTE, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVOS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO, CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR.

3.PARA QUE OTORQUE PODERES Y CONSTITUYAN MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON

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EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LOS INTERROGATORIOS DE PARTE, A LAS DIVERSAS AUDIENCIAS, ENTRE ELLAS LAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES, JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO.

4.PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO Y EXPEDIR CERTIFICACIONES LABORALES.

5.PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A., EN NINGUN CASO, QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES Y A ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DILIGENCIAS DE INTERROGATORIOS DE PARTE.

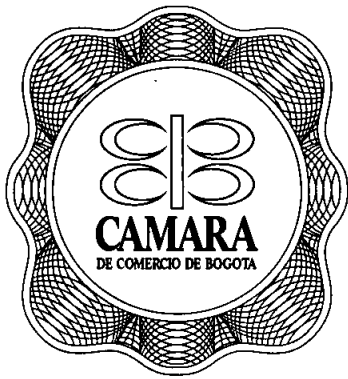
6.SUSCRIBIR LOS CONTRATOS DE PRENDA SOBRE VEHICULOS DE PROPIEDAD DE TERCEROS PARA RESPALDAR LOS PRESTAMOS QUE LA EMPRESA OTORQUE Y TODO LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA SU FORMALIZACION ANTE LAS SECRETARIAS DE TRANSITO Y/O MOVILIDAD DE LOS RESPECTIVOS MUNICIPIOS. ESTE PODER TAMBIEN COMPRENDE LA CANCELACION DE LAS PRENDAS Y LA FIRMA DE TODOS LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA TAL FIN.

7.PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO ADQUIERA Y ENAJENE TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. ESTOS PODERES ESTARAN VIGENTES HASTA TANTO SEAN REVOCADOS O MODIFICADOS EXPRESAMENTE POR DOCUMENTO PRIVADO.

CERTIFICA:

QUE POR ESCRITURA NRO. 1853 DEL 07 DE MAY DE 2009 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 15 DE MAY DE 2009 BAJO EL NRO. 64 DEL LIBRO V SE CONCEDIO PODER ESPECIAL AMPLIO Y SUFICIENTE A ANTONIO JAIRO RAMIREZ ECHAVE, IDENTIFICADO CON LA CÉDULA DE CIUDADANÍA NO.16 741 040 DE CALI Y PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No.58 401 DEL C.S DE LA J. , Y/O A BEATRIZ EUGENIA TORRES HURTADO, IDENTIFICADA. CON LA CEDULA DE CIUDADANIA NO 1.130.672.089 DE CALI Y PORTADORA DE LA TARJETA PROFESIONAL DE ABOGADA No. 168

