

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicación: 92009167 00000006 Folios: 134
Fecha (AMB): 2004-10-22 16:46:03
Trámite: 811 PCT-PATENT 279 FASE NNCI 490 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE OPOSICIÓN

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OPOSICIÓN 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.

SOLICITUD
PUBLICADA

Número del expediente: 02-089167
Solicitante: ASTRAZENECA AS
Apoderado: RAMIRO CASTRO DUSSE
Título de la nueva creación o denominación del signo: NUOVA COMBINACION DE UN SET DE BLOQUEADOR Y UN AGENTE QUE REDUCE EL DOLOR
Gaceta: 242

3 OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: <u>PROCAPA S.A.</u>	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual <u> </u> Número <u>890 106 527-5</u>
	Dirección: <u>Calle 80 # 788-201</u> Nacionalidad o Domicilio: <u>BARRANQUILLA</u> Lugar de Constitución: <u>COLOMBIA</u> Teléfono: <u>3530783</u> Fax: <u>3533949</u> E-mail: <u> </u>	
REPRESENTANTE O APODERADO	Nombre: <u>Luis Fernando Rincon</u>	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual <u> </u> Número <u>79532486</u> TP <u>113438</u>
	Dirección: <u>Calle 119 A # 53-99</u> Teléfono: <u>6133418</u> Fax: <u>6244787</u> E-mail: <u>rineon@optimum-co.com</u>	

4 FUNDAMENTOS DE LA OPOSICIÓN: (ART. 14 Decisión 486 del CAN)

Causal: No cumple con los requisitos de patentabilidad

Signo opositor:

Justificación: La presente solicitud no cumple con los tres requisitos de patentabilidad dado que no se ha revelado la solución técnica en el estado de la técnica con anterioridad y además se refiere a un método terapéutico que no es patentable.

Comprobante de pago No. _____

Fecha _____

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⑥ ANEXOS

103

- ☒ 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.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

NOMBRE:

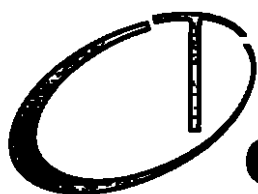
Luis Fernando Rincón Cuella

FIRMA:

[Firma manuscrita]

C.C. 79532186

TP. 43438



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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

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SUPERINDUSTRIA Y COMERCIO

Radicación : 02089167 00000006

Folios: 134

Fecha (CMI) : 2004-10-22 16:46:03

Trámite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Referencia : Expediente N° 02-089167

Asunto : Oposición a la solicitud de patente de Invención titulada "NUEVA COMBINACIÓN DE UN BETA-BLOQUEADOR Y UN AGENTE QUE REDUCE EL COLESTEROL".

Solicitante: ASTRAZENECA AB.

Opositora: PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 542 del 30 de julio de 2004

Yo, Luis Fernando Rincón Cuellar, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad PROCAPS S.A. conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invención titulada "NUEVA COMBINACIÓN DE UN BETA-BLOQUEADOR Y UN AGENTE QUE REDUCE EL COLESTEROL", solicitada por ASTRAZENECA AB., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

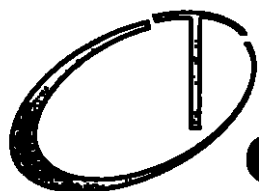
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2. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada debido a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida atentaría directamente a la comercialización que mi representada pretende con la presentación farmacéutica elaborada con base en una combinación farmacéutica que comprende un beta-bloqueador y un inhibidor de reductasa HMG-CoA. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

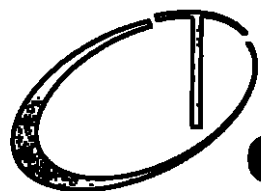
3. FUNDAMENTOS DE HECHOS

3.1. La solicitud objeto de la presente oposición fue presentada el 3 de octubre de 2002, reivindicando prioridad bajo SE0001188-2 del 03-04-2000 y SE0002352-3 del 22-06-2000, cuya fecha de inicio en la fase nacional fue el 3 de noviembre de 2002, con publicación internacional N° WO 01/74394 del 11 de octubre de 2001 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 542, del 30 de Julio de 2004, bajo el N° de publicación NP. 189 (página 331).

3.2. La solicitud colombiana 02-089167 objeto de la presente oposición, comprende según sus cláusulas 1 a 43, una combinación farmacéutica que comprende un beta-bloqueador y un inhibidor de reductasa HMG-CoA donde el beta-bloqueador se selecciona a partir del grupo que consiste de:

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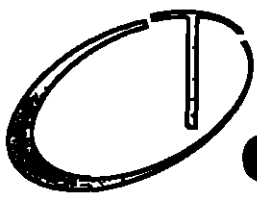
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acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol. Betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, buprandolol, butofilolol, carazolol, careolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, indenolol, labetalol, levobunolol, mepindolol, metiprenalol, metoprolol, nadolol, nadoxolol, nebivalol, nipradilol, oxprenolol, perbutolol. Pindolo, practolol, pronethalol, propanolol, sotalol, sufinalol, talindol, ter-tatolol, tillsolol. Timolol, toliprolol, xibenolol, y sus sales o solvatos farmacéuticamente aceptables o solvatos de dichas sales; y el inhibidor de reductasa HMG-CoA se selecciona a partir del grupo que consiste de cerivastarin, itavastatin, lovastatin, mevastatin. Nicostatin. Nivastatin, y (E)-7-{4-(4-FLUOROFENIL)-6 isopropil-2-[metil(metilsulfonil)-amino]-pirimidin-5il}(3R,5S)-3,5-dihidroxihept-6-ácido enólico o su sal aceptable farmacéuticamente o solvato o un solvato de una sal tal. Adicionalmente, reivindica que el beta-bloqueador es metoprolol o su sal farmacéuticamente aceptable o solvato, o un solvato de una sal tal y la combinación farmacéutica donde el beta-bloqueador es seleccionado de metoprolol; tartrato de metoprolol o fumarato de metoprolol. Adicionalmente reivindica un juego de partes, un método de tratamiento y un uso.

3.3. En primera instancia, se debe advertir que las reivindicaciones 6, 10, 14, 18, 22, 27, 31 y 40 caracterizan el general de la técnica, son generales y no definen las características propias para ser considerado como una invención. De dichas reivindicaciones no se puede establecer un avance inventivo, susceptible de estudio sobre los requisitos de patentabilidad. Adicionalmente, las reivindicaciones 36 a 43 se refieren al uso y según la legislación, decisión 486 de la Comunidad Andina de

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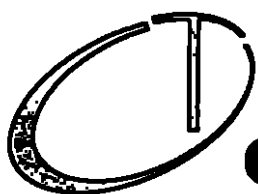
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Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*, los usos no están contemplados como patentables. Solo serán patentables los productos o procedimientos.

3.4. Así mismo, se está también tratando de reivindicar un método de tratamiento profiláctico o terapéutico en las reivindicaciones 27 a 35. La decisión 486 de la CAN establece claramente en su artículo número 20: *"No serán patentables: ...d) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o animales"*. De aquí se deduce claramente que el objeto de la presente solicitud no puede ser objeto de patente en Colombia.

3.5. La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación Industrial ya que como se demostró en el apartado anterior reclaman un método de tratamiento y estos no son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la naturaleza; y segundo no es repetible ya que usados los medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

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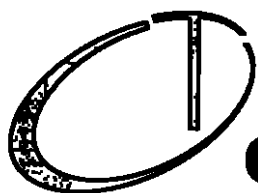
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3.6. Adicionalmente en las reivindicaciones 14 a 26 intentan registrar un juego de partes con intención comercial. La legislación, la Decisión 486 de la CAN consagra en su artículo 15 lo siguiente: *"No se considerarán invenciones: (...) d) los planes, reglas y métodos para el ejercicio de actividades intelectuales, juegos o actividades económico-comerciales; (...)".* Como tal, estas reivindicaciones intentan proteger un plan comercial de venta al público que incluye dos vasos y las instrucciones de uso. Demás de representar un plan comercial, no tendría nada de novedosa la configuración de venta al público. A la luz de la legislación de propiedad industrial en Colombia, estas reivindicaciones a todas luces no representan objeto de protección.

3.7. Dicho artículo 14 de la Decisión 486 de la CAN, se refiere a que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la novedad y el nivel inventivo de la presente solicitud:

- D1: WO9802357 (22-01-98)
- D2: WO9911260 (11-03-99)
- D3: WO9738694 (23-10-97)
- D4: C.J. EAGLES ET AL.: BR. J. CLIN. PHARMACOL., vol 43, N° 3, 1997, Pag. 291-300, XP00294411319.
- D5: OLAV PER FOSS ET AL.: SCAND. J. PRIMARY HEALTH CARE, vol 17, 1999, Pag., 122-127, XP002941325.
- D6: JAMES L. POOL ET AL.: HYPERTENSIÓN, vol 19, N° 3, Marzo de 1992, Pag., 242-248, XP0029411325.

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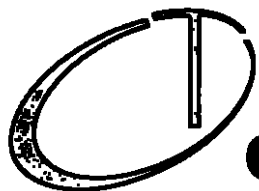
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- 3.8. Por su parte, el documento D1, en la reivindicación 20 en combinación con lo indicado en la página 7, líneas 29 a 30, define una combinación del inhibidor de reductasa HMG-CoA de Fluvastatin con un betabloqueador tal como metoprolol o un isosorbidmononitrato. Este documento D1, entonces, afectaría la novedad directamente del objeto que se intenta proteger. A todas luces, la intención de proteger dicha combinación de un inhibidor de reductasa con un betabloqueador se aparta del requisito más importante de patentabilidad, la NOVEDAD. En consecuencia, la solicitud colombiana objeto de oposición pretende la protección de una combinación que hace parte del estado del arte, específicamente respecto a lo que dictan el documento D1 publicado antes de la fecha de prioridad y que describe la combinación propuesta en la presente solicitud con basta anterioridad.
- 3.7. La referencia D2 claramente relaciona, según sus reivindicaciones 1, 2 y 8 en conjunto con las reivindicaciones 47, 49, 52 y lo descrito en las páginas 18, líneas 22 a página 20 línea 12, la combinación de un inhibidor de reductasa HMG-CoA de atorvastatina con un betabloqueador, en particular con un carvediol, para el tratamiento de la hipertensión, hiperlipidemia y arteriosclerosis. Así las cosas, este documento D2, afecta la novedad de lo reivindicado en la presente solicitud objeto de oposición. En consecuencia, la solicitud colombiana objeto de oposición revela el mismo objeto indicado con anterioridad en el documento D2 ya que describe la combinación indicada para tratar la arteriosclerosis. Por lo tanto, ni su combinación, ni su método de tratamiento, ni su uso son NOVEDOSOS a los ojos del documento D2.

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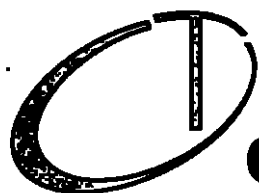
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- 3.8. Ahora bien, el documento D3, en sus reivindicaciones 1, 4 y 7, define una combinación de inhibidor de reductasa HMG-CoA tal como lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina y rivastatina y un betabloqueador para reducir el riesgo de enfermedades de arteriosclerosis. Por lo tanto, se demuestra un uso de dicha combinación con anterioridad para reducir el riesgo de enfermedades de arteriosclerosis, de manera que a la luz de este documento D3, la presente solicitud objeto de oposición pierde su estado de NOVEDAD.
- 3.9. De igual forma, el documento D4, verse resumen, define la combinación de dos betabloqueadores tales como el metoprolol y atenolol, con dos drogas reductoras de lípidos tales como fluvastatina y bezafibrato, así como su uso para reducir el metabolismo de grasas. Allí se revela que una de las drogas de reducción de lípidos tal como el fluvastatin es un inhibidor de reductasa HMG-CoA. Lo aquí expuesto en este documento anterior D4, afectaría directamente el requisito de NOVEDAD de lo reivindicado en la presente solicitud. En consecuencia, la solicitud colombiana objeto de oposición pretende la protección de una combinación que hace parte del estado del arte, específicamente respecto a lo que dicta el documento D4 publicado antes de la fecha de prioridad y que describe la combinación propuesta en la presente solicitud con anterioridad.
- 3.10. Por su parte el documento D5, según lo descrito en su resumen, define la combinación para ser usada como un betabloqueador antihipertensivo tal como un atenolol con un reductor de colesterol tal como un inhibidor de reductasa HMG-CoA de pravastatina para el tratamiento de la hipertensión y la hipercolesterolemia. Tanto la indicación de dicha combinación y el uso en el tratamiento de la

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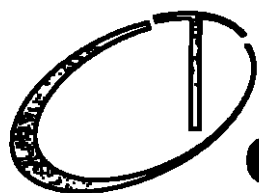
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hipertensión y la hipercolesterolemia, afecta directamente la NOVEDAD del producto reivindicado en la presente solicitud. Así las cosas, la solicitud colombiana objeto de oposición revela el mismo objeto indicado con anterioridad en el documento D5 ya que describe la combinación indicada para tratar el tratamiento de la hipertensión y la hipercolesterolemia. Por lo tanto, ni su combinación, ni su método de tratamiento, ni su uso son NOVEDOSOS a la luz del documento D5.

- 3.11. Por último el documento D6, revela según su resumen, define una combinación de un inhibidor de reductasa HMG-CoA tal como lovastatin con un betabloqueador de artenolol, metoprolol, labetanol, ropanol, nadolol y timolol para el tratamiento para la preexistencia de hipertensión e hipercolesterolemia. Nótese que en este documento se revela la no eficacia en la reducción del colesterol con el uso de exclusivo de lovastatina. Por lo tanto, se demuestra un uso de dicha combinación con anterioridad para el tratamiento para la preexistencia de hipertensión e hipercolesterolemia, de manera que a la luz de este documento D6, la presente solicitud objeto de oposición pierde su estado de NOVEDAD.
- 3.12. Ahora bien, la combinación de un betabloqueador tal como metoprolol y un agente reductor de colesterol tal como un inhibidor de reductasa HMG-CoA, especialmente estatina, para el tratamiento profiláctico o terapéutico en enfermedades asociadas con arteriosclerosis, tal como la hipertensión, hipercolesterolemia y enfermedades coronarias se pueden derivar de manera evidente de la combinación de los documentos D1, D2, D3, D4, D5, y D6. Ello es tan cierto que la misma solicitud objeto de oposición ha puntualizado en su página 2, líneas 1 a página 3 línea 20 que algunas de las combinaciones de la invención son

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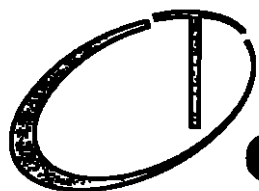
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conocidas y de lo allí descrito no se evidencia ninguna mejora respecto al arte anterior encontrado. Así las cosas, lo expuesto en la solicitud colombiana 02-089167 en las reivindicaciones, se deriva evidentemente del arte anterior de los documentos D1 a D6 en combinación, de manera que se demuestra que es obvio para cualquier persona versada en la materia. Por lo tanto, la combinación del conocimiento revelado en las solicitudes D1 a D6 en conjunto, afecta de manera directa el requisito de ALTURA INVENTIVA de la solicitud colombiana que se pretende proteger.

3.13. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 02-089167 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los TRES requisitos necesarios para su protección.

3.14. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

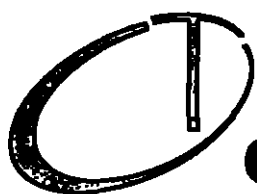
3.14.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 3 de abril de 2000, ya era conocido, pues como se demostró, era parte del arte anterior la materia sobre la cual busca protección en el capítulo reivindicatorio con base en los documentos D1, D2 y D3.



3.14.2. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"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."* A la fecha de presentación, 3 de abril de 2000, los documentos D1 a D6 en combinación, es posible deducir el uso y las alternativas combinatorias para el tratamiento profiláctico o terapéutico en enfermedades asociadas con arteriosclerosis, tal como la hipertensión, hipercolesterolemia y enfermedades coronarias.

3.14.3. **CARENCIA DE APLICACIÓN INDUSTRIAL.** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."* La presente solicitud carece de aplicación Industrial ya que como se demostró lo que se está reclamando es un método de tratamiento. Éstos no son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la naturaleza; y segundo no es repetible ya que usados los medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

3.15. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o*



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de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial." La solicitud pretendida no cumple con los tres requisitos de patentabilidad.

3.16. Por consiguiente, si se concede el registro solicitado se induciría al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486.

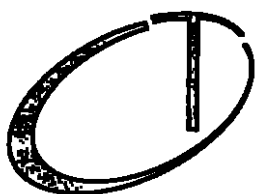
3.17. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"NUEVA COMBINACIÓN DE UN BETA-BLOQUEADOR Y UN AGENTE QUE REDUCE EL COLESTEROL"**, solicitada por **ASTRAZENECA AB.**, solicitud Colombiana que apareció publicada en la Gaceta 542 de la Propiedad Industrial bajo el NP. 189 (página 331).

4. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO9802357 (22-01-98)
- D2: WO9911260 (11-03-99)
- D3: WO9738694 (23-10-97)
- D4: C.J. EAGLES ET AL.:BR. J. CLIN. PHARMACOL., vol 43, N° 3, 1997, Pag, 291-300, XP00294411319.

Oficina Norte: Calle 119ª N° 53-99.
Oficina Centro: Diag. 35 N° 5ª -22.
Tél. (571) 6 13 33 74 - 6 13 34 18
www.optimum-co.com
Bogotá-Colombia



ptimum

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Derech de la Competencia, Propiedad
Industrial y Comercl Exterior

- D5: OLAV PER FOSS ET AL.: SCAND. J. PRIMARY HEALTH CARE, vol 17, 1999, Pag., 122-127, XP002941325.
 - D6: JAMES L. POOL ET AL.: HYPERTENSIÓN, vol 19, N° 3, Marzo de 1992, Pag., 242-248, XP0029411325.
- 115

5. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

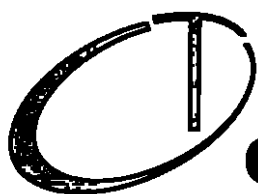
- 5.1. Numeral 1 del artículo 586 del Código de Comercio.
- 5.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 5.3. En las demás normas concordantes.

6. ANEXOS

Para los efectos correspondientes anexo al presente, aquellas referenciadas en el capítulo de pruebas así como los siguientes documentos:

- 6.1. Recibo de pago expedido por el Fondo Especial de esa Superintendencia, en el cual consta que se ha pagado el valor correspondiente a la tasa por tramitación de esta oposición.
- 6.2. Copia de la oposición para el traslado al solicitante.
- 6.3. Poder para actuar a nombre de mi representada.

Oficina Norte: Calle 119ª N° 53-99.
Oficina Centro: Diag. 35 N° 5ª -22.
Tél. (571) 6 13 33 74 – 6 13 34 18
www.optimum-co.com
Bogotá - Colombia



Optimum

13 **Derech de la Competencia, Propiedad Industrial y Comercio Exterior**

7. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas de abogado situadas en la calle 119ª N° 53-99 de esta ciudad de Bogotá.

Señora Jefe,


LUIS FERNANDO RINCÓN CUELLAR
C.C. FT 32626
T.P.A. 113418

Oficina Norte: Calle 119ª N° 53-99.
Oficina Centro: Diagonal 35 N° 5ª -22.
Tel. (571) 6 13 33 74 - 6 13 34 18
www.optimum-co.com
Bogotá - Colombia

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.



PODER ESPECIAL

H-9
1.8

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
Ciudad

Referencia: Poder- Oposición a la solicitud de patente N° 02-89167.

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad, identificado con la cédula de ciudadanía No. 16.251.923 expedida en Palmira (Valle), domiciliado y residente en la ciudad de Barranquilla, actuando en nombre y representación de la sociedad **PROCAPS S.A.**, con NIT 890.106.527-5, manifiesto que confiero poder especial, amplio y suficiente al doctor **LUIS FERNANDO RINCÓN CUELLAR**, abogado en ejercicio, identificado con la cédula de ciudadanía número 79.532.186 de Bogotá y con tarjeta profesional número 113.438 expedida por el Consejo Superior de la Judicatura, para que adelante y lleve hasta su culminación la Oposición en relación a la patentabilidad de la solicitud de la referencia titulada "NUEVA COMBINACIÓN DE UN BETA-BLOQUEADOR Y UN AGENTE QUE REDUCE EL COLESTEROL".

Mi apoderado cuenta con amplias facultades para el ejercicio del presente poder, en especial las de recibir, transigir, sustituir, reasumir y desistír.

Atentamente.

WALTER TANAKA TATEKAWA
PROCAPS S.A.
C.C. No. 16.251.923 de Palmira

Acepto,

LUIS FERNANDO RINCON CUELLAR
C.C. 79.532.186 de Bogotá
T.P. 113.438 del C.S.J.

— D

DILIGENCIA DE PRESENTACION PERSONAL

DECRETO 940 DE 1970 - ART. 68

MARIA DEL S. ROMAN DE ARTETA - NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA

CERTIFICA

En Barranquilla a los 20 días del mes de Oct de 1985 forma en esta diligencia en su presencia: Walter Fomako Totekaua

Portadores de las cédulas: 16251.923

Expedidos en Palacio

y declaro que la firma y huella que aparecen en el presente memorial son ajenas y que el contenido del mismo es cierto.

Comparecen: Walter Fomako Totekaua

LA NOTARIA PUBLICA DE COLOMBIA

DILIGENCIA DE RECONOCIMIENTO Y PRESENTACION PERSONAL

Ante mí, Notaria Pública del Segundo Circulo de Bogotá, compareció

Quien exhibió la C.C. No. 16251.923

T.F. 16251.923

expedida en

y declaró que la firma y huella que aparecen en el presente memorial son ajenas y que el contenido del mismo es cierto.

Memorial dirigido a

Santafé de Bogotá, D.C.

22 OCT 1985

Firma del Declarante

HUELLA

Autorizada por el Notario

NOTARIA ONCE DEL CIRCULO DE SANTAFÉ

MONICA T. BAUTISTA N
NOTARIA ONCE(E)



***** Pag.01
CAMARA DE COMERCIO
DE BARRANQUILLA
07*****
CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Publica Nro. 1190 del 22 de Julio de 1,976, otorgada en la Notaria Tercera de Barranquilla, ----- inscrita en esta Camara de Comercio, el 28 de Julio de 1,976 baj el No. 6,070 del libro respectivo, fue constituida la sociedad limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Publica Nro. 1307 del 28 de Junio de 1,979, otorgada en la Notaria Tercera de Barranquilla, ----- inscrita en esta Camara de Comercio, el 23 de Julio de 1,979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3810 del 31 de Dic/bre de 1,980, otorgada en la Notaria Primera de Barranquilla, ----- inscrita en esta Camara de Comercio, el 30 de Enero de 1,981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3755 del 10 de Nov/bre de 1,983, otorgada en la Notaria Unica de Soledad, ----- inscrita en esta Camara de Comercio, el 22 de Nov/bre de 1,983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3615 del 6 de Dic/bre de 1,996, otorgada en la Notaria 2a. de Barranquilla ----- inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 baj

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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PROCAPS S.A. -----

el No. 67,218 del libro respectivo, la sociedad antes mencionada
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Publica Nro. 3775 del 18 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 23 de Enero de 1,997 bajo
el No. 67,704 del libro respectivo, la sociedad antes mencionada
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

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

Numero	mm/dd/aaaa	Notaria	No.Ins o Reg	mm/dd/aaaa
39	1/18/1979	Notaria 3a. de Barranquilla	9,452	1/24/1979
992	4/30/1981	Notaria 1a. de Barranquilla	13,112	5/ 6/1981
1,464	8/27/1982	Notaria Unica de Soledad	15,533	9/ 8/1982
2,744	8/18/1983	Notaria Unica de Soledad	17,416	8/26/1983
3,826	7/16/1984	Notaria Unica de Soledad	19,554	7/27/1984
3,835	8/26/1985	Notaria Unica de Soledad	22,230	9/ 4/1985
2,260	9/10/1986	Notaria Unica de Soledad.	24,995	9/15/1986
1,849	7/11/1989	Notaria 2a. de Barranquilla	33,909	7/13/1989
444	2/21/1990	Notaria 2a. de Barranquilla	36,101	3/16/1990
3,090	12/17/1991	Notaria 2a. de Barranquilla	43,993	1/28/1992
269	2/ 1/1993	Notaria 2a. de Barranquilla	48,428	2/16/1993
2,342	7/28/1993	Notaria 2a. de Barranquilla	50,582	8/10/1993
3,652	11/ 9/1993	Notaria 2a. de Barranquilla	51,798	11/22/1993
3,615	12/ 6/1996	Notaria 2a. de Barranquilla	67,218	12/20/1996
89	1/16/1997	Notaria 2a. de Barranquilla	67,704	1/23/1997
2,070	7/17/1997	Notaria 2a. de Barranquilla	70,627	7/31/1997
2,281	8/ 4/1997	Notaria 2a. de Barranquilla	70,813	8/14/1997
765	4/22/1999	Notaria 3a. de Barranquilla	80,628	4/23/1999
459	2/21/2001	Notaria 2a. de Barranquilla	91,502	2/23/2001
2,608	10/ 5/2001	Notaria 2a. de Barranquilla	95,771	11/ 8/2001
1,730	7/29/2004	Notaria 2. de Barranquilla	112,999	8/26/2004

C E R T I F I C A

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

DENOMINACION O RAZON SOCIAL: -----

PROCAPS S.A. -----

Sigla: PROCAPS -----

DOMICILIO PRINCIPAL: BARRANQUILLA -----

Nit No. 890,106,527-5 -----

MATRICULA MERCANTIL: 24,802 -----

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



***** Pag.02
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

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

PROCAPS S.A. -----

C E R T I F I C A

Direccion para notificaciones judiciales
CL 80 # 78B -201
de la ciudad de BARRANQUILLA

C E R T I F I C A

DURACION: El termino de duracion de la sociedad se fijo hasta el
18 de Agosto del ano 2,073. -----

C E R T I F I C A

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

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

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

PROCAPS S.A. -----

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

C E R T I F I C A

CAPITAL:	Nro. Acciones	Valor Accion
AUTORIZADO:		
\$*****2,000,000,000.00	2,000,000.00	1,000.00
SUSCRITO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00
PAGADO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00

C E R T I F I C A

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

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



***** Pag.03
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

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

PROCAPS S.A. -----

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

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

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

PROCAPS S.A. -----

ello acreditar la ausencia del principal. La sociedad tendra un gerente general con su respectivo suplente, quienes tambien ejerceran la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el presidente y el vicepresidente. El gerente general, tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o superior al equivalente en pesos colombianos cincuenta mil dolares de los estados unidos de America (US\$50.000) liquidados a la tasa de cambio representativa del mercado vigente el dia en que surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del presidente. Las demas funciones que les correspondan como representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El gerente lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades.-----

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo,
y por Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

J U N T A D I R E C T I V A

Principales	Suplentes
1. Minski Gontovnik Ruben	Minski Zilberblum Elliot
2. Minski Gontovnik Meyer	Minski Deitel Daniel
3. Minski Gontovnik Jose	Minski Sharon

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificaci n
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***** C O N T I N U A *****



***** Pag.04
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

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

PROCAPS S.A. -----

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

C E R T I F I C A

Que segun Acta No. 124 del 29 de Marzo de 1,999, correspondiente
a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 4
de Agosto de 1,999 bajo el No. 82,226 del libro respectivo, fueron
hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Revisor Fiscal Ppal.	Vargas Pertuz Ana Isabel	C.****32,696,645=

C E R T I F I C A

Que segun Acta No. 127 del 22 de Marzo de 2,000, correspondiente
a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 29
de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron
hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Revisor Fiscal.	Lozada Villareal Milena	C.****32,748,111=

C E R T I F I C A

Que segun Acta No. 11 del 1 de Febrero de 2,001, correspondiente
a la Junta Directiva en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 12
de Febrero de 2,001 bajo el No. 91,273 del libro respectivo, fueron
hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Gerente General.	Uribe Ochoa Guillermo Luis	C.****70,073,754=

C E R T I F I C A

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

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

PROCAPS S.A. -----

Que segun Acta No. 406 del 2 de Sep/bre de 2,004, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----

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cuya parte pertinente se inscribio en esta Camara de Comercio, el 9 de Sep/bre de 2,004 bajo el No.113,263 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Gerente.	Tanaka Walter	C.****16,251,923=

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, torgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1.-Se confiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, com-

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



***** Pag.05
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

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

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parecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No.1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el señor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.-----

C E R T I F I C A

Que en esta Camara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolucion, liquidacion o nombramientos de representantes legales de la expresada sociedad.-----

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

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

PROCAPS S.A. -----

C E R T I F I C A

Que su ultima Renovacion fue el: 31 de Marzo de 2,004. -----

**La informacion sobre embargos de establecimientos se suministra en
Certificados de Matricula, la de contratos sujetos a registro, en
Certificados Especiales.**

C E R T I F I C A

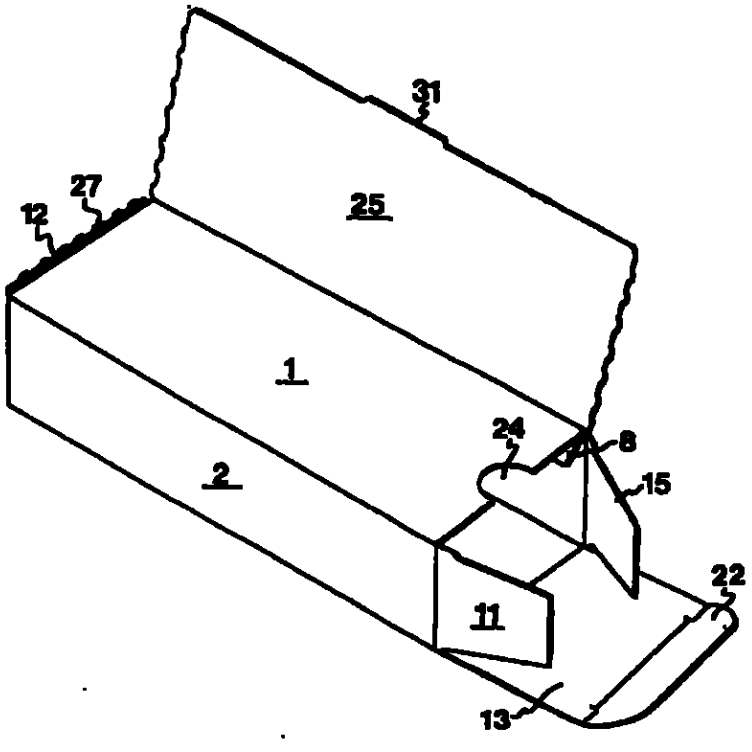
**Que los actos de registro aqui certificados quedan en firme cinco dias
habiles despues de la fecha de la publicacion en la noticia de la
correspondiente inscripcion, siempre que, dentro de dicho termino, no
sean objeto de los recursos de reposicion ante esta entidad, y/o de
apelacion para ante la Superintendencia de Industria y Comercio.--**

NO CAUSA IMPUESTO DE TIMBRE


**EL SECRETARIO
MARIBEL REYES OVIEDO**

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ANEXO 1

(51) International Patent Classification ⁶ : B65D 5/44, 51/24, 77/28 // A61J 1/03	A1	(11) International Publication Number: WO 98/02357 (43) International Publication Date: 22 January 1998 (22.01.98)
(21) International Application Number: PCT/SE97/01162 (22) International Filing Date: 27 June 1997 (27.06.97) (30) Priority Data: 9602762-8 12 July 1996 (12.07.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (73) Inventors/Applicants (for US only): GRÜNFELD, Tina [SE/SE]; Urbergavägen 2, S-435 41 Mölnlycke (SE). NY, Magnus [SE/SE]; Håstensgatan 50, S-432 34 Varberg (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, 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, TO). Published <i>With international search report.</i>
(54) Title: CARTON AND BLANK FOR FORMING THE SAME (57) Abstract A carton which is intended especially for drugs, as well as a blank for forming the same. The carton comprises a sleeve portion consisting of at least three wall-forming panels (1, 2, 4, 6) which are interconnected by folding lines (3, 5, 7) and by a closure tab (8), which is attached to a first wall-forming panel (1) along a folding line (9) and engages a second wall-forming panel (6), ends flaps (10, 11; 12, 13; 14, 15) attached to the ends of the sleeve portion along folding lines (16, 17, 18, 19, 20, 21) and closing the ends of the sleeve portion and the carton comprises an additional panel (25), which is connected to one of the wall-forming panels (1, 2, 4, 6) along a folding line (26) and which overlies at least one of the wall-forming panels (1, 2, 4, 6). The use of the carton for carrying at least one pharmaceutically active substance is described. 		

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126**CARTON AND BLANK FOR FORMING THE SAME****Field of the invention**

- 5 The present invention relates to a carton, which is intended especially for drugs, as well as a blank for forming the same.

Background of the invention and prior art

- 10 Conventionally, drugs are packed in e.g. blister packs, which in turn are stacked in a separate box or carton. This carton has the shape of a rectangular parallelepiped and comprises a sleeve portion consisting of four walls which are interconnected by folding lines. End flaps are connected to the sleeve portion along folding lines in order to close the ends of the carton. Normally, one end of the carton is permanently closed, the end flaps
15 being for example glued to one another. The other end of the carton is closed by means of a tuck-in tab, which is connected along a folding line to one of the end flaps. Consequently, the carton can easily be opened and reclosed at this end, such that the patient can remove a blister pack from the carton. User instructions are generally enclosed in the form of a separate leaflet, which is placed inside the carton.

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- This kind of tubular carton is made from an essentially rectangular blank having a sleeve-forming portion with four wall-forming panels arranged side by side and being interconnected by folding lines. A closure tab is connected along a folding line to a first wall-forming panel on one side of the sleeve-forming portion. When the carton is erected,
25 the closure tab is engaged, for example by means of adhesive, with a second wall-forming panel on the other side of the sleeve-forming portion. The blank further comprises end flaps, which are connected along folding lines to both ends of the sleeve-forming portion.

- One disadvantage of this conventional carton is that all information concerning the drug,
30 e.g. composition, secondary effects, manufacturer, user instructions, etc., is printed on the

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separate leaflet or folder that accompanies the blister packs in the carton. Thus, the leaflet contains a considerable amount of information, and it will require some effort on the part of the patient to find a certain piece of information, e.g. the user instructions. Due to the difficulty of finding these instructions, it might be impossible for an elderly or confused patient to administer the drug himself. This problem is even more pronounced when the carton contains different drugs that should be administered in combination.

Another drawback of this known carton is that the leaflet is lying loose in the carton. The user might therefore unintentionally lose the only item carrying vital information, or even deliberately throw it away.

A further drawback of this known carton resides in the fact that a receiver, e.g. a patient or a pharmacist, in no way can make sure that the carton has not been opened prior to delivery. Even if a separate seal is attached to the carton, e.g. a piece of tape, this is no guarantee that the contents have not been tampered with.

Outline of the invention

The object of the invention is to solve or alleviate some or all of the problems described above. More specifically, the carton according to the invention should enhance the possibility that the patient will comply with the user instructions when taking the drug (patient compliance), and reduce the risk that these instructions may be lost during use.

This object is achieved by the carton and the blank for forming the same set forth in the appended claims.

In addition to the solution to the above-mentioned problems, the invention or its embodiments confer the following advantages, which cannot be obtained with prior-art technique.

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- The problems mentioned above will be solved essentially without any change in the outer appearance of the carton. Thus, the patient will confidently recognise the package at the point of sale, e.g. a pharmacy.
- Notwithstanding this lack of change in outer appearance, the carton will, after being opened for the first time, present large areas that can carry particularly important information, such as user instructions, these areas being an integral part of the carton.
- In one preferred embodiment, the carton will be tamper-proof prior to delivery to the patient, since the securing flaps of the additional panel engage the end flaps of the carton. An attempt to illicitly open the carton will therefore result in the break lines being broken.

Brief description of the drawings

The invention will now be described in more detail with reference to the accompanying drawings, in which

Fig. 1a is a plan view of a first embodiment of the carton blank, Fig. 1b is a perspective view of a carton erected from the blank in Fig. 1a, and Fig. 1c is a perspective view of the carton in Fig. 1b after opening; and

Fig. 2a is a plan view of a second embodiment of the carton blank, Fig. 2b is a perspective view of a carton erected from the blank in Fig. 2a, and Fig. 2c is a perspective view of the carton in Fig. 2b after opening.

The integral blank of Fig. 1a has a rectangular sleeve-forming portion consisting of four wall-forming panels which are arranged side by side, namely a top wall panel 1, a first sidewall panel 2 connected to the top wall panel 1 along a first folding line 3, a bottom wall panel 4 connected to the first sidewall panel 2 along a second folding line 5, and a second sidewall panel 6 connected to the bottom wall panel 4 along a third folding line 7, said folding lines 3, 5, 7 being parallel. The top wall panel 1 has essentially the same

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dimensions as the bottom wall panel 4, and the first sidewall panel 2 has essentially the same dimensions as the second sidewall panel 6. When erected, the blank is thus formed into a rectangular parallelepiped.

- 5 On one side of the sleeve-forming portion, a closure tab 8 is connected to the top wall panel 1 along a fourth folding line 9.

At each end of the first sidewall panel 2, the bottom wall panel 4 and the second sidewall panel 6, an end flap 10, 11, 12, 13, 14, 15 is connected to the panel at issue along a folding line 16, 17, 18, 19, 20, 21. One of the end flaps 13 on the bottom wall panel 4 is in turn
10 connected to a tuck-in tab 22 along a folding line 23. In the top wall panel 1, a cut-out 24 is formed on the same end of the sleeve-forming portion as the end flap 13 carrying the tuck-in tab 22.

- 15 An additional panel 25 is permanently connected to the second sidewall panel 6 along a fifth folding line 26, said additional panel 25 having essentially the same dimensions as said top wall panel 1. On each end of the additional panel 25, there is provided a securing flap 27, 28, which is connected to the additional panel 25 along a break line 29, 30. The securing flaps 27, 28 essentially have the same size as the end flaps 12, 13 of the bottom
20 wall panel 4. Further, a lug 31 is formed on the additional panel 25 on the side facing away from said fifth folding line 26.

To assemble the carton, the closure tab 8 is coated with adhesive and brought into engagement with the second sidewall panel 6, such that the fourth folding line 9 essentially
25 coincides with the fifth folding line 26. The carton is then erected to form a sleeve, whereupon one end of the sleeve is closed by first folding in the end flaps 10, 14 of the sidewall panels 2, 6 and then folding in the end flap 12 of the bottom wall panel 4. Finally, the securing flap 27 on this end of the carton is folded down so as to overlie and be fixed to the end flap 12 of the bottom wall panel 4, preferably by means of adhesive. Subsequently,
30 the carton is loaded with goods, e.g. blister packs, at the other, open end. After loading, the

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carton is closed by first folding in the end flaps 11, 15 of the sidewall panels 2, 6 and then folding in the end flap 13 of the bottom wall panel 4, whereby the tuck-in tab 22 is inserted between the end flaps 11, 15 of the sidewall panels 2, 6 and the top wall panel 1 such that the cut-out 24 uncovers part of the tuck-in tab 22. Finally, the securing flap 28 is folded
5 down so as to overlie and be fixed to the end flap 13 of the bottom wall panel 4, preferably by means of adhesive.

In Fig. 1b, the carton is shown in erected and sealed condition. It will be appreciated that the carton is tamper-proof in so far as no one can have access to the contents without
10 breaking either of the break lines 29, 30.

The carton in Fig. 1b is initially opened by the patient gripping the lug 31 and pulling the additional panel 25 in the direction indicated by arrow A away from the top wall 1, thereby separating the additional panel 25 from the securing flaps 27, 28 along the break lines 29,
15 30. Then, the carton can be opened in conventional manner by the patient gripping the tuck-in tab 22 through the cut-out 24 and pulling said tab 22 away from the sleeve. A carton that has been thus opened is shown in Fig. 1c.

If desired, the carton could obviously have more than one tuck-in tab, namely one at each
20 end of the sleeve.

By using an additional panel 25 according to the invention, large areas are provided on the surface of the top wall 1 as well as the surface of the additional panel 25 facing said top wall 1. In this area, text and/or explanatory drawings can convey the most important user
25 instructions, which consequently can be separated from the general information given on the leaflet.

The fact that the instructions can be printed on the additional panel or the underlying wall, i.e. on an integral part of the carton, alleviates the risk that these instructions will be lost by
30 the patient during treatment.

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Further, since the additional panel 25 covers the top wall 1 when the carton is delivered to the patient, the text thereon is hidden and will not disturb or in any way alter the outer appearance of the carton.

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In Figs 2a-c, a second preferred embodiment is shown. As compared with Fig. 1, like elements have been given like reference numerals.

The blank of the second embodiment, as shown in Fig. 2a, differs from the blank of the first embodiment in that it has only one securing flap 28, which is connected along a break line 30 to one end of the additional panel 25. Further, an end flap 32 is, on the opposite end of the blank, connected along a folding line 33 to the top wall panel 1. This end flap 32 has essentially the same dimensions as the end flap 12 of the bottom wall panel 4.

The carton is assembled in a similar manner as the carton of the first embodiment. First, the closure tab 8 is brought into engagement with the second sidewall panel 6. Second, the carton is erected to form a sleeve, whereupon one end of the sleeve is closed by first folding in the end flaps 10, 14 of the sidewall panels 2, 6 and then folding in the end flap 12 of the bottom wall panel 4. Finally, the end flap 32 of the top wall panel 1 is folded down so as to overlie and be fixed to the end flap 12 of the bottom wall panel 4, preferably by means of adhesive.

After being loaded with goods, the carton is closed by first folding in the end flaps 11, 15 of the sidewall panels 2, 6 and then folding in the tuck-in tab 22. Finally, the additional panel 25 is folded onto the top wall panel 1, whereupon the securing flap 28 is folded so as to overlie and be fixed to the end flap 13 carrying the tuck-in tab 22, preferably by means of adhesive.

From Fig. 2b, which shows the carton in erected and sealed condition, it is evident that the carton is tamper-proof.

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The carton in Fig. 2b is opened in the same manner as the embodiment of Fig 1b, and a carton that has been thus opened is shown in Fig. 2c.

5 Apart from having the same advantages as the first embodiment, the carton of the second embodiment confers the further advantage that it can be completely sealed off even after the patient has broken said break line 30. From Fig. 1c, it is apparent that the carton of the first embodiment, once opened, provides on the end opposite to the tuck-in tab 22 a gap between the top wall panel 1 and the end flaps 10, 12, 14. In the second embodiment, the
10 end flap 32 of the top wall panel 1 seals off this gap at all times. Thus, there is no risk that particles or dust will enter the carton.

In both embodiments shown, an additional fixing means, such as a string or dots of adhesive, could be used to bring the additional panel 25 into engagement with the top wall
15 1. Evidently, the additional fixing means could allow the additional panel 25 to be releasably attached to the top wall 1. Thus, the information on the additional panel 25 and the top wall 1 can be concealed when it is not being consulted.

In one embodiment (not shown), the additional panel lacks securing flaps. In this case, an
20 additional fixing means must be provided to bring the additional panel into engagement with the top wall. This kind of carton could increase the patient's compliance with the user instructions and alleviate the risk that these instructions are lost during use. However, this embodiment has the disadvantage of not being tamper-proof prior to delivery.

25 In one preferred embodiment, the carton according to the invention is used for carrying medication for the treatment of coronary diseases, said medication being for instance a combination of at least one beta blocker, preferably metoprolol or isosorbidmononitrate, and at least one anti-inflammatory substance, preferably acetylsalicylic acid. Another suitable combination is a beta blocker, such as metoprolol or isosorbidmononitrate, and a
30 lipid lowering substance, such fluvastatin.

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In another preferred embodiment, the carton according to the invention is used for carrying medication for treatment of *Helibacter pylori*, e.g. a combination of an acid-secretion-inhibiting substance, preferably omeprazole, and at least one antibacterial substance, such as one or more selected from the following antibiotics: clarithromycin, erythromycin, roxithromycin, azithromycin, amoxicillin, metronidazole, tinidazole and tetracycline. A combination of omeprazole with clarithromycin and/or metronidazole is especially suitable.

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CLAIMS

1. Blank for forming a carton, comprising a sleeve-forming portion having at least three wall-forming panels (1, 2, 4, 6) arranged side by side and interconnected by folding lines (3, 5, 7), a closure tab (8) connected along a folding line (9) to a first wall-forming panel (1) on one side of the sleeve-forming portion in order to engage a second wall-forming panel (6) on the other side of the sleeve-forming portion when the carton is erected, end flaps (10, 11, 12, 13, 14, 15) connected to the ends of the sleeve-forming portion along folding lines (16, 17, 18, 19, 20, 21) in order to close the ends of the erected carton, characterised by an additional panel (25), which is connected along a folding line (26) to said second wall-forming panel (6) and is adapted to overlie at least one of the wall-forming panels (1, 2, 4, 6) when the carton is erected.
2. Blank as claimed in claim 1, wherein a tuck-in tab (22) is connected along a folding line (23) to at least one of said end flaps (10, 11, 12, 13, 14, 15).
3. Blank as claimed in claim 1 or 2, wherein the additional panel (25) has at least one securing flap (27, 28), each securing flap (27, 28) being connected along a break line (29, 30) to one end of the additional panel (25) and adapted to engage one of said end flaps (10, 12, 14; 11, 13, 15) when the carton is erected.
4. Blank as claimed in claim 3, wherein said at least one securing flap (27, 28) is adapted to overlie the end flap (13) that is connected to said tuck-in tab (22).
5. Blank as claimed in any one of claims 1-4, wherein the additional panel (25) is adapted to overlie said first wall-forming panel (1) when the carton is erected.
6. Blank as claimed in any one of claims 3-5, wherein the additional panel (25) has only one securing flap (28), which is formed on one side of the blank, and wherein the wall-

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forming panel (1, 6) underlying the additional panel (25) when the carton is erected is connected along a folding line (33) to an end flap (32) on the opposite side of the blank.

7. Blank as claimed in any one of claims 1-6, wherein said additional panel (25) has a
5 lug (31) on the side opposite to said folding line (26).

8. Blank as claimed in any one of claims 1-7, wherein the additional panel (25) has the same dimensions as or smaller dimensions than the underlying wall-forming panel (1, 6).

10 9. Carton comprising a sleeve portion consisting of at least three wall-forming panels (1, 2, 4, 6) which are interconnected by folding lines (3, 5, 7) and by a closure tab (8), which is attached to a first wall-forming panel (1) along a folding line (9) and engages a second wall-forming panel (6), end flaps (10, 11; 12, 13; 14, 15) attached to the ends of the sleeve portion along folding lines (16, 17, 18, 19, 20, 21) and closing the ends of the sleeve
15 portion, c h a r a c t e r i s e d by an additional panel (25), which is connected to one of the wall-forming panels (1, 2, 4, 6) along a folding line (26) and which overlies at least one of the wall-forming panels (1, 2, 4, 6).

20 10. Carton as claimed claim 9, wherein a tuck-in tab (22) is connected along a folding line (23) to at least one of said end flaps (10, 11; 12, 13; 14, 15).

11. Carton as claimed in claim 9 or 10, wherein the additional panel (25) has at least one securing flap (27, 28), said securing flap (27, 28) being connected along a break line (29, 30) to one end of the additional panel (25) and engaging one of said end flaps (10, 12, 14;
25 11, 13, 15).

12. Carton as claimed in claim 11, wherein said at least one securing flap (27, 28) overlies the end flap (13) that is connected to said tuck-in tab (22).

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13. Carton as claimed in any one of claims 9-12, wherein the folding line (26) of the additional panel (25) coincides with one of the folding lines (3, 5, 7; 16, 17, 18, 19, 20, 21) of the sleeve portion.
14. Carton as claimed in any one of claims 9-13, wherein the additional panel (25) overlies said first wall-forming panel (1).
15. Carton as claimed in any one of claims 11-14, wherein the additional panel (25) has only one securing flap (28) on one side of the carton, and wherein, on the opposite side of the carton, said wall-forming panel (1, 2, 4, 6) underlying the additional panel (25) is connected to an end flap (32) along a folding line (33).
16. Carton as claimed in any one of claims 9-15, wherein said additional panel (25) has a lug (31), which is formed on the additional panel (25) opposite to the folding line (26) and protrudes from the carton.
17. Carton as claimed in any one of claims 9-16, wherein the additional panel (25) has the same dimensions as or smaller dimensions than the underlying wall-forming panel (1, 2, 4, 6).
18. Use of a carton as claimed in any one of claims 9-17 for carrying at least one pharmaceutically active substance.
19. Use as claimed in claim 18, wherein said substance is an acid-secretion-inhibiting substance.
20. Use of a carton as claimed in any one of claims 9-17 for carrying a system of drugs that should be administered in combination.