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064 DEL C. S. DE LA J. PARA QUE, CONJUNTAMENTE O POR SEPARADO, REPRESENTEN A LA SOCIEDAD EN TODOS LOS ASUNTOS QUE DEBAN TRAMITARSE ANTE: A) EL INSTITUTO NACIONAL DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA, O LAS OFICINAS O AUTORIDADES NACIONALES QUE CORRESPONDAN, INCLUIDO, PERO SIN LIMITARSE A TODO LO RELACIONADO CON EL TRÁMITE DE OBTENCIÓN, RENOVACIÓN, MODIFICACIÓN Y CERTIFICACIÓN DE REGISTROS SANITARIOS, RESPUESTAS DE AUTOS, CAMBIOS DE NOMBRE Y MARCAS DE PRODUCTOS, REFORMULACIONES Y ADICIONES EN LA LÍNEA DE PRODUCTOS, CAMBIOS DE IMPORTADOR Y FABRICANTE, CESIONES DE REGISTROS SANITARIOS, CERTIFICACIONES DE FÓRMULA Y EXCLUSIVIDAD, MODIFICACIONES EN LA MODALIDAD DEL REGISTRO SANITARIO, RENUNCIAS A REGISTROS SANITARIOS, DESISTIMIENTOS DE TRÁMITES, CERTIFICACIONES SOBRE LA LÍNEA COMPLETA DE PRODUCTOS, LICENCIAS DE FUNCIONAMIENTO DE LAS PLANTAS, CERTIFICADOS DE BUENAS PRÁCTICAS DE MANUFACTURA (BPM), CERTIFICADOS DE CAPACIDAD Y DE NORMAS TÉCNICAS DE FABRICACIÓN, CERTIFICACIONES DE EXCLUSIÓN DE IVA, TRÁMITES DE SOLICITUD DE AUTORIZACIÓN DE PUBLICIDAD Y RECURSOS ANTE EL COMITÉ DE PUBLICIDAD Y LA COMISIÓN REVISORA, SUSCRIPCIÓN DE ACTAS DE VISITA, ASÍ COMO RESPONDER REQUERIMIENTOS POR QUEJAS O INVESTIGACIONES QUE HAGA LA SUBDIRECCIÓN DE VIGILANCIA Y CONTROL DEL INVIMA, O CUALQUIERA DE SUS DEPENDENCIAS Y DE LAS DEMÁS ENTIDADES; LOS APODERADOS QUEDAN IGUALMENTE FACULTADOS PARA ELEVAR SOLICITUDES, PETICIONES, RECLAMACIONES, FORMULAR ENMIENDAS, PRESENTAR RECURSOS; OPOSICIONES, SOLICITUDES DE CORRECCIÓN, SOLICITUD DE CONCEPTOS, PRESENTAR DENUNCIAS, ABONAR TODOS LOS IMPUESTOS Y CUOTAS, Y EFECTUAR TODOS LOS PAGOS DETERMINADOS POR LA LEY, RECIBIR TODOS LOS DOCUMENTOS Y VALORES, LLENAR CUALQUIER OTRO REQUISITO, TOMAR TODAS LAS MEDIDAS QUE CREYEREN CONDUCTENTES AL RESGUARDO DE LOS DERECHOS E INTERESES DE ÉSTA COMPAÑÍA, RECIBIR, NOTIFICARSE Y NOMBRAR APODERADOS JUDICIALES Y EXTRAJUDICIALES Y EN GENERAL PARA ADELANTAR CUALQUIER TRÁMITE QUE SE REQUIERA ANTE EL INSTITUTO Y SUS DEPENDENCIAS, O ANTE LA OFICINA O AUTORIDAD QUE CORRESPONDA. B) LA DIRECCIÓN NACIONAL DE ESTUPEFACIENTES, INCLUIDO PERO SIN LIMITARSE A LA SOLICITUD DE AUTORIZACIÓN DE CUPOS DE SUSTANCIAS CONTROLADAS, SOLICITUDES DE CORRECCIÓN DE RESOLUCIONES, DESISTIMIENTOS DE TRÁMITES Y SOLICITUDES, ACLARACIONES, RESPUESTAS A REQUERIMIENTOS SOLICITUD DE CONCEPTOS Y EN GENERAL CUALQUIER TRÁMITE QUE SEA NECESARIO ADELANTAR ANTE ÉSTA ENTIDAD O LA QUE HAGA SUS VECES. C) FONDO NACIONAL DE ESTUPEFACIENTES, INCLUIDO PERO SIN LIMITARSE A LOS TRÁMITES NECESARIOS PARA LA APROBACIÓN DE COMPRA DE MEDICAMENTOS Y MATERIAS PRIMAS DE