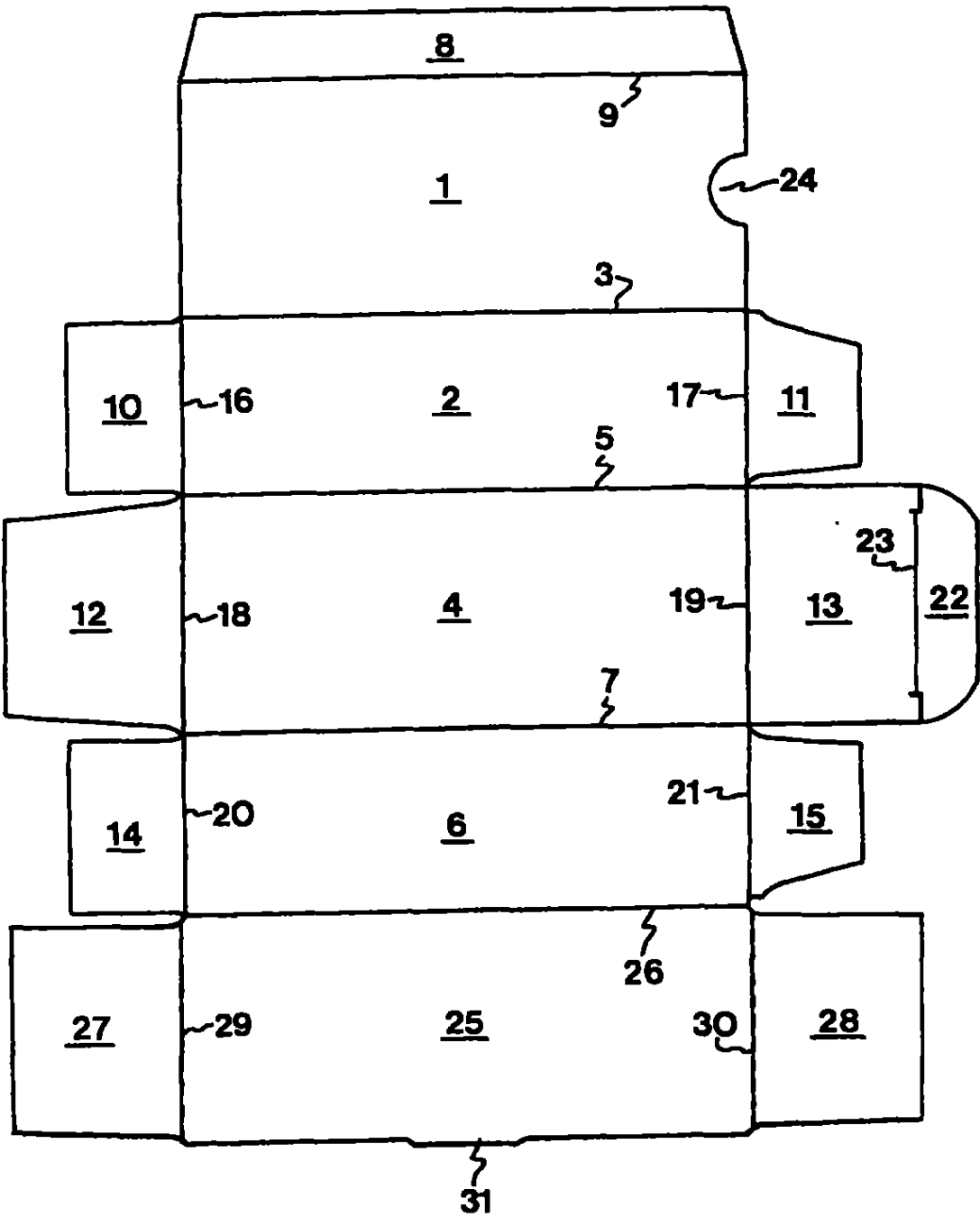
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21. Use as claimed in claim 20, wherein said system of drugs comprises at least one beta blocker and at least one anti-inflammatory substance.

22. Use as claimed in claim 20, wherein said system of drugs comprises an acid-secretion-inhibiting substance and one or more antibacterial substances.

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FIG 1a



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FIG 1b

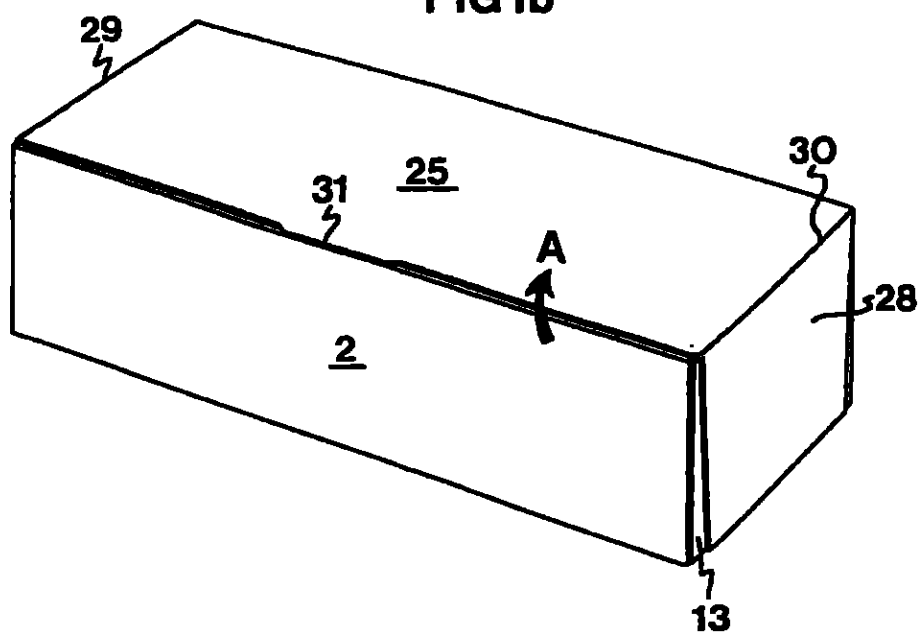
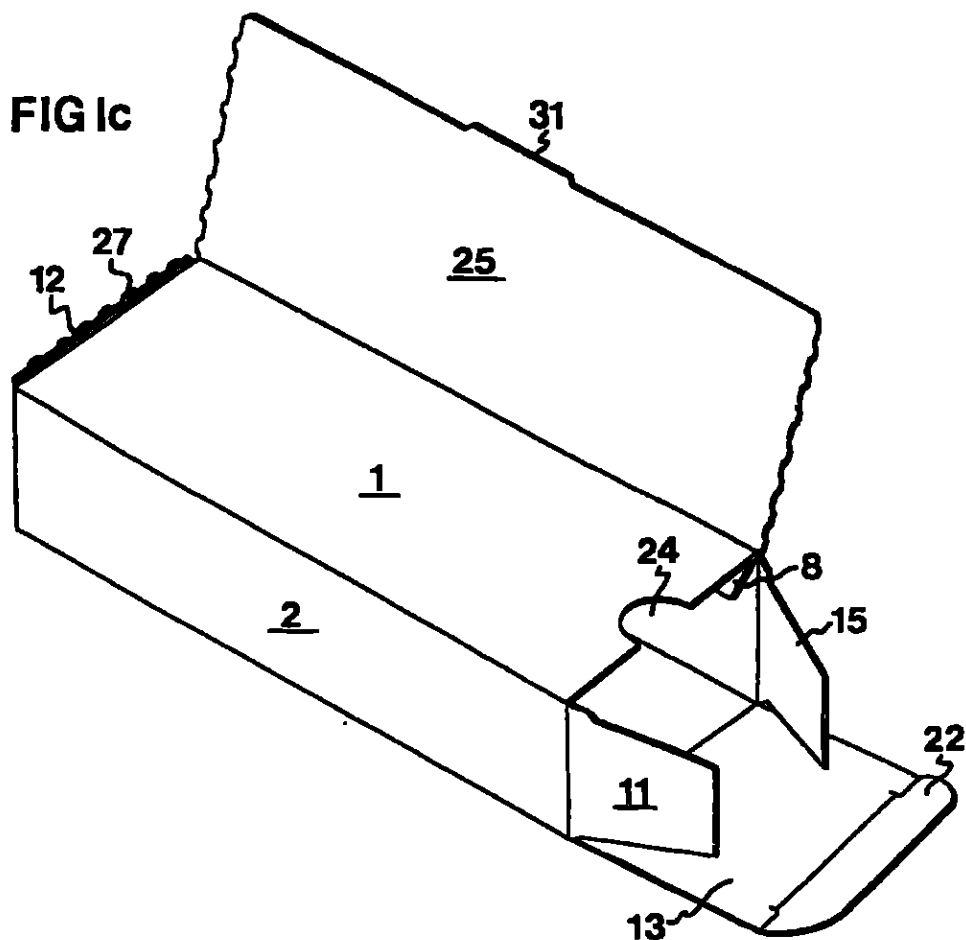
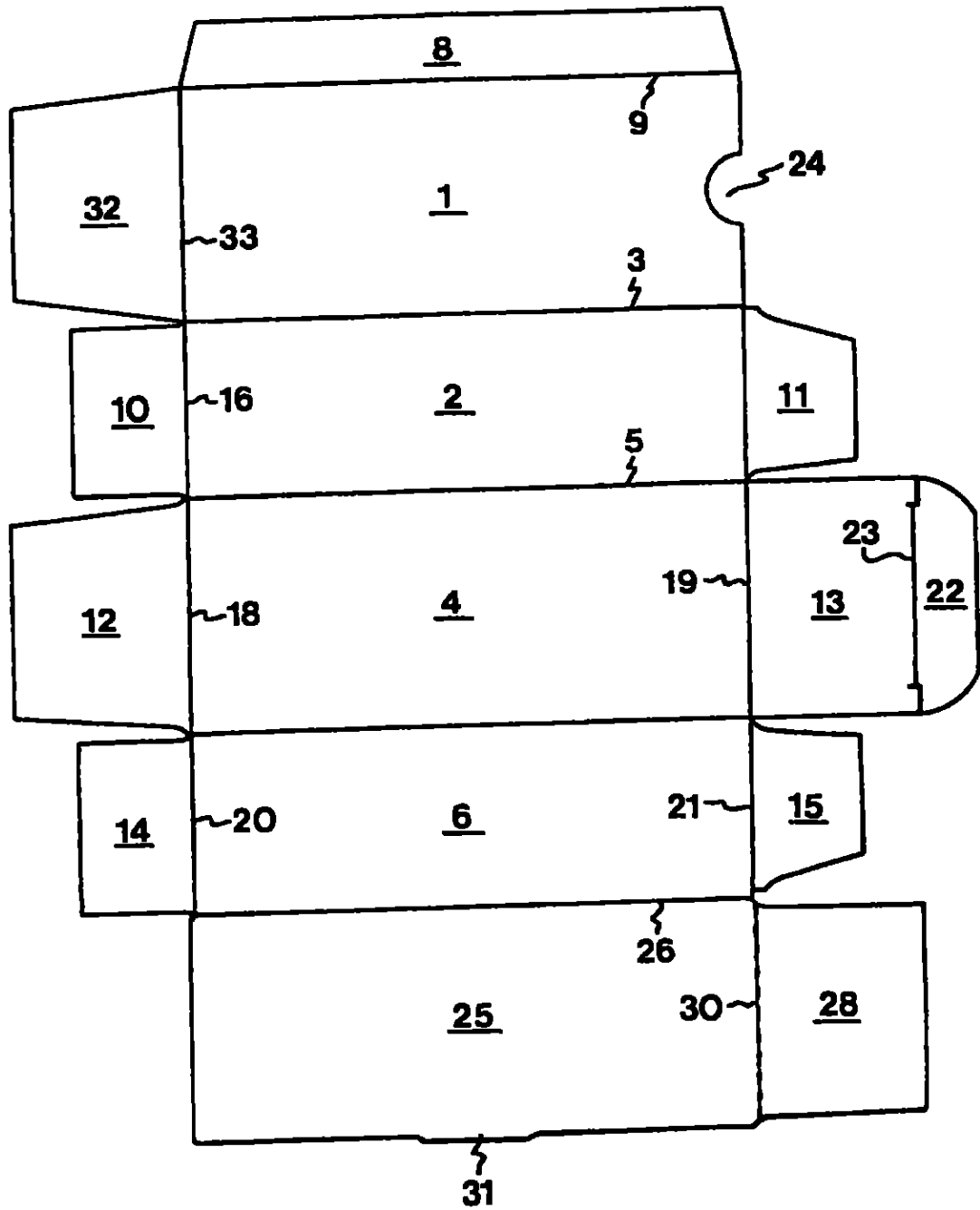


FIG 1c



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FIG 2a



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FIG 2b

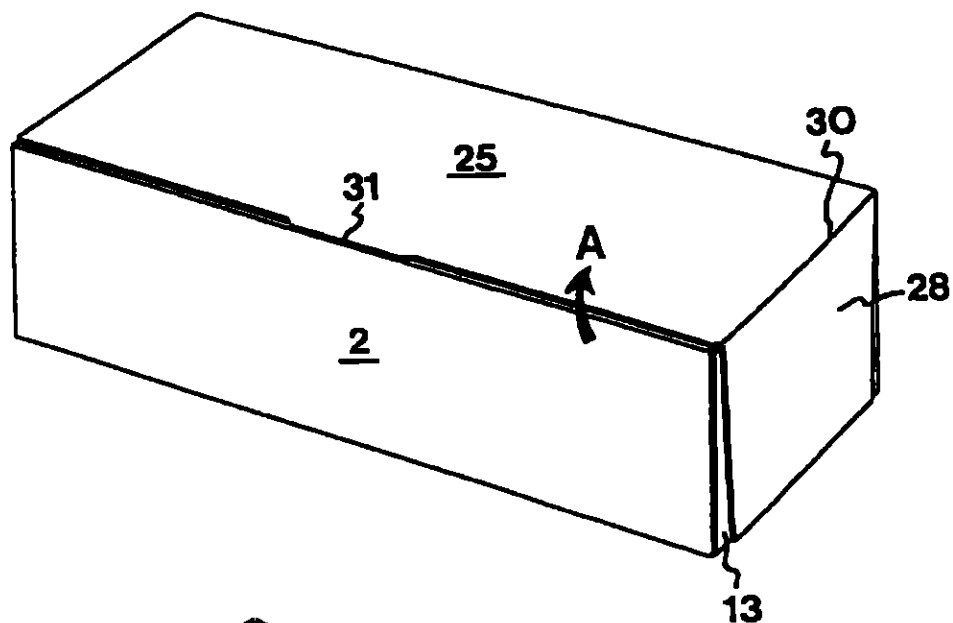
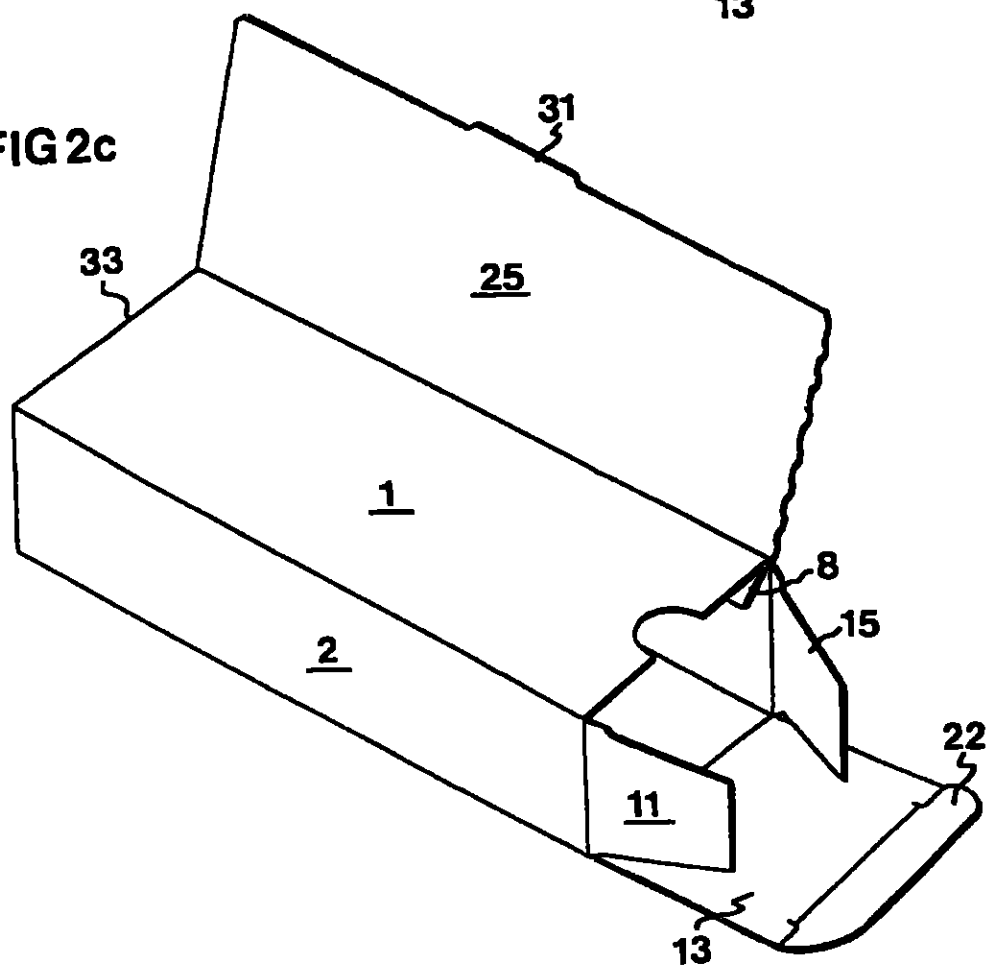


FIG 2c



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ANEXO 2

PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/40 // (A61K 31/40, 31:00)	A1	(11) International Publication Number: WO 99/11260 (43) International Publication Date: 11 March 1999 (11.03.99)
(21) International Application Number: PCT/IB98/01230 (22) International Filing Date: 11 August 1998 (11.08.98) (30) Priority Data: 60/057,276 29 August 1997 (29.08.97) US (71) Applicant (for all designated States except US): PFIZER INC. (US/US); 235 East 42nd Street, New York, NY 10017 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): SCOTT, Robert, Andrew, Donald [ZA/US]; 302 Riverside Avenue, Riverside, CT 06878 (US). (74) Agents: SPIEGEL, Allen, J.; c/o Simpson, Alison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB) et al.	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: COMBINATION THERAPY COMPRISING ATORVASTATIN AND AN ANTIHYPERTENSIVE AGENT (57) Abstract This invention relates to pharmaceutical combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents whereby these synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms of cardiac risk, including humans.		

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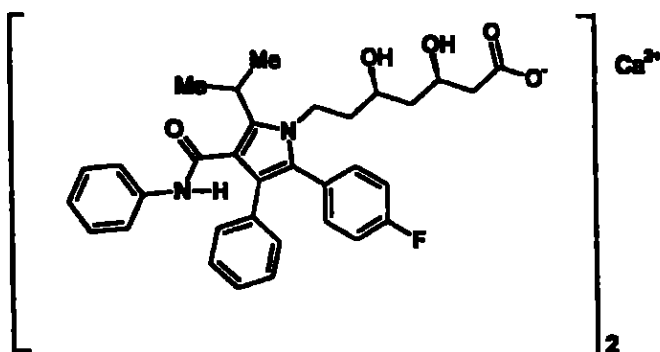
COMBINATION THERAPY COMPRISING ATORVASTATIN AND AN ANTIHYPERTENSIVE AGENT

This invention relates to pharmaceutical combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents whereby those additive and synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms or signs of cardiac risk, including humans.

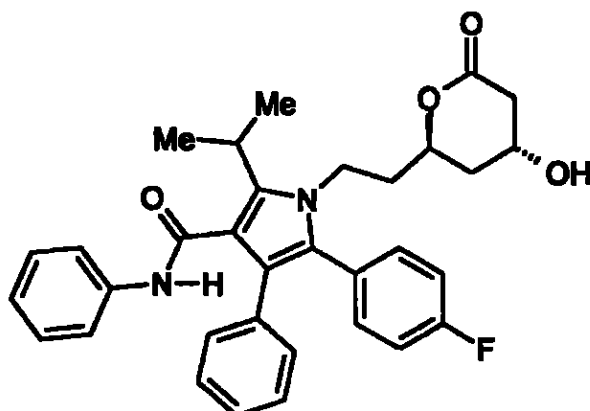
BACKGROUND OF THE INVENTION

The conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate is an early and rate-limiting step in the cholesterol biosynthetic pathway. This step is catalyzed by the enzyme HMG-CoA reductase. Statins inhibit HMG-CoA reductase from catalyzing this conversion. As such, statins are collectively potent lipid lowering agents.

Atorvastatin calcium, disclosed in U.S. Patent No. 5,273,995, which is incorporated herein by reference, is currently sold as Lipitor[®] and has the formula



Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA. As such, atorvastatin calcium is a potent lipid lowering compound. The free carboxylic acid form of atorvastatin exists predominantly as the lactone of the formula:

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and is disclosed in U.S. Patent No. 4,681,893, which is incorporated herein by reference.

5 Several classes of compounds are known to have activity as antihypertensive agents. These include calcium channel blockers, ACE inhibitors, A-II antagonists, diuretics, beta-adrenergic receptor blockers, vasodilators and alpha-adrenergic receptor blockers.

Atherosclerosis is a condition characterized by irregularly distributed lipid deposits in the intima of arteries, including coronary, carotid and peripheral arteries.
10 Atherosclerotic coronary heart disease (hereinafter termed "CHD") accounts for 53% of all deaths attributable to a cardiovascular event. CHD accounts for nearly one-half (about \$50-60 billion) of the total U.S. cardiovascular healthcare expenditures and about 6% of the overall national medical bill each year. Despite attempts to modify secondary risk factors such as, *inter alia*, smoking, obesity and lack of exercise, and
15 treatment of dyslipidemia with dietary modification and drug therapy, CHD remains the most common cause of death in the United States.

High levels of blood cholesterol and blood lipids are conditions involved in the onset of atherosclerosis. It is well known that inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) are effective in lowering the level of
20 blood plasma cholesterol, especially low density lipoprotein cholesterol (LDL-C), in man (Brown and Goldstein, New England Journal of Medicine, 1981, 305, No. 9, 515-517). It has now been established that lowering LDL-C levels affords protection from coronary heart disease (see, e.g., The Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart
25 disease: the Scandinavian Simvastatin Survival Study (4S), Lancet, 1994, 344, 1383-

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89; and Shepherd, J. et al., Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia, New England Journal of Medicine, 1995, 333, 1301-07).

5 Angina pectoris is a severe constricting pain in the chest, often radiating from the precordium to the left shoulder and down the left arm. Often angina pectoris is due to ischemia of the heart and is usually caused by coronary disease.

10 Currently the treatment of symptomatic angina pectoris varies significantly from country to country. In the U.S., patients who present with symptomatic, stable angina pectoris are frequently treated with surgical procedures or PTCA. Patients who undergo PTCA or other surgical procedures designed to treat angina pectoris frequently experience complications such as restenosis. This restenosis may be manifested either as a short term proliferative response to angioplasty-induced trauma or as long term progression of the atherosclerotic process in both graft vessels and angioplastied segments.

15 The symptomatic management of angina pectoris involves the use of a number of drugs, frequently as a combination of two or more of the following classes: beta blockers, nitrates and calcium channel blockers. Most, if not all, of these patients require therapy with a lipid lowering agent as well. The National Cholesterol Education Program (NCEP) recognizes patients with existing coronary artery disease as a special class requiring aggressive management of raised LDL-C.

20 Amlodipine helps to prevent myocardial ischemia in patients with exertional angina pectoris by reducing Total Peripheral Resistance, or afterload, which reduces the rate pressure product and thus myocardial oxygen demand at any particular level of exercise. In patients with vasospastic angina pectoris, amlodipine has been demonstrated to block constriction and thus restore myocardial oxygen supply.

25 Further, amlodipine has been shown to increase myocardial oxygen supply by dilating the coronary arteries.

30 Hypertension frequently coexists with hyperlipidemia and both are considered to be major risk factors for developing cardiac disease ultimately resulting in adverse cardiac events. This clustering of risk factors is potentially due to a common mechanism. Further, patient compliance with the management of hypertension is generally better than patient compliance with hyperlipidemia. It would therefore be

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advantageous for patients to have a single therapy which treats both of these conditions.

Coronary heart disease is a multifactorial disease in which the incidence and severity are affected by the lipid profile, the presence of diabetes and the sex of the subject. Incidence is also affected by smoking and left ventricular hypertrophy which is secondary to hypertension. To meaningfully reduce the risk of coronary heart disease, it is important to manage the entire risk spectrum. For example, hypertension intervention trials have failed to demonstrate full normalization in cardiovascular mortality due to coronary heart disease. Treatment with cholesterol synthesis inhibitors in patients with and without coronary artery disease reduces the risk of cardiovascular morbidity and mortality.

The Framingham Heart Study, an ongoing prospective study of adult men and women, has shown that certain risk factors can be used to predict the development of coronary heart disease. (see Wilson et al., Am. J. Cardiol. 1987, 59(14):91G-94G). These factors include age, gender, total cholesterol level, high density lipoprotein (HDL) level, systolic blood pressure, cigarette smoking, glucose intolerance and cardiac enlargement (left ventricular hypertrophy on electrocardiogram, echocardiogram or enlarged heart on chest X-ray). Calculators and computers can easily be programmed using a multivariate logistic function that allows calculation of the conditional probability of cardiovascular events. These determinations, based on experience with 5,209 men and women participating in the Framingham study, estimate coronary artery disease risk over variable periods of follow-up. Modeled incidence rates range from less than 1% to greater than 80% over an arbitrarily selected six year interval. However, these rates are typically less than 10% and rarely exceed 45% in men and 25% in women.

Kramech et al., Journal of Human Hypertension (1995) (Suppl. 1), 53-59 discloses the use of calcium channel blockers, including amlodipine, to treat atherosclerosis. That reference further suggests that atherosclerosis can be treated with a combination of amlodipine and a lipid lowering agent. Human trials have shown that calcium channel blockers have beneficial effects in the treatment of early atherosclerotic lesions. (see, e.g., Lichtlen, P.R. et al., Retardation of angiographic progression of coronary artery disease by nifedipine, Lancet, 1990, 335, 1109-13; and Waters, D. et al., A controlled clinical trial to assess the effect of a calcium channel

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- blocker on the progression of coronary atherosclerosis, *Circulation*, 1990, 82, 1940-53.) U.S. 4,881,893 discloses that certain statins, including atorvastatin, are hypolipidemic agents and as such are useful in treating atherosclerosis. Jukema et al., *Circulation*, 1995 (Suppl. 1), 1-197 disclose that there is evidence that calcium
- 5 channel blockers act synergistically in combination with lipid lowering agents (e.g., HMG-CoA reductase inhibitors), specifically pravastatin. Orekhov et al., *Cardiovascular Drugs and Therapy*, 1997, 11, 350 disclose the use of amlodipine in combination with lovastatin for the treatment of atherosclerosis.

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149**SUMMARY OF THE INVENTION**

This invention is directed to a pharmaceutical composition, hereinafter termed "Composition A", comprising:

- a. an amount of atorvastatin or a pharmaceutically acceptable salt thereof;
- b. an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof; and
- c. a pharmaceutically acceptable carrier or diluent;

provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition AA" of Composition A wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker, a vasodilator or an alpha-adrenergic receptor blocker.

This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition AB", of Composition AA comprising the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a pharmaceutical composition, hereinafter termed "Composition AC", of Composition AB wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker being verapamil, diltiazem, nifedipine, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine.

This invention is still more particularly directed to a pharmaceutical composition of composition AC wherein said calcium channel blocker is felodipine or nifedipine.

This invention is also more particularly directed to a pharmaceutical composition of Composition AB wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinopril ortrandolapril.

This invention is also more particularly directed to a pharmaceutical composition of Composition AB wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan.

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This invention is also more particularly directed to a pharmaceutical composition of Composition AB wherein said antihypertensive agent is a diuretic, said diuretic being amiloride or bendroflumethiazide.

5 This invention is also more particularly directed to a pharmaceutical composition of Composition AB wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol.

This invention is also more particularly directed to a pharmaceutical composition of Composition AB wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha-adrenergic receptor blocker being doxazosin,
10 prazosin or trimazosin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition B", for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the sum of the therapeutic effect achieved by administering said
15 first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a
20 pharmaceutically acceptable carrier or diluent; provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition BA", of Composition B wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II
25 antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition BB", of Composition BA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

30 This invention is still more particularly directed to a pharmaceutical composition, hereinafter termed "Composition BC", of Composition BB wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker

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being verapamil, diltiazem, milbepradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nifedipine, nitrendipine or felodipine.

This invention is still more particularly directed to a pharmaceutical composition of Composition BC wherein said calcium channel blocker is felodipine or
5 nifedipine.

This invention is still more particularly directed to a pharmaceutical composition of Composition BB wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinopril ortrandolapril.

10 This invention is still more particularly directed to a pharmaceutical composition of Composition BB wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan.

This invention is also more particularly directed to a pharmaceutical composition of Composition BB wherein said antihypertensive agent is a diuretic, said
15 diuretic being amiloride or bendroflumethiazide.

This invention is also more particularly directed to a pharmaceutical composition of Composition BB wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol.

This invention is also more particularly directed to a pharmaceutical composition of Composition BB wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha-adrenergic receptor blocker being doxazosin,
20 prazosin or trimazosin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition C", for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the sum of the therapeutic effect achieved by administering said
25 first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said antihypertensive agent is not
30 amlodipine or a pharmaceutically acceptable acid addition salt thereof.

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This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition CA", of Composition C wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition CB", of Composition CA comprising the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a pharmaceutical composition hereinafter termed "Composition CC", of Composition CB wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker being verapamil, diltiazem, mibefradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine.

This invention is still more particularly directed to a pharmaceutical composition of Composition CC wherein said calcium channel blocker is felodipine or nifedipine.

This invention is also more particularly directed to a pharmaceutical composition of Composition CB wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril ortrandolapril.

This invention is also more particularly directed to a pharmaceutical composition of Composition CB wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan.

This invention is also more particularly directed to a pharmaceutical composition of Composition CB wherein said antihypertensive agent is a diuretic, said diuretic being amiloride or bendroflumethiazide.

This invention is still more particularly directed to a pharmaceutical composition of Composition CB wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol.

This invention is still more particularly directed to a pharmaceutical composition of Composition CB wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha-adrenergic receptor blocker being doxazosin, prazosin or trimazosin.

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This invention is also particularly directed to a pharmaceutical composition of Composition B wherein said therapeutic effect is antiaxinal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

5 This invention is particularly directed to a pharmaceutical composition of Composition BB wherein said therapeutic effect is antiaxinal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also particularly directed to a pharmaceutical composition of Composition C wherein said therapeutic effect is antiaxinal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

10 This invention is also particularly directed to a pharmaceutical composition of Composition CB wherein said therapeutic effect is antiaxinal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition D", for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the therapeutic effect achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

25 This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition DA", of Composition D wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

30 This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition DB", of Composition DA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

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This invention is also particularly directed to a pharmaceutical composition of Composition D wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also directed to a pharmaceutical composition of
5 Composition DB wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition E", for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which
10 effect is greater than the therapeutic effect achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first
15 pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition EA", of Composition E wherein said
20 antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition EB", of Composition EA comprising the hemicalcium
25 salt of atorvastatin.

This invention is also particularly directed to a pharmaceutical composition of Composition E wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also particularly directed to a pharmaceutical composition of
30 Composition EB wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also directed to a kit, hereinafter termed "Kit A", for achieving a therapeutic effect in a mammal comprising:

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a. an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;

5 b. an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and

c. container means for containing said first and second dosage forms, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

10 This invention is particularly directed to a kit, hereinafter termed "Kit AA", of Kit A comprising the hemicalcium salt of atorvastatin.

This invention is more particularly directed to a kit, hereinafter termed "Kit AB", of Kit AA wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an
15 alpha-adrenergic receptor blocker.

This invention is still more particularly directed to a kit of Kit AB wherein said therapeutic effect is antilanginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also directed to a method, hereinafter termed "Method A", for
20 treating a mammal in need of therapeutic treatment comprising administering to said mammal

(a) an amount of a first compound, said first compound being atorvastatin or a pharmaceutically acceptable salt thereof; and

(b) an amount of a second compound, said second compound being
25 an antihypertensive agent or a pharmaceutically acceptable salt thereof; wherein said first compound and said second compound are each optionally and independently administered together with a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

30 This invention is particularly directed to a method, hereinafter termed "Method AA", of Method A comprising the hemicalcium salt of atorvastatin.

This invention is more particularly directed to a method, hereinafter termed "Method AB", of Method AA wherein said antihypertensive agent is a calcium channel

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blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker, or an alpha-adrenergic receptor blocker.

This invention is also particularly directed to a method, hereinafter termed "Method AC", of Method A wherein said first compound and said second compound
5 are administered sequentially in either order.

This invention is also particularly directed to a method, hereinafter termed "Method AD", of Method A wherein said first compound and said second compound are administered simultaneously.

This invention is still more particularly directed to a method, hereinafter
10 termed "Method AE", of Method AB wherein said first compound and said second compound are administered sequentially in either order.

This invention is still more particularly directed to a method, hereinafter termed "Method AF", of Method AB wherein said first compound and said second compound are administered simultaneously.

15 This invention is also particularly directed to a method of Method A wherein said therapeutic treatment comprises antihypertensive and antihyperlipidemic treatment.

This invention is also particularly directed to a method of Method AE wherein said therapeutic treatment comprises antihypertensive and antihyperlipidemic
20 treatment.

This invention is also particularly directed to a method of Method AF wherein said therapeutic treatment comprises antihypertensive and antihyperlipidemic treatment.

This invention is also particularly directed to a method of Method A wherein
25 said therapeutic treatment comprises antianginal treatment.

This invention is also particularly directed to a method of Method AE wherein said therapeutic treatment comprises antianginal treatment.

This invention is also particularly directed to a method of Method AF wherein said therapeutic treatment comprises antianginal treatment.

30 This invention is also particularly directed to a method of Method A wherein said therapeutic treatment comprises cardiac risk management.

This invention is also particularly directed to a method of Method AE wherein said therapeutic treatment comprises cardiac risk management.

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This invention is also particularly directed to a method of Method AF wherein said therapeutic treatment comprises cardiac risk management.

This invention is also particularly directed to a method of Method A wherein said therapeutic treatment comprises the treatment of atherosclerosis.

5 This invention is also particularly directed to a method of Method AE wherein said therapeutic treatment comprises the treatment of atherosclerosis.

This invention is also particularly directed to a method of Method AF wherein said therapeutic treatment comprises the treatment of atherosclerosis.

10 Amlodipine is a racemic compound due to the symmetry at position 4 of the dihydropyridine ring. The R and S enantiomers may be prepared as described by Arrowsmith et al., J. Med. Chem., 1988, 29, 1696. The calcium channel blocking activity of amlodipine is substantially confined to the S(-) isomer and to the racemic mixture containing the R(+) and S(-) forms. (see International Patent Application Number PCT/EP94/02697). The R(+) isomer has little or no calcium channel
15 blocking activity. However, the R(+) isomer is a potent inhibitor of smooth muscle cell migration. Thus, the R(+) isomer is useful in the treatment or prevention of atherosclerosis. (see International Patent Application Number PCT/EP95/00847). Based on the above, a skilled person could choose the R(+) isomer, the S(-) isomer or the racemic mixture of the R(+) isomer and the S(-) isomer for use in the
20 combination of this invention.