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CONTROL ESPECIAL, ELEVAR SOLICITUDES DE CORRECCIÓN DE RESOLUCIONES, DESISTIMIENTOS, ACLARACIONES, RESPUESTAS A REQUERIMIENTOS, SOLICITUD DE CONCEPTOS Y EN GENERAL CUALQUIER TRÁMITE QUE SEA NECESARIO ADELANTAR ANTE ÉSTA ENTIDAD O LA QUE HAGA SUS VECES. D) EMPRESA TERRITORIAL PARA LA SALUD.-ETESA, INCLUIDO PERO SIN LIMITARSE A LA SOLICITUD DE NO OBJECCIÓN PARA LA REALIZACIÓN DE ACTIVIDADES PROMOCIONALES CONSISTENTES EN JUEGOS DE SUERTE Y AZAR QUE REALICE LA COMPAÑÍA CON EL FIN DE IMPULSAR SUS VENTAS, RESPONDER REQUERIMIENTOS, HACER ACLARACIONES, PRESENTAR RECURSOS, SOLICITAR CONCEPTOS Y EN GENERAL CUALQUIER TRÁMITE Y SOLICITUD QUE SEA NECESARIO ADELANTAR ANTE ÉSTA ENTIDAD O LA QUE HAGA SUS VECES, E) INSTITUTO COLÓMBIANO AGROPECUARIO Y MINISTERIO DE MEDIO AMBIENTE, INCLUIDO PERO SIN LIMITARSE A LA SOLICITUD DE - LICENCIAS, AUTORIZACIONES PARA IMPORTAR OBTENCIÓN DE REGISTROS, SOLICITUD DE CONTESTAR REQUERIMIÉNTOS, SUMINISTRAR INFORMACIÓN REQUERIDA, SOLICITAR CONCEPTOS Y EN GENERAL CUALQUIER TRÁMITE Y SOLICITUD QUE SEA NECESARIO ADELANTAR ANTE ÉSTA ENTIDAD O LA QUE HAGA SUS VECES F) MINISTERIO DE PROTECCIÓN SOCIAL, SECRETARÍAS DE SALUD E INSTITUTO NACIONAL DE SALUD, INCLUIDO PERO SIN LIMITARSE A LA PRESENTACIÓN DE CUALQUIER SOLICITUD DE APERTURA DE INVESTIGACIÓN, SOLICITUD CONCEPTO, RESPONDER REQUERIMIENTOS POR QUEJAS O INVESTIGACIONES Y DEMÁS SOLICITUDES Y TRÁMITES QUE DEBAN ADELANTARSE ANTE ÉSTAS ENTIDADES O LAS QUE HAGAN SUS VECES. G) CUALQUIER ENTIDAD DEL ORDEN NACIONAL, LOCAL O MUNICIPAL, QUE HAGA REQUERIMIENTOS O SOLICITE ACLARACIONES A LA COMPAÑÍA EN EL CURSO DE CUALQUIER TIPO DE TRÁMITE ADMINISTRATIVO, PARA LO CUAL LOS APODERADOS QUEDAN DEBIDAMENTE FACULTADOS PARA CONTESTAR Y ACLARAR Y SOLICITAR TODO CUANTO SEA DEBIDO PARA EFECTOS DE TODO LO ANTERIOR, FACULTO A LOS APODERADOS AQUÍ NOMBRADOS, PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS PASOS NECEDARIOS, PRESENTAR SOLICITUDE, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPLOTACIONES, SOLICITAR TESTIMONIOS, RECIBIR DOCUMENTOS, FORMULAR TODOS LOS RECURSOS QUE SEAN PROCEDENTES, PETICIONES, RECLAMOS CON ATRIBUCIONES PARA DESISTIR Y CONCILIAR, OTORGAR PODERES, SUSTITUIRLOS. ASÍ MISMO, LOS APODERADOS ESTÁN AUTORIZADOS PARA HACER CUANTO FUERE NECESARIO ANTE LAS AUTORIDADES ADMINISTRATIVAS PARA LOS FINES ARRIBA INDICADOS CON TODAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE FUEREN NECESARIAS, PUDIENDO ATENDER ASÍ MISMO LAS NOTIFICACIONES QUE DIRECTA O INDIRECTAMENTE SE GENEREN DE LOS ACTOS, ACTUACIONES, DILIGENCIAS O GESTIONES QUE TENGAN RELACIÓN DE CAUSALIDAD POR LOS SUSODICHOS TRÁMITES. LA ACEPTACION DE LA GESTION POR PARTE

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DE ANTONIO JAIRO RAMIREZ ECHAVE Y BEATRIZ EUGENIA TORRES HURTADO SE ENTENDERÁ PRESTADA CON EL DOCUMENTO EN QUE SOLICITEN CADA TRAMITE ANTE LA ENTIDAD RESPECTIVA. ESTE MANDATO SE OTORGA POR TÉRMINO INDEFINIDO.

CERTIFICA:

QUE POR ESCRITURA NRO. 2687 DEL 26 DE JUNE DE 2009 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 06 DE JULY DE 2009 BAJO EL NRO. 103 DEL LIBRO V SE OTORGO PODER GENERAL, AMPLIO Y SUFICIENTE PARA ATENDER LOS ASUNTOS DESCRITOS A LAS SIGUIENTES

PERSONAS:

PRIMERO: A ANTONIO JAIRO ECHAVE, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NO 16.741.040 DE CALI Y PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO NO. 58.401 DEL C.S DE LA J., Y/O A ANÁ MARÍA ALVAREZ ROBLEDO., CON C.C. 31.170.896 DE CALI, PARA QUE DE MANERA CONJUNTA O SEPARADA EJERZAN LAS SIGUIENTES FACULTADE EN NOMBRE DE TECNOQUIMICAS S.A.:

1. REPRESENTAR A LA SOCIEDAD, SIN LIMITACIÓN ALGUNA EN TODAS LAS LICITACIONES PÚBLICAS, PRIVADAS O DE CUALQUIER OTRA MODALIDAD DE CONTRATACIÓN EN QUE ESTÉ INTERESADA PARTICIPAR TECNOQUÍMICAS S.A. ESTA FACULTAD COMPRENDE LA DE PRESENTAR PROPUESTAS, ACEPTAR ADJUDICACIONES, FIRMAR TODOS LOS ANEXOS QUE SEAN REQUERIDOS DENTRO DEL RESPECTIVO PROCESO LICITATORIO (TALES COMO CARTA DE PRESENTACIÓN, FORMATOS DE KÁRDEX, PROPUESTAS ECONÓMICAS, FORMATOS TÉCNICOS, ETC) Y DEMÁS DOCUMENTOS QUE REQUIERAN LA FIRMA DEL REPRESENTANTE LEGAL.
2. FORMULAR Y SUSCRIBIR LAS OBSERVACIONES QUE SE HAGAN A LOS PLIEGOS DE LAS LICITACIONES Y PARTICIPAR EN TODOS LOS TRÁMITES QUE ANTECEDAN A LA APERTURA DE LAS LICITACIONES, ASÍ COMO LA DE INTERPONER TODOS LOS RECURSOS QUE SEAN PROCEDENTES EN LA VÍA GUBERNATIVA E INICIAR LAS ACCIONES QUE SEAN PROCEDENTES ANTE LA JURISDICCIÓN CONTENCIOSA ADMINISTRATIVA CON FACULTADES PARA DESIGNAR APODERADOS PARA LA ATENCIÓN DE ELLOS.
3. CONTRATAR Y FIRMAR TODAS LAS PÓLIZAS QUE SE REQUIERAN PARA CONCURRIR A LAS LICITACIONES Y PARA FIRMAR Y FORMALIZAR LOS CONTRATOS QUE SEAN ADJUDICADOS A LA SOCIEDAD.
4. SUSCRIBIR LAS MODIFICACIONES, CORRECCIONES Y ACLARACIONES DE LOS CONTRATOS ASÍ COMO LAS ACTAS DE LIQUIDACIÓN DE ELLOS.
5. INSCRIBIR A LA SOCIEDAD Y RENOVAR SU REGISTRO UNICO DE PROPONENTES -RUP- O DE LA FIGURA QUE LA SUSTITUYA O MODIFIQUE.

LOS APODERADOS EJERCERÁN ESTAS ATRIBUCIONES DE MANERA INDEPENDIENTE SIN QUE SE

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REQUIERA LA FIRMA CONJUNTA PARA LA ATENCIÓN DE LOS ASUNTOS ENCOMENDADOS.

SEGUNDO: A ANTONIO JAIRO RAMÍREZ ECHAVE, IDENTIFICADO CON LA CÉDULA DE CIUDADANÍA NO. 16.741.040 DE CALI Y PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO NO. 58.401 DEL C.S DE LA J., Y/O RODRIGO VELÁSQUEZ LÓPEZ, CON CÉDULA NO. 16.589.361 DE CALI Y PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO NO. 27037 DEL CONSEJO SUPERIOR DE LA JUDICATURA, PARA QUE DE MANERA CONJUNTA O SEPARADA EJERZAN LAS SIGUIENTES FACULTADES EN NOMBRE DE TECNOQUÍMICAS SA.:

1. NOTIFICARSE, CONTESTAR DEMANDAS O REQUERIMIENTOS, CONCILIAR, DESISTIR, ALLANARSE EN CUALQUIER PROCESO JUDICIAL, ADMINISTRATIVO O GUBERNATIVO, SIN IMPORTAR LA CUANTIA NI LA NATURALEZA DE LA ACCIÓN, QUE SE LE FORMULE A TECNOQUÍMICAS, BIEN SEA POR PERSONA NATURAL, JURÍDICA, EMPRESA INDUSTRIAL Y COMERCIAL DEL ESTADO, ESTABLECIMIENTOS PÚBLICOS Y/O ENTIDADES GUBERNATIVAS DE CUALQUIER ORDEN, EN LA QUE LA EMPRESA TENGA INTERÉS COMO ACTOR, DEMANDADO, TERCERO INTERVINIENTE O LLAMADO EN GARANTÍA Y/O EN CUALQUIER MODALIDAD PROCESAL EN QUE SEA VINCULADA.

2. ASISTIR A LAS AUDIENCIAS DE CONCILIACIÓN EN LA QUE SEA CONVOCADA LA EMPRESA COMO PARTE DEMANDANTE O DEMANDADA, CON PLENAS FACULTADES PARA CONCILIAR, DESISTIR, ALLANARSE Y COMPROMETER.

3. REPRESENTAR A LA SOCIEDAD PARA ATENDER LAS DILIGENCIAS DE DECLARACIÓN DE PARTE EN CUALQUIER PROCESO JUDICIAL O TRÁMITE GUBERNATIVO AL QUE SEAN CONVOCADO EL REPRESENTANTE LEGAL DE LA SOCIEDAD.

4. INICIAR TODA CLASE DE PROCESOS Y TRÁMITES ANTE LA AUTORIDADES JUDICIALES O GUBERNATIVAS EN LA QUE LA SOCIEDAD TENGA INTERÉS.

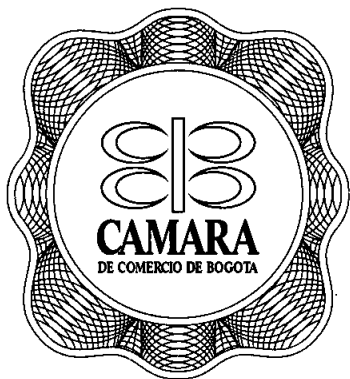
PARAGRAFO: PARA EL EJERCICIO DE LAS FACULTADES PREVISTAS EN LOS NUMERALES 1 Y 4 PODRÁN OTORGAR PODER A TERCEROS PARA LA ATENCIÓN DE LOS ASUNTOS MENCIONADOS.

TERCERO. LA ACEPTACIÓN DE LA GESTIÓN POR PARTE DE ANTONIO JAIRO RAMÍREZ ECHAVE, ANA MARÍA ALVAREZ Y RODRIGO VELÁSQUEZ LÓPEZ SE ENTENDERÁ PRESTADA CON EL EJERCICIO DE LAS FACULTADES CONFERIDAS Y/O LA SUSCRIPCIÓN DE LOS DOCUMENTOS.

ESTE MANDATO SE OTORGA POR TERMINO INDEFINIDO.

COMPARECEN ANTONIO JAIRO RAMIREZ ECHAVE CON DOMICILIO Y RESIDENCIA EN LA CIUDAD DE CALI, IDENTIFICADO CON LA C.C. NO. 16.741.040 DE CALI, ANA MARÍA ALVAREZ ROBLEDO CON C.C. 31.170.896 DE CALI Y RODRIGO VELASQUEZ LOPEZ, CON C. C. 16.589.361 DE CALI, Y MANIFIESTAN QUE ACEPTAN EL PODER GENERAL QUE SE LES

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/12/28

HORA: 17:17:44

OPERACION: 02XMA1228173

PAGINA: 31

CONFIERE POR ÉSTE INSTRUMENTO.
CERTIFICA:

CAPITAL AUTORIZADO: \$27,200,000,000
NUMERO DE ACCIONES: 54,400,000
VALOR NOMINAL: \$500
CAPITAL SUSCRITO: \$21,792,754,000
NUMERO DE ACCIONES: 43,585,508
VALOR NOMINAL: \$500
CAPITAL PAGADO: \$21,792,754,000
NUMERO DE ACCIONES: 43,585,508
VALOR NOMINAL: \$500