Where used herein, the term "cardiac risk" means the likelihood that a subject will suffer a future adverse cardiac event such as, e.g., myocardial infarction, cardiac arrest, cardiac failure, cardiac ischaemia. Cardiac risk is calculated using the Framingham Risk Equation as set forth above. The term "cardiac risk management"
25 means that the risk of future adverse cardiac events is substantially reduced.

It will be recognized by those skilled in the art that certain of the antihypertensive agents which are used in combination with atorvastatin or a pharmaceutically acceptable salt of atorvastatin contain either an acidic moiety or a basic moiety which may be reacted with either a base to form a cationic salt or an
30 acid to form an acid addition salt, respectively. All of the pharmaceutically acceptable salts of the antihypertensive agents disclosed herein are within the scope of the combination of this invention.

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159**DETAILED DESCRIPTION OF THE INVENTION**

The pharmaceutical compositions of this invention comprise atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent or a pharmaceutically acceptable salt thereof.

Atorvastatin may readily be prepared as described in U.S. Patent No. 4,681,893, which is incorporated herein by reference. The hemicalcium salt of atorvastatin, which is currently sold as Lipitor[®], may readily be prepared as described in U.S. Patent No. 5,273,995, which is incorporated herein by reference.

The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. The expression "pharmaceutically-acceptable cationic salts" is intended to define but is not limited to such salts as the alkali metal salts, (e.g., sodium and potassium), alkaline earth metal salts (e.g., calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically-acceptable acid addition salts" is intended to define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

Besides the hemicalcium salt, other pharmaceutically-acceptable cationic salts of atorvastatin may be readily prepared by reacting the free acid form of atorvastatin with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, piperazine and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In many cases, salts are preferably prepared by mixing a solution of the acid with a solution of a different salt of the cation (sodium or potassium ethylhexanoate, magnesium oleate), and employing a

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solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent. The acid addition salts of atorvastatin may be readily prepared by reacting the free base form of atorvastatin with the appropriate acid. When the salt is of a monobasic acid (e.g.,
5 the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate
10 or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

The pharmaceutically acceptable acid addition and cationic salts of the
15 antihypertensive agents used in the combination of this invention may be prepared in a manner analogous to that described for the preparation of the pharmaceutically acceptable acid addition and cationic salts of atorvastatin, but substituting the desired antihypertensive compound for atorvastatin.

The antihypertensive agents which may be used in accordance with this
20 invention are members of different classes of antihypertensive agents, including calcium channel blockers (excluding amlodipine and pharmaceutically acceptable acid addition salts thereof), ACE inhibitors, A-II antagonists, diuretics, beta-adrenergic receptor blockers, vasodilators and alpha-adrenergic receptor blockers.

Calcium channel blockers which are within the scope of this invention include,
25 but are not limited to: bepridil, which may be prepared as disclosed in U.S. Patent No. 3,862, 238 or U.S. Release No. 30,577; clemizem, which may be prepared as disclosed in U.S. Patent No. 4,567,175; diltiazem, which may be prepared as disclosed in U.S. Patent No. 3,562, fendiline, which may be prepared as disclosed in U.S. Patent No. 3,262,977; gallopamil, which may be prepared as disclosed in U.S.
30 Patent No. 3,251,858; mibefradil, which may be prepared as disclosed in U.S. Patent No. 4,808,605; prenylamine, which may be prepared as disclosed in U.S. Patent No. 3,152,173; semotiadil, which may be prepared as disclosed in U.S. Patent No. 4,786,635; terodiline, which may be prepared as disclosed in U.S. Patent No.

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3,371,014; verapamil, which may be prepared as disclosed in U.S. Patent No. 3,261,859; aranipine, which may be prepared as disclosed in U.S. Patent No. 4,572,909; barnidipine, which may be prepared as disclosed in U.S. Patent No. 4,220,649; benidipine, which may be prepared as disclosed in European Patent
5 Application Publication No. 106,275; clindipine, which may be prepared as disclosed in U.S. Patent No. 4,672,068; efonidipine, which may be prepared as disclosed in U.S. Patent No. 4,885,284; elgodipine, which may be prepared as disclosed in U.S. Patent No. 4,952,592; felodipine, which may be prepared as disclosed in U.S. Patent No. 4,264,611; isradipine, which may be prepared as disclosed in U.S. Patent No.
10 4,466,972; lacidipine, which may be prepared as disclosed in U.S. Patent No. 4,801,599; lercanidipine, which may be prepared as disclosed in U.S. Patent No. 4,705,797; manidipine, which may be prepared as disclosed in U.S. Patent No. 4,892,875; nicardipine, which may be prepared as disclosed in U.S. Patent No. 3,985,758; nifedipine, which may be prepared as disclosed in U.S. Patent No.
15 3,485,847; nilvadipine, which may be prepared as disclosed in U.S. Patent No. 4,338,322; nimodipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; nisoldipine, which may be prepared as disclosed in U.S. Patent No. 4,154,839; nitrendipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; cinnarizine, which may be prepared as disclosed in U.S. Patent No.
20 2,882,271; flunarizine, which may be prepared as disclosed in U.S. Patent No. 3,773,939; lidoflazine, which may be prepared as disclosed in U.S. Patent No. 3,267,104; lomertizine, which may be prepared as disclosed in U.S. Patent No. 4,663,325; bencyclane, which may be prepared as disclosed in Hungarian Patent No. 151,865; etafenone, which may be prepared as disclosed in German Patent No.
25 1,285,758; and perhexiline, which may be prepared as disclosed in British Patent No. 1,025,578. The disclosures of all such U.S. Patents are incorporated herein by reference.

Angiotensin Converting Enzyme Inhibitors (ACE-inhibitors) which are within the scope of this invention include, but are not limited to: alacepril, which may be
30 prepared as disclosed in U.S. Patent No. 4,248,883; benazepril, which may be prepared as disclosed in U.S. Patent No. 4,410,520; captopril, which may be prepared as disclosed in U.S. Patent Nos. 4,046,889 and 4,105,776; ceronapril, which may be prepared as disclosed in U.S. Patent No. 4,452,790; delapril, which

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may be prepared as disclosed in U.S. Patent No. 4,385,051; enalapril, which may be prepared as disclosed in U.S. Patent No. 4,374,829; fosinopril, which may be prepared as disclosed in U.S. Patent No. 4,337,201; imadapril, which may be prepared as disclosed in U.S. Patent No. 4,508,727; lisinopril, which may be prepared as disclosed in U.S. Patent No. 4,555,502; moxetopril, which may be prepared as disclosed in Belgian Patent No. 893,553; perindopril, which may be prepared as disclosed in U.S. Patent No. 4,508,728; quinapril, which may be prepared as disclosed in U.S. Patent No. 4,344,949; ramipril, which may be prepared as disclosed in U.S. Patent No. 4,587,258; spirapril, which may be prepared as disclosed in U.S. Patent No. 4,470,972; temocapril, which may be prepared as disclosed in U.S. Patent No. 4,699,905; andtrandolapril, which may be prepared as disclosed in U.S. Patent No. 4,933,361. The disclosures of all such U.S. patents are incorporated herein by reference.

Angiotensin-II receptor antagonists (A-II antagonists) which are within the scope of this invention include, but are not limited to: candesartan, which may be prepared as disclosed in U.S. Patent No. 5,196,444; eprosartan, which may be prepared as disclosed in U.S. Patent No. 5,185,351; irbesartan, which may be prepared as disclosed in U.S. Patent No. 5,270,317; losartan, which may be prepared as disclosed in U.S. Patent No. 5,138,069; and valsartan, which may be prepared as disclosed in U.S. Patent No. 5,399,578. The disclosures of all such U.S. patents are incorporated herein by reference.

Beta-adrenergic receptor blockers (beta- or β -blockers) which are within the scope of this invention include, but are not limited to: acebutolol, which may be prepared as disclosed in U.S. Patent No. 3,857,952; alprenolol, which may be prepared as disclosed in Netherlands Patent Application No. 6,605,692; amosutolol, which may be prepared as disclosed in U.S. Patent No. 4,217,305; arotinolol, which may be prepared as disclosed in U.S. Patent No. 3,932,400; atenolol, which may be prepared as disclosed in U.S. Patent No. 3,863,607 or 3,836,671; befunolol, which may be prepared as disclosed in U.S. Patent No. 3,853,923; betaxolol, which may be prepared as disclosed in U.S. Patent No. 4,252,984; bevantolol, which may be prepared as disclosed in U.S. Patent No. 3,857,981; bisoprolol, which may be prepared as disclosed in U.S. Patent No. 4,171,370; bopindolol, which may be

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prepared as disclosed in U.S. Patent No. 4,340,541; bucumolol, which may be prepared as disclosed in U.S. Patent No. 3,663,570; bufetolol, which may be prepared as disclosed in U.S. Patent No. 3,723,476; bufuralol, which may be prepared as disclosed in U.S. Patent No. 3,929,836; bunitrolol, which may be prepared as disclosed in U.S. Patent Nos. 3,940,489 and 3,981,071; buprandolol, which may be prepared as disclosed in U.S. Patent No. 3,309,406; butiridine hydrochloride, which may be prepared as disclosed in French Patent No. 1,390,056; butofilolol, which may be prepared as disclosed in U.S. Patent No. 4,252,825; carazolol, which may be prepared as disclosed in German Patent No. 2,240,599; 5
10 carteolol, which may be prepared as disclosed in U.S. Patent No. 3,910,924; carvedilol, which may be prepared as disclosed in U.S. Patent No. 4,503,067; celiprolol, which may be prepared as disclosed in U.S. Patent No. 4,034,009; cetamolol, which may be prepared as disclosed in U.S. Patent No. 4,059,622; cloranolol, which may be prepared as disclosed in German Patent No. 2,213,044; 15
dilevalol, which may be prepared as disclosed in Clifton et al., Journal of Medicinal Chemistry, 1982, 25, 670; epanolol, which may be prepared as disclosed in European Patent Publication Application No. 41,491; indenolol, which may be prepared as disclosed in U.S. Patent No. 4,045,482; labetalol, which may be prepared as disclosed in U.S. Patent No. 4,012,444; levobunolol, which may be prepared as disclosed in U.S. Patent No. 4,463,176; mepindolol, which may be prepared as disclosed in Seeman et al., Helv. Chim. Acta, 1971, 54, 241; 20
metipranolol, which may be prepared as disclosed in Czechoslovakian Patent Application No. 128,471; metoprolol, which may be prepared as disclosed in U.S. Patent No. 3,873,600; moprolol, which may be prepared as disclosed in U.S. Patent 25
No. 3,501,769; nadolol, which may be prepared as disclosed in U.S. Patent No. 3,935, 287; nadoxolol, which may be prepared as disclosed in U.S. Patent No. 3,819,702; nebivalol, which may be prepared as disclosed in U.S. Patent No. 4,654,362; nipradilol, which may be prepared as disclosed in U.S. Patent No. 4,394,382; oxprenolol, which may be prepared as disclosed in British Patent No. 30
1,077,603; perbutolol, which may be prepared as disclosed in U.S. Patent No. 3,551,493; pindolol, which may be prepared as disclosed in Swiss Patent Nos. 469,002 and 472,404; practolol, which may be prepared as disclosed in U.S. Patent

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No. 3,408,387; pronethalol, which may be prepared as disclosed in British Patent No. 909,357; propranolol, which may be prepared as disclosed in U.S. Patent Nos. 3,337,628 and 3,520,919; sotalol, which may be prepared as disclosed in Uloth et al., Journal of Medicinal Chemistry, 1966, 9, 88; sufinalol, which may be prepared as disclosed in German Patent No. 2,728,641; talindol, which may be prepared as disclosed in U.S. Patent Nos. 3,935,259 and 4,038,313; tertatolol, which may be prepared as disclosed in U.S. Patent No. 3,980,891; tilisolol, which may be prepared as disclosed in U.S. Patent No. 4,129,565; timolol, which may be prepared as disclosed in U.S. Patent No. 3,655,663; toliprolol, which may be prepared as disclosed in U.S. Patent No. 3,432,545; and xibenolol, which may be prepared as disclosed in U.S. Patent No. 4,018,824. The disclosures of all such U.S. patents are incorporated herein by reference.

Alpha-adrenergic receptor blockers (alpha- or α -blockers) which are within the scope of this invention include, but are not limited to: amosulalol, which may be prepared as disclosed in U.S. Patent No. 4,217,307; arotinolol, which may be prepared as disclosed in U.S. Patent No. 3,932,400; dapiprazole, which may be prepared as disclosed in U.S. Patent No. 4,252,721; doxazosin, which may be prepared as disclosed in U.S. Patent No. 4,188,390; fenspiride, which may be prepared as disclosed in U.S. Patent No. 3,399,192; indoramin, which may be prepared as disclosed in U.S. Patent No. 3,527,761; labetalol, which may be prepared as disclosed above; naftopidil, which may be prepared as disclosed in U.S. Patent No. 3,997,666; nicergoline, which may be prepared as disclosed in U.S. Patent No. 3,228,943; prazosin, which may be prepared as disclosed in U.S. Patent No. 3,511,636; tamsulosin, which may be prepared as disclosed in U.S. Patent No. 4,703,063; tolazoline, which may be prepared as disclosed in U.S. Patent No. 2,161,938; trimazosin, which may be prepared as disclosed in U.S. Patent No. 3,669,968; and yohimbine, which may be isolated from natural sources according to methods well known to those skilled in the art. The disclosures of all such U.S. patents are incorporated herein by reference.

The term "vasodilator," where used herein, is meant to include cerebral vasodilators, coronary vasodilators and peripheral vasodilators. Cerebral vasodilators within the scope of this invention include, but are not limited to:

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bencyclane, which may be prepared as disclosed above; cinnarizine, which may be prepared as disclosed above; citicoline, which may be isolated from natural sources as disclosed in Kennedy et al., Journal of the American Chemical Society, 1955, 77, 250 or synthesized as disclosed in Kennedy, Journal of Biological Chemistry, 1956, 222, 185; cyclandelate, which may be prepared as disclosed in U.S. Patent No. 3,863,597; ciclonicate, which may be prepared as disclosed in German Patent No. 1,910,481; diisopropylamine dichloroacetate, which may be prepared as disclosed in British Patent No. 862,248; ebumamonine, which may be prepared as disclosed in Hermann et al., Journal of the American Chemical Society, 1979, 101, 1540; fasudil, which may be prepared as disclosed in U.S. Patent No. 4,678,783; fenoxedil, which may be prepared as disclosed in U.S. Patent No. 3,818,021; flunarizine, which may be prepared as disclosed in U.S. Patent No. 3,773,939; ibudilast, which may be prepared as disclosed in U.S. Patent No. 3,850,941; ifenprodil, which may be prepared as disclosed in U.S. Patent No. 3,509,164; lomerizine, which may be prepared as disclosed in U.S. Patent No. 4,863,325; nafronyl, which may be prepared as disclosed in U.S. Patent No. 3,334,096; nicametate, which may be prepared as disclosed in Blöcke et al., Journal of the American Chemical Society, 1942, 64, 1722; nicergoline, which may be prepared as disclosed above; nimodipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; papaverine, which may be prepared as reviewed in Goldberg, Chem. Prod. Chem. News, 1954, 17, 371; pentifylline, which may be prepared as disclosed in German Patent No. 860,217; tinofedrine, which may be prepared as disclosed in U.S. Patent No. 3,563,997; vincamine, which may be prepared as disclosed in U.S. Patent No. 3,770,724; vinpocetine, which may be prepared as disclosed in U.S. Patent No. 4,035,750; and viquidil, which may be prepared as disclosed in U.S. Patent No. 2,500,444. The disclosures of all such U.S. patents are incorporated herein by reference.

Coronary vasodilators within the scope of this invention include, but are not limited to: amotriphene, which may be prepared as disclosed in U.S. Patent No. 3,010,965; bendazol, which may be prepared as disclosed in J. Chem. Soc. 1958, 2426; benfurodil hemisuccinate, which may be prepared as disclosed in U.S. Patent No. 3,355,463; benzlodarone, which may be prepared as disclosed in U.S. Patent No. 3,012,042; chloracizine, which may be prepared as disclosed in British Patent No. 740,932; chromonar, which may be prepared as disclosed in U.S. Patent No.