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 12 DE MARZO DE 2009
INSCRIPCION: 18 DE MARZO DE 2009 BAJO EL NRO. 3193 DEL LIBRO IX
CONSTA LA SITUACION DE CONTROL
SOCIEDAD CONTROLANTE
DENOMINACION: INVERSIONES TQ S.A.
NIT. 900.220.408-1
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE INVERSIONES TQ S.A. CORRESPONDEN A LA INVERSION EN SOCIEDADES MERCANTILES DE CUALQUIER NATURALEZA O ESPECIE, BIEN SEA NACIONALES O EXTRANJERAS QUE TENGAN COMO OBJETO SOCIAL LA FABRICACION, ENVASADO, DISTRIBUCION Y COMERCIALIZACION EN GENERAL DE PRODUCTOS BIOLOGICOS Y QUIMICOS; MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR; PRODUCTOS VETERINARIOS, AGRICOLAS; ALIMENTOS NATURALES O PROCESADOS; PRODUCTOS DE CONSUMO POPULAR Y SERVICIOS EN GENERAL.

SOCIEDAD CONTROLADA
DENOMINACION: TECNOQUIMICAS S.A.
NIT. 890.300.466-5
DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE TECNOQUIMICAS CORRESPONDEN A LA FABRICACION, EL ENVASADO, LA IMPORTACION, LA EXPORTACION, LA VENTA Y DISTRIBUCION DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/12/28

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EFFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS Y PRODUCTO DE CONSUMO POPULAR DE CUALQUIER NATURALEZA.

SUBORDINACION. INVERSIONES TQ S.A. TIENE SUSCRITAS Y PAGADAS ACCIONES EN TECNOQUIMICAS S.A. EN PORCENTAJE EQUIVALENTE AL 94.90% DEL CAPITAL SUSCRITO Y PAGADO DE DICHA SOCIEDAD, LO QUE CONFIGURA SITUACION DE SUBORDINACION EN LA QUE LA PRIMERA ES LA MATRIZ Y LA SEGUNDA LA FILIAL.

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 14 DE SEPTIEMBRE 2009

INSCRIPCIÓN: 18 DE SEPTIEMBRE DE 2009 NRO.10818 DEL LIBRO IX

CONSTA EL GRUPO EMPRESARIAL:

MATRIZ: TECNOQUÍMICAS S.A.

NIT: 890300466-5

DOMICILIO: SANTIAGO DE CALI.

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: DEDICADA A LAS SIGUIENTES ACTIVIDADES: LA FABRICACIÓN, EL ENVASADO, LA IMPORTACIÓN, LA EXPORTACIÓN, LA VENTA Y DISTRIBUCIÓN DE PRODUCTOS BIOLÓGICOS Y QUÍMICOS, MEDICAMENTOS O PRODUCTOS FARMACÉUTICOS, PERFUMERÍA O EFFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS Y PRODUCTO DE CONSUMO POPULAR DE CUALQUIER NATURALEZA.

SUBORDINADA: ADHESIVOS INTERNACIONALES S.A.-ADHINTER S.A.

NIT: 805003416-4

DOMICILIO: CALI VALLE DEL CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LA CUAL DESARROLLA LAS SIGUIENTES ACTIVIDADES: PRODUCCIÓN Y COMERCIALIZACIÓN EN EL MERCADO NACIONAL E INTERNACIONAL DE ADHESIVOS MEDICINALES TALES COMO CURAS, VENDITAS, ESPARADRAPOS, PARCHES, VENDAS; ADHESIVOS PARA USO EN OFICINA TALES COMO CINTAS, PEGANTES, PAPELES ADHESIVOS; Y CINTAS ADHESIVAS PARA USO INDUSTRIAL.