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3,282,938; clobenfuril, which may be prepared as disclosed in British Patent No. 1,160,925; clonitrate, which may be prepared from propanediol according to methods well known to those skilled in the art, e.g., see *Annalen*, 1870, 165, 165; cloricromen, which may be prepared as disclosed in U.S. Patent No. 4,452,811; dilaazep, which
5 may be prepared as disclosed in U.S. Patent No. 3,532,685; dipyridamole, which may be prepared as disclosed in British Patent No. 807,826; droprenilamine, which may be prepared as disclosed in German Patent No. 2,521,113; efloxate, which may be prepared as disclosed in British Patent Nos. 803,372 and 824,547; erythrityl tetranitrate, which may be prepared by nitration of erythritol according to methods
10 well-known to those skilled in the art; etafenone, which may be prepared as disclosed in German Patent No. 1,265,758; fendiline, which may be prepared as disclosed in U.S. Patent No. 3,262,977; floredil, which may be prepared as disclosed in German Patent No. 2,020,464; gangiefene, which may be prepared as disclosed in U.S.S.R. Patent No. 115,905; hexestrol, which may be prepared as disclosed in U.S. Patent
15 No. 2,357,985; hexobendine, which may be prepared as disclosed in U.S. Patent No. 3,267,103; itramin tosylate, which may be prepared as disclosed in Swedish Patent No. 188,308; khellin, which may be prepared as disclosed in Baxter et al., *Journal of the Chemical Society*, 1949, S 30; lidoflazine, which may be prepared as disclosed in U.S. Patent No. 3,267,104; mannitol hexanitrate, which may be prepared by the
20 nitration of mannitol according to methods well-known to those skilled in the art; medibazine, which may be prepared as disclosed in U.S. Patent No. 3,119,826; nitroglycerin; pentaerythritol tetranitrate, which may be prepared by the nitration of pentaerythritol according to methods well-known to those skilled in the art; pentritnitrol, which may be prepared as disclosed in German Patent No. 638,422-3;
25 perhexiline, which may be prepared as disclosed above; pinefylline, which may be prepared as disclosed in U.S. Patent No. 3,350,400; prenylamine, which may be prepared as disclosed in U.S. Patent No. 3,152,173; propetyl nitrate, which may be prepared as disclosed in French Patent No. 1,103,113; trapidil, which may be prepared as disclosed in East German Patent No. 55,956; tricromyl, which may be
30 prepared as disclosed in U.S. Patent No. 2,769,015; trimetazidine, which may be prepared as disclosed in U.S. Patent No. 3,262,852; trolnitrate phosphate, which may be prepared by nitration of triethanolamine followed by precipitation with phosphoric

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acid according to methods well-known to those skilled in the art; viadine, which may be prepared as disclosed in U.S. Patent Nos. 2,816,118 and 2,980,699. The disclosures of all such U.S. patents are incorporated herein by reference.

Peripheral vasodilators within the scope of this invention include, but are not limited to: aluminum nicotinate, which may be prepared as disclosed in U.S. Patent No. 2,970,082; bamethan, which may be prepared as disclosed in Corrigan et al., *Journal of the American Chemical Society*, 1945, 67, 1894; bencyclane, which may be prepared as disclosed above; betahistine, which may be prepared as disclosed in Walter et al., *Journal of the American Chemical Society*, 1941, 63, 2771; bradykinin, which may be prepared as disclosed in Hamburg et al., *Arch. Biochem. Biophys.*, 1958, 76, 252; brovincamine, which may be prepared as disclosed in U.S. Patent No. 4,146,643; bufenide, which may be prepared as disclosed in U.S. Patent No. 3,542,870; buflomedil, which may be prepared as disclosed in U.S. Patent No. 3,895,030; butalamine, which may be prepared as disclosed in U.S. Patent No. 3,338,899; cetiedil, which may be prepared as disclosed in French Patent Nos. 1,460,571; clonicate, which may be prepared as disclosed in German Patent No. 1,910,481; cinepazide, which may be prepared as disclosed in Belgian Patent No. 730,345; cinnarizine, which may be prepared as disclosed above; cyclandelate, which may be prepared as disclosed above; diisopropylamine dichloroacetate, which may be prepared as disclosed above; edoisin, which may be prepared as disclosed in British Patent No. 984,810; fenoxedil, which may be prepared as disclosed above; flunarizine, which may be prepared as disclosed above; hepronicate, which may be prepared as disclosed in U.S. Patent No. 3,384,642; kenprodil, which may be prepared as disclosed above; iloprost, which may be prepared as disclosed in U.S. Patent No. 4,682,484; inositol niacinate, which may be prepared as disclosed in Badgett et al., *Journal of the American Chemical Society*, 1947, 69, 2907; isoxsuprine, which may be prepared as disclosed in U.S. Patent No. 3,056,838; kallidin, which may be prepared as disclosed in *Biochem. Biophys. Res. Commun.*, 1961, 6, 210; kallikrein, which may be prepared as disclosed in German Patent No. 1,102,973; moxosylate, which may be prepared as disclosed in German Patent No. 905,738; nafrotyl, which may be prepared as disclosed above; nicametate, which may be prepared as disclosed above; nicergoline, which may be prepared as disclosed above; nicofuranoes, which may be prepared as disclosed in Swiss Patent

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No. 366,523; nylidrin, which may be prepared as disclosed in U.S. Patent Nos. 2,661,372 and 2,661,373; pentifyline, which may be prepared as disclosed above; pentoxifyline, which may be prepared as disclosed in U.S. Patent No. 3,422,107; piribedil, which may be prepared as disclosed in U.S. Patent No. 3,299,067;
5 prostaglandin E₁, which may be prepared by any of the methods referenced in the Merck Index, Twelfth Edition, Budaverl, Ed., New Jersey, 1996, p. 1353; sulotidil, which may be prepared as disclosed in German Patent No. 2,334,404; tolazoline, which may be prepared as disclosed in U.S. Patent No. 2,161,938; and xanthinol niacinate, which may be prepared as disclosed in German Patent No. 1,102,750 or
10 Korbonits et al, Acta. Pharm. Hung., 1988, 38, 98. The disclosures of all such U.S. patents are incorporated herein by reference.

The term "diuretic," within the scope of this invention, is meant to include diuretic benzothiadiazine derivatives, diuretic organomercurials, diuretic purines, diuretic steroids, diuretic sulfonamide derivatives, diuretic uracils and other diuretics
15 such as amanozine, which may be prepared as disclosed in Austrian Patent No. 168,063; amiloride, which may be prepared as disclosed in Belgian Patent No. 639,388; arbutin, which may be prepared as disclosed in Tschitschabin, Annalen, 1930, 479, 303; chlorazasil, which may be prepared as disclosed in Austrian Patent No. 168,063; ethacrynic acid, which may be prepared as disclosed in U.S. Patent No.
20 3,255,241; etozolin, which may be prepared as disclosed in U.S. Patent No. 3,072,653; hydracarbazine, which may be prepared as disclosed in British Patent No. 856,409; isosorbide, which may be prepared as disclosed in U.S. Patent No. 3,160,641; mannitol; metochalcone, which may be prepared as disclosed in Freudenberg et al., Ber., 1957, 80, 957; muzolimine, which may be prepared as
25 disclosed in U.S. Patent No. 4,018,890; perhexiline, which may be prepared as disclosed above; ticrynafen, which may be prepared as disclosed in U.S. Patent No. 3,758,506; triamterene which may be prepared as disclosed in U.S. Patent No. 3,081,230; and urea. The disclosures of all such U.S. patents are incorporated herein by reference.

30 Diuretic benzothiadiazine derivatives within the scope of this invention include, but are not limited to: althiazide, which may be prepared as disclosed in British Patent No. 902,858; bendroflumethiazide, which may be prepared as disclosed in U.S. Patent No. 3,285,573; benzthiazide, McManus et al., 136th Am. Soc. Meeting

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(Atlantic City, September 1959), Abstract of papers, pp 13-O; benzylhydrochlorothiazide, which may be prepared as disclosed in U.S. Patent No. 3,108,097; buthiazide, which may be prepared as disclosed in British Patent Nos. 861,367 and 885,078; chlorothiazide, which may be prepared as disclosed in U.S. Patent Nos. 2,809,194 and 2,937,169; chlorthalidone, which may be prepared as disclosed in U.S. Patent No. 3,055,904; cyclopenthiazide, which may be prepared as disclosed in Belgian Patent No. 587,225; cyclothiazide, which may be prepared as disclosed in Whitehead et al., Journal of Organic Chemistry, 1961, 26, 2814; epithiazide, which may be prepared as disclosed in U.S. Patent No. 3,009,911; ethiazide, which may be prepared as disclosed in British Patent No. 861,367; fenquizone, which may be prepared as disclosed in U.S. Patent No. 3,870,720; indapamide, which may be prepared as disclosed in U.S. Patent No. 3,565,911; hydrochlorothiazide, which may be prepared as disclosed in U.S. Patent No. 3,164,588; hydroflumethiazide, which may be prepared as disclosed in U.S. Patent No. 3,254,076; methyclothiazide, which may be prepared as disclosed in Close et al., Journal of the American Chemical Society, 1960, 82, 1132; meticrane, which may be prepared as disclosed in French Patent Nos. M2790 and 1,385,504; metolazone, which may be prepared as disclosed in U.S. Patent No. 3,360,518; paraflutizide, which may be prepared as disclosed in Belgian Patent No. 620,829; polythiazide, which may be prepared as disclosed in U.S. Patent No. 3,009,911; quinethazone, which may be prepared as disclosed in U.S. Patent No. 2,976,289; tectlothiazide, which may be prepared as disclosed in Close et al., Journal of the American Chemical Society, 1960, 82, 1132; and trichlormethiazide, which may be prepared as disclosed in deStevens et al., Experientia, 1960, 16, 113. The disclosures of all such U.S. patents are incorporated herein by reference.

Diuretic sulfonamide derivatives within the scope of this invention include, but are not limited to: acetazolamide, which may be prepared as disclosed in U.S. Patent No. 2,980,679; ambside, which may be prepared as disclosed in U.S. Patent No. 3,188,329; azosemide, which may be prepared as disclosed in U.S. Patent No. 3,665,002; bumetanide, which may be prepared as disclosed in U.S. Patent No. 3,634,583; butazolamide, which may be prepared as disclosed in British Patent No. 769,757; chloraminophenamide, which may be prepared as disclosed in U.S. Patent Nos. 2,809,194, 2,965,655 and 2,965,656; clofenamide, which may be prepared as

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disclosed in Olivier, Rec. Trav. Chim., 1918, 37, 307; clopamide, which may be prepared as disclosed in U.S. Patent No. 3,459,756; clorexolone, which may be prepared as disclosed in U.S. Patent No. 3,183,243; disulfamide, which may be prepared as disclosed in British Patent No. 851,287; ethoxolamide, which may be prepared as disclosed in British Patent No. 795,174; furosemide, which may be prepared as disclosed in U.S. Patent No. 3,058,882; mefruside, which may be prepared as disclosed in U.S. Patent No. 3,356,692; methazolamide, which may be prepared as disclosed in U.S. Patent No. 2,783,241; piretanide, which may be prepared as disclosed in U.S. Patent No. 4,010,273; torasemide, which may be prepared as disclosed in U.S. Patent No. 4,018,929; triparamide, which may be prepared as disclosed in Japanese Patent No. 73 05,585; and xipamide, which may be prepared as disclosed in U.S. Patent No. 3,567,777. The disclosures of all such U.S. patents are incorporated herein by reference.

In addition, atorvastatin and pharmaceutically acceptable salts thereof may occur as hydrates or solvates. Further, the antihypertensive agents which may be used in accordance with this invention and the pharmaceutically acceptable salts thereof may occur as hydrates or solvates. Said hydrates and solvates are also within the scope of the invention.

The pharmaceutical combinations and methods of this invention are all adapted to therapeutic use as agents in the treatment of atherosclerosis, angina pectoris, and a condition characterized by the presence of both hypertension and hyperlipidemia in mammals, particularly humans. Further, since these diseases and conditions are closely related to the development of cardiac disease and adverse cardiac conditions, these combinations and methods, by virtue of their action as antiatherosclerotics, antianginals, antihypertensives and antihyperlipidemics, are useful in the management of cardiac risk.

The utility of the compounds of the present invention as medical agents in the treatment of atherosclerosis in mammals (e.g. humans) is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below.

**Effect of Atorvastatin and an Antihypertensive Agent Alone
and in Combination on the Treatment**

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170of Atheroarteriosclerosis

This study is a prospective randomized evaluation of the effect of a combination of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent on the progression/regression of coronary and carotid artery disease. The study is used to show that a combination of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent is effective in slowing or arresting the progression or causing regression of existing coronary artery disease (CAD) as evidenced by changes in coronary angiography or carotid ultrasound, in subjects with established disease.

10 This study is an angiographic documentation of coronary artery disease carried out as a double-blind, placebo-controlled trial of a minimum of about 500 subjects and preferably of about 780 to about 1200 subjects. It is especially preferred to study about 1200 subjects in this study. Subjects are admitted into the study after satisfying certain entry criteria set forth below.

15 Entry criteria: Subjects accepted for entry into this trial must satisfy certain criteria. Thus the subject must be an adult, either male or female, aged 18-80 years of age in whom coronary angiography is clinically indicated. Subjects will have angiographic presence of a significant focal lesion such as 30% to 50% on subsequent evaluation by quantitative coronary angiography (QCA) in a minimum of
20 one segment (non-PTCA, non-bypassed or non-MI vessel) that is judged not likely to require intervention over the next 3 years. It is required that the segments undergoing analysis have not been interfered with. Since percutaneous transluminal cardiac angioplasty (PTCA) interferes with segments by the insertion of a balloon catheter, non-PTCA segments are required for analysis. It is also required that the
25 segments to be analyzed have not suffered a thrombotic event, such as a myocardial infarct (MI). Thus the requirement for non-MI vessels. Segments that will be analyzed include: left main, proximal, mid and distal left anterior descending, first and second diagonal branch, proximal and distal left circumflex, first or largest space obtuse marginal, proximal, mid and distal right coronary artery. Subjects will have an
30 ejection fraction of greater than 40% determined by catheterization or radionuclide ventriculography or ECHO cardiogram at the time of the qualifying angiogram or within the previous three months of the acceptance of the qualifying angiogram

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provided no intervening event such as a thrombotic event or procedure such as PTCA has occurred.

Generally, due to the number of patients and the physical limitations of any one facility, the study is carried out at multiple sites. At entry into the study, subjects
5 undergo quantitative coronary angiography as well as B-mode carotid artery ultrasonography and assessment of carotid arterial compliance at designated testing centers. This establishes baselines for each subject. Once admitted into the test, subjects are randomized to receive an antihypertensive agent or a pharmaceutically acceptable salt thereof (the dose is dependent upon the particular antihypertensive
10 agent or salt thereof chosen) and placebo or atorvastatin calcium (80 mgs) and placebo or an antihypertensive agent or a pharmaceutically acceptable salt thereof (the dose is dependent upon the particular antihypertensive agent or salt thereof chosen) and atorvastatin calcium (80 mgs). It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base
15 form or other salt forms of the statin may be used in this invention. Calculation of the dosage amount for these other forms of the statin and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. The amount of the antihypertensive agent may be varied as required. The amount of the statin will be titrated down from 80 mg if it is determined
20 by the physician to be in the best interests of the subject. The subjects are monitored for a one to three year period, generally three years being preferred. B-mode carotid ultrasound assessment of carotid artery atherosclerosis and compliance are performed at regular intervals throughout the study.

Generally, six month intervals are suitable. Typically this assessment is
25 performed using B-mode ultrasound equipment. However, a person skilled in the art may use other methods of performing this assessment. Coronary angiography is performed at the conclusion of the one to three year treatment period. The baseline and post-treatment angiograms and the intervening carotid artery B-mode ultrasonograms are evaluated for new lesions or progression of existing
30 atherosclerotic lesions. Arterial compliance measurements are assessed for changes from baseline and over the 6-month evaluation periods.

The primary objective of this study is to show that the combination of an antihypertensive agent and atorvastatin reduces the progression of atherosclerotic

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lesions as measured by quantitative coronary angiography (QCA) in subjects with clinical coronary artery disease. QCA measures the opening in the lumen of the arteries measured.

The primary endpoint of the study is the change in the average mean segment diameter of the coronary artery tree. Thus, the diameter of an arterial segment is measured at various portions along the length of that segment. The average diameter of that segment is then determined. After the average segment diameter of many segments has been determined, the average of all segment averages is determined to arrive at the average mean segment diameter. The mean segment diameter of subjects taking atorvastatin or a pharmaceutically acceptable salt thereof and amlodipine or a pharmaceutically acceptable acid addition salt thereof will decline more slowly, will be halted completely, or there will be an increase in the mean segment diameter. These results represent slowed progression of atherosclerosis, halted progression of atherosclerosis and regression of atherosclerosis, respectively.

The secondary objective of this study is that the combination of an antihypertensive agent and atorvastatin or a pharmaceutically acceptable salt thereof reduces the rate of progression of atherosclerosis in the carotid arteries as measured by the slope of the maximum intimal-medial thickness measurements averaged over 12 separate wall segments (Mean Max) as a function of time, more than does amlodipine or a pharmaceutically acceptable acid addition salt thereof or atorvastatin or a pharmaceutically acceptable salt thereof alone. The intimal-medial thickness of subjects taking atorvastatin or a pharmaceutically acceptable salt thereof and amlodipine or a pharmaceutically acceptable acid addition salt thereof will increase more slowly, will cease to increase or will decrease. These results represent slowed progression of atherosclerosis, halted progression of atherosclerosis and regression of atherosclerosis, respectively. Further, these results may be used to facilitate dosage determinations.