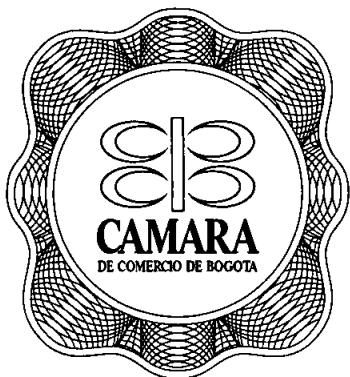
PRESUPUESTO DE CONTROL: TECNOQUIMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD ADHESIVOS INTERNACIONALES S.A.-ADHINTER S.A. Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26,27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: INDUGRAFICAS S A S

NIT: 890304375-1

DOMICILIO: CALI, VALLE DEL CAUCA.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/12/28

HORA: 17:17:44

OPERACION: 02XMA1228173

PAGINA: 33

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN AL DESARROLLO DE NEGOCIOS RELACIONADOS CON LAS ARTES GRÁFICAS, LA DISTRIBUCIÓN DE LAS MISMAS YA SEA DE SUS PRODUCTOS PROPIOS O POR CONTRATO, TANTO EN EL MERCADO NACIONAL COMO EN EL INTERNACIONAL.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD INDUGRAFICAS S A S Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26,27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: TECNOFAR TQ SAS

NIT: 817003055

DOMICILIO: VILLA RICA, CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN A LA PRODUCCIÓN Y COMERCIALIZACIÓN DE MEDICAMENTOS, FARMACÉUTICOS, BIOLÓGICOS, COSMÉTICOS Y ARTÍCULOS DE TOCADOR, QUÍMICOS, VETERINARIOS, AGRÍCOLAS, PRODUCTOS DE ASEO PARA EL HOGAR Y ENVASES PLÁSTICOS PARA TODO TIPO DE USO.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD TECNOFAR TQ S A S Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26,27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: COLOMBIANA DE ADHESIVOS COLDESIVOS S.A.S

NIT: 890302608-3

DOMICILIO: CALI, VALLE DEL CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES CORRESPONDIENTES A LA FABRICACIÓN, IMPORTACIÓN Y EXPORTACIÓN DE PRODUCTOS ADHESIVOS, ABRASIVOS Y AISLANTES Y DE CONSUMO POPULAR.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD COLOMBIANA DE ADHESIVOS COLDESIVOS S.A.S. Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26,27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: TECNOQUÍMICAS DE ECUADOR S.A

DOMICILIO: DISTRITO METROPOLITANO DE QUITO, REPÚBLICA DE ECUADOR

NACIONALIDAD: ECUATORIANA

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/12/28

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OPERACION: 02XMA1228173

PAGINA: 34

ACTIVIDAD: LA CUAL DESARROLLA LAS ACTIVIDADES DE VENTA AL POR MAYOR DE PRODUCTOS FARMACÉUTICOS, VETERINARIOS Y AGRÍCOLAS, DE SUSTANCIAS ADHESIVAS, COSMÉTICAS Y DE HIGIENE Y DE PRODUCTOS QUÍMICOS ORGÁNICOS E INORGÁNICOS.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD TECNOQUIMICAS DE ECUADOR S.A. Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26,27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: LABORATORIOS TERAMED S.A DE C.V.

DOMICILIO: SAN SALVADOR

NACIONALIDAD: SALVADOREÑA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN A LA PRODUCCIÓN Y COMERCIALIZACIÓN DE MEDICAMENTOS Y PRODUCTOS BIOLÓGICOS PARA CONSUMO HUMANO.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD LABORATORIOS TERAMED S.A DE C.V. Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26, 27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: DISTRIBUIDORA PRINCIPAL S.A DE C.V.

DOMICILIO: SAN SALVADOR

NACIONALIDAD: SALVADOREÑA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN A LA COMERCIALIZACIÓN Y DISTRIBUCIÓN DE MEDICAMENTOS Y PRODUCTOS BIOLÓGICOS PARA CONSUMO HUMANO.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD DISTRIBUIDORA PRINCIPAL S.A DE C.V Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26, 27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: GALEMI S.A. DE C.V

DOMICILIO: SAN SALVADOR

NACIONALIDAD: SALVADOREÑA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN A LA COMERCIALIZACIÓN Y DISTRIBUCIÓN DE MEDICAMENTOS Y PRODUCTOS BIOLÓGICOS PARA CONSUMO HUMANO.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD GALEMI S.A DE C.V. Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26, 27, Y

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/12/28

HORA: 17:17:44

OPERACION: 02XMA1228173

PAGINA: 35

28 DE LA LEY 222 DE 1995

SUBORDINADA: DROGUERÍA FARMACÉUTICA MONTREAL S.A.

DOMICILIO: GUATEMALA

NACIONALIDAD: GUATEMALTECA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN A LA COMERCIALIZACIÓN Y DISTRIBUCIÓN DE MEDICAMENTOS Y PRODUCTOS BIOLÓGICOS PARA CONSUMO HUMANO

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD DROGUERÍA FARMACÉUTICA MONTREAL S.A Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26, 27, Y 28 DE LA LEY 222 DE 1995

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.7050-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS

UBICADO EN: CL. 23 NRO. 7 39 DE CALI

RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.311235-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS

UBICADO EN: CL. 23 NRO. 4 66 DE CALI

FECHA MATRICULA : 22 DE APRIL DE 1992

RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.606730-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A JAMUNDI

UBICADO EN: --CARRETERA JAMUNDI KM. 23 DE JAMUNDI

FECHA MATRICULA : 14 DE APRIL DE 2003

RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.606736-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A YUMBO

UBICADO EN: --CL. 15 NRO. 30 98 AUTOPISTA CALI-YUMBO KILOMETRO 4 DE YUMBO

FECHA MATRICULA : 14 DE APRIL DE 2003

RENOVO : POR EL AÑO 2009

CERTIFICA:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/12/28

HORA: 17:17:44

OPERACION: 02XMA1228173

PAGINA: 36

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.754339-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS MK FEMME
UBICADO EN: CL. 23 NRO. 7 34 DE CALI
FECHA MATRICULA : 19 DE DECEMBER DE 2008
RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.754340-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS MK
UBICADO EN: CL. 23 NRO. 7 34 DE CALI
FECHA MATRICULA : 19 DE DECEMBER DE 2008
RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.754341-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS MK VISION
UBICADO EN: CL. 23 NRO. 7 34 DE CALI
FECHA MATRICULA : 19 DE DECEMBER DE 2008
RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.754342-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS MK CARDIO
UBICADO EN: CL. 23 NRO. 7 34 DE CALI
FECHA MATRICULA : 19 DE DECEMBER DE 2008
RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.761356-2 ESTABLECIMIENTO DE COMERCIO: ALMACEN VENTA A EMPLEADOS
UBICADO EN: CL. 23 NRO. 6 65 DE CALI
FECHA MATRICULA : 30 DE MARCH DE 2009

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 30 DE
MARCH DE 2009 .

CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL
PRESENTE CERTIFICADO.

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES

*** CONTINUA ***

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 97.816
FECHA : DICIEMBRE 29 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-053058- -00004-0000

Fecha: 2009-12-29 13:47:09 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVIER Folios: 126

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	169669544	29/12/2009	574,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES ✓	
		12 MARCAS Y LEAS COMERCIALES	287,000.00
		TOTAL :	287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No.09-053058

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **608** DE
FECHA **30 DE SEPTIEMBRE DE 2009** EL TÉRMINO HÁBIL SEÑALADO POR
LA LEY EXPIRA EL **30 DE DICIEMBRE DEL 2009**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ☒ X _____

NO__

2020
Bogotá, D.C.,

Doctor:
Álvaro Correa Ordóñez
Apoderado

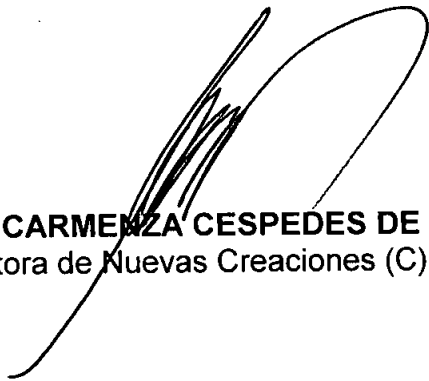
Oficio N°: 2584

ASUNTO:	Radicación PCT N°	09-53058
	Trámite	011
	Evento	379
	Actuación	440
	Folios	106

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

26 FEB. 2010

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021