The utility of the compounds of the present invention as medical agents in the treatment of angina pectoris in mammals (e.g., humans) is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

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Effect of Atorvastatin and an Antihypertensive Agent Alone
and in Combination on the
Treatment of Angina

5 This study is a double blind, parallel arm, randomized study to show the effectiveness of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent given in combination in the treatment of symptomatic angina.

Entry criteria: Subjects are males or females between 18 and 80 years of age with a history of typical chest pain associated with one of the following objective evidences of cardiac ischemia: (1) stress test segment elevation of about one
10 millimeter or more from the ECG; (2) positive treadmill stress test; (3) new wall motion abnormality on ultrasound; or (4) coronary angiogram with a significant qualifying stenosis. Generally a stenosis of about 30-50% is considered to be significant.

Each subject is evaluated for about ten to thirty-two weeks. At least ten
15 weeks are generally required to complete the study. Sufficient subjects are used in this screen to ensure that about 200 to 800 subjects and preferably about 400 subject are evaluated to complete the study. Subjects are screened for compliance with the entry criteria, set forth below, during a four week run in phase. After the screening criteria are met, subjects are washed out from their current anti-anginal medication
20 and stabilized on a long acting nitrate such as nitroglycerine, isosorbide-5-mononitrate or isosorbide dinitrate. The term "washed out", when used in connection with this screen, means the withdrawal of current anti-anginal medication so that substantially all of said medication is eliminated from the body of the subject. A period of eight weeks is preferably allowed for both the wash out period and for the
25 establishment of the subject on stable doses of said nitrate. Subjects having one or two attacks of angina per week while on stable doses of long acting nitrate are generally permitted to skip the wash out phase. After subjects are stabilized on nitrates, the subjects enter the randomization phase provided the subjects continue to have either one or two angina attacks per week. In the randomization phase, the
30 subjects are randomly placed into one of the four arms of the study set forth below. After completing the wash out phase, subjects in compliance with the entry criteria undergo twenty four hour ambulatory electrocardiogram (ECG) such as Holter monitoring, exercise stress testing such as a treadmill and evaluation of myocardial

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perfusion using PET (photon emission tomography) scanning to establish a baseline for each subject. When conducting a stress test, the speed of the treadmill and the gradient of the treadmill can be controlled by a technician. The speed of the treadmill and the angle of the gradient are generally increased during the test. The time
5 intervals between each speed and gradient increase is generally determined using a modified Bruce Protocol.

After the baseline investigations have been completed, subjects are initiated on one of the following four arms of the study: (1) placebo; (2) atorvastatin (about 10 mg to about 80 mg); (3) an antihypertensive agent (dose is dependent upon the
10 particular antihypertensive agent chosen); or (4) a combination of the above doses of atorvastatin and antihypertensive agent together. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of the statin may be used in this invention. Calculation
15 of the dosage amount for these other forms of the statin and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. The subjects are then monitored for two to twenty four weeks.

After the monitoring period has ended, subjects will undergo the following investigations: (1) twenty four hour ambulatory ECG, such as Holter monitoring; (2) exercise stress testing (e.g. treadmill using said modified Bruce Protocol); and (3)
20 evaluation of myocardial perfusion using PET scanning. Patients keep a diary of painful ischemic events and nitroglycerine consumption. It is generally desirable to have an accurate record of the number of anginal attacks suffered by the patient during the duration of the test. Since a patient generally takes nitroglycerin to ease the pain of an anginal attack, the number of times that the patient administers
25 nitroglycerine provides a reasonably accurate record of the number of anginal attacks.

To demonstrate the effectiveness and dosage of the drug combination of this invention, the person conducting the test will evaluate the subject using the tests described. Successful treatment will yield fewer instances of ischemic events as
30 detected by ECG, will allow the subject to exercise longer or at a higher intensity level on the treadmill, or to exercise without pain on the treadmill, or will yield better perfusion or fewer perfusion defects on ultrasound.

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The utility of the compounds of the present invention as medical agents in the treatment of hypertension and hyperlipidemia in mammals (e.g., humans) suffering from a combination of hypertension and hyperlipidemia is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

Effect of Atorvastatin and an Antihypertensive Agent, Alone and in Combination, on the Treatment of Subjects Having Both Hypertension and Hyperlipidemia

This study is a double blind, parallel arm, randomized study to show the effectiveness of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent given in combination in controlling both hypertension and hyperlipidemia in subjects who have mild, moderate, or severe hypertension and hyperlipidemia.

Each subject is evaluated for 10 to 20 weeks and preferably for 14 weeks. Sufficient subjects are used in this screen to ensure that about 400 to 800 subjects are evaluated to complete the study.

Entry criteria: Subjects are male or female adults between 18 and 80 years of age having both hyperlipidemia and hypertension. The presence of hyperlipidemia is evidenced by evaluation of the low density lipoprotein (LDL) level of the subject relative to certain positive risk factors. If the subject has no coronary heart disease (CHD) and has less than two positive risk factors, then the subject is considered to have hyperlipidemia which requires drug therapy if the LDL of the subject is greater than or equal to 190. If the subject has no CHD and has two or more positive risk factors, then the subject is considered to have hyperlipidemia which requires drug therapy if the LDL of the subject is greater than or equal to 160. If the subject has CHD, then the subject is considered to have hyperlipidemia if the LDL of the subject is greater than or equal to 130.

Positive risk factors include (1) male over 45, (2) female over 55 wherein said female is not undergoing hormone replacement therapy (HRT), (3) family history of premature cardiovascular disease, (4) the subject is a current smoker, (5) the subject has diabetes, (6) an HDL of less than 45, and (7) the subject has hypertension. An HDL of greater than 60 is considered a negative risk factor and will offset one of the above mentioned positive risk factors.

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The presence of hypertension is evidenced by a sitting diastolic blood pressure (BP) of greater than 90 or sitting systolic BP of greater than 140. All blood pressures are generally determined as the average of three measurements taken five minutes apart.

- 5 Subjects are screened for compliance with the entry criteria set forth above. After all screening criteria are met, subjects are washed out from their current antihypertensive and lipid lowering medication and are placed on the NCEP ATP II Step 1 diet. The NCEP ATP II (adult treatment panel, 2nd revision) Step 1 diet sets forth the amount of saturated and unsaturated fat which can be consumed as a
- 10 proportion of the total caloric intake. The term "washed out" where used in connection with this screen, means the withdrawal of current antihypertensive and lipid lowering medication so that substantially all of said medication is eliminated from the body of the subject. Newly diagnosed subjects generally remain untreated until the test begins. These subjects are also placed on the NCEP Step 1 diet. After the four
- 15 week wash out and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure and (2) fasting lipid screen. The fasting lipid screen determines baseline lipid levels in the fasting state of a subject. Generally, the subject abstains from food for twelve hours, at which time lipid levels are measured.
- 20 After the baseline investigations are performed subjects are started on one of the following: (1) a fixed dose of an antihypertensive agent, dose dependent upon the particular antihypertensive agent chosen; (2) a fixed dose of atorvastatin, generally about 10 to 80mg; or (3) a combination of the above doses of atorvastatin and an antihypertensive agent together. It will be recognized by a skilled person that the free
- 25 base form or other salt forms of amlodipine besylate or the free base form or other salt forms of the statin may be used in this invention. Calculation of the dosage amount for these other forms of the statin and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. Subjects remain on these doses for a minimum of six weeks, and
- 30 generally for no more than eight weeks. The subjects return to the testing center at the conclusion of the six to eight weeks so that the baseline evaluations can be repeated. The blood pressure of the subject at the conclusion of the study is compared with the blood pressure of the subject upon entry. The lipid screen

measures the total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apoB, VLDL (very low density lipoprotein) and other components of the lipid profile of the subject. Improvements in the values obtained after treatment relative to pretreatment values indicate the utility of the drug combination.

- 5 The utility of the compounds of the present invention as medical agents in the management of cardiac risk in mammals (e.g., humans) at risk for an adverse cardiac event is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

10 Effects of Atorvastatin and an Antihypertensive Agent, Alone
 and in Combination, on Subjects at Risk
 of Future Cardiovascular Events

- This study is a double blind, parallel arm, randomized study to show the effectiveness of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent given in combination in reducing the overall calculated risk of
15 future events in subjects who are at risk for having future cardiovascular events. This risk is calculated by using the Framingham Risk Equation. A subject is considered to be at risk of having a future cardiovascular event if that subject is more than one standard deviation above the mean as calculated by the Framingham Risk Equation.

- The study is used to evaluate the efficacy of a fixed combination of atorvastatin or a
20 pharmaceutically acceptable salt thereof and an antihypertensive agent in controlling cardiovascular risk by controlling both hypertension and hyperlipidemia in patients who have both mild to moderate hypertension and hyperlipidemia.

- Each subject is evaluated for 10 to 20 weeks and preferably for 14 weeks. Sufficient subjects are recruited to ensure that about 400 to 800 subjects are
25 evaluated to complete the study.

- Entry criteria: Subjects included in the study are male or female adult subjects between 18 and 80 years of age with a baseline five year risk which risk is above the median for said subject's age and sex, as defined by the Framingham Heart Study, which is an ongoing prospective study of adult men and women showing that certain
30 risk factors can be used to predict the development of coronary heart disease. The age, sex, systolic and diastolic blood pressure, smoking habit, presence or absence of carbohydrate intolerance, presence or absence of left ventricular hypertrophy, serum cholesterol and high density lipoprotein (HDL) of more than one standard

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deviation above the norm for the Framingham Population are all evaluated in determining whether a patient is at risk for adverse cardiac event. The values for the risk factors are inserted into the Framingham Risk equation and calculated to determine whether a subject is at risk for a future cardiovascular event.

- 5 Subjects are screened for compliance with the entry criteria set forth above. After all screening criteria are met, patients are washed out from their current antihypertensive and lipid lowering medication and any other medication which will impact the results of the screen. The patients are then placed on the NCEP ATP II Step 1 diet, as described above. Newly diagnosed subjects generally remain
- 10 untreated until the test begins. These subjects are also placed on the NCEP ATP II Step 1 diet. After the four week wash out and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure; (2) fasting; (3) lipid screen; (4) glucose tolerance test; (5) ECG; and (6) cardiac ultrasound. These tests are carried out using standard procedures well known to persons skilled in the art.
- 15 The ECG and the cardiac ultrasound are generally used to measure the presence or absence of left ventricular hypertrophy.

- After the baseline investigations are performed patients will be started on one of the following: (1) a fixed dose of an antihypertensive agent, dose dependent upon the particular antihypertensive agent chosen; (2) a fixed dose of atorvastatin (about
- 20 10 to 80mg); or (3) the combination of the above doses of atorvastatin and an antihypertensive agent. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of the statin may be used in this invention. Calculation of the dosage amount for these other forms of the statin and amlodipine besylate is easily accomplished by
- 25 performing a simple ratio relative to the molecular weights of the species involved. Patients are kept on these doses and are asked to return in six to eight weeks so that the baseline evaluations can be repeated. At this time the new values are entered into the Framingham Risk equation to determine whether the subject has a lower, greater or no change in the risk of future cardiovascular event.

- 30 The above assays demonstrating the effectiveness of amlodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof in the treatment of angina pectoris, atherosclerosis, hypertension and hyperlipidemia together, and the management of

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cardiac risk, also provide a means whereby the activities of the compounds of this invention can be compared between themselves and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

5 The following dosage amounts and other dosage amounts set forth elsewhere in this specification and in the appendant claims are for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine the dosage amount required for a subject whose weight falls outside the 65 kg to 70 kg range, based upon the medical history of the subject and
10 the presence of diseases, e.g., diabetes, in the subject. All doses set forth herein, and in the appendant claims, are daily doses.

In general, in accordance with this invention, the below-listed antihypertensive agent is administered in the following dosage amounts:

15 diltiazem, generally about 120 mg to about 480 mg;
verapamil, generally about 20 mg to about 48 mg;
felodipine, generally about 2.5 mg to about 40 mg;
isradipine, generally about 2.5 mg to about 40 mg;
lacidipine, generally about 1 mg to about 6 mg;
20 nicardipine, generally about 32 mg to about 120 mg;
nifedipine, generally about 10 mg to about 120 mg;
nimodipine, generally about 120 mg to about 480 mg;
nisoldipine, generally about 5 mg to about 80 mg;
nitrendipine, generally about 5 mg to about 20 mg;
25 benazepril, generally about 10 mg to about 80 mg;
captopril, generally about 50 mg to about 150 mg;
enalapril, generally about 5 mg to about 40 mg;
fosinopril, generally about 10 mg to about 80 mg;
lisinopril, generally about 10 mg to about 80 mg;

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- quinapril, generally about 10 mg to about 80 mg;
losartan, generally about 25 mg to about 100 mg;
valsartan, generally about 40 mg to about 640 mg;
doxazosin, generally about 0.5 mg to about 16 mg;
5 prazosin, generally about 1 mg to about 40 mg;
trimazosin, generally about 1 mg to about 20 mg; and
amiloride, generally about 5 mg to about 20 mg.

It will be recognized by those skilled in the art that dosages for the above antihypertensive compounds must be individualized to each specific subject. This individualization will depend upon the medical history of the subject and whether the
10 subject is concurrently taking other medications which may or may not interfere or have an adverse effect in combination with the above antihypertensives. Individualization is then achieved by beginning with a low dose of the compound and titrating the amount up until the desired therapeutic effect is achieved.

15 In general, in accordance with this invention, atorvastatin calcium is generally administered in a dosage of about 2.5 mg to about 160 mg. Preferably, atorvastatin calcium is administered in a dosage of about 10 mg to about 80 mg.

The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of
20 this invention together with a pharmaceutically acceptable carrier or diluent. Thus, the compounds of this invention can be administered either individually or together in any conventional oral, parenteral or transdermal dosage form.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets
25 containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate
30 and talc are often very useful for tableting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are

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desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

5 The combination of this invention may also be administered in a controlled-release dosage formulation such as a slow release or a fast release formulation. Such controlled release dosage formulations of the combination of this invention may be prepared according to methods well known to those skilled in the art. The method of administration will be determined by the attendant physician after an evaluation of
10 the subject's condition and requirements.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient
15 saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

Methods of preparing various pharmaceutical compositions with a certain
20 amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

Pharmaceutical compositions according to the invention may contain 0.1%-95% of the compound(s) of this invention, preferably 1%-70%. In any event, the
25 composition or formulation to be administered will contain a quantity of a compound(s) according to the invention in an amount effective to treat the condition or disease of the subject being treated.

Since the present invention relates to the treatment of diseases and conditions with a combination of active ingredients which may be administered
30 separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit includes two separate pharmaceutical compositions: an antihypertensive agent or a pharmaceutically acceptable salt thereof, wherein said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid

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- addition salt thereof and atorvastatin or a pharmaceutically acceptable salt thereof. The kit includes container means for containing the separate compositions such as a divided bottle or a divided foil packet. however, the separate compositions may also be contained within a single, undivided container. Typically the kit includes directions
- 5 for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.
- 10 It should be understood that the invention is not limited to the particular embodiments described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

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183PRODUCT CLAIMS

1. A pharmaceutical composition comprising:
- 5 a. an amount of atorvastatin or a pharmaceutically acceptable salt thereof;
- b. an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof; and
- c. a pharmaceutically acceptable carrier or diluent;
- 10 provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.
2. A pharmaceutical composition of claim 1 wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic
- 15 receptor blocker.
3. A pharmaceutical composition of claim 2 comprising the hemicalcium salt of atorvastatin.
4. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker
- 20 being verapamil, diltiazem, milbefradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine or a pharmaceutically acceptable salt of said calcium channel blocker.
5. A pharmaceutical composition of claim 4 wherein said calcium channel blocker is felodipine, nifedipine or a pharmaceutically acceptable salt thereof.
- 25 6. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan or a pharmaceutically acceptable salt of said A-II antagonist.
7. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is a diuretic, said diuretic being amiloride, bendroflumethiazide
- 30 or a pharmaceutically acceptable salt thereof.
8. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol or a pharmaceutically acceptable salt thereof.

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9. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, capopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, trandolapril or a pharmaceutically acceptable salt thereof.

5 10. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha-adrenergic receptor blocker being doxazosin, prazosin, trimazosin or a pharmaceutically acceptable salt thereof.

10 11. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the sum of the therapeutic effect achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or
15 diluent, said first pharmaceutical composition comprising an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

20 12. A pharmaceutical composition of claim 11 wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

13. A pharmaceutical composition of claim 12 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

25 14. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker being verapamil, diltiazem, mibefradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine.

30 15. A pharmaceutical composition of claim 14 wherein said calcium channel blocker is felodipine or nifedipine.

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16. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan.

5 17. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is a diuretic, said diuretic being amiloride or bendroflumethiazide.

18. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol.

10 19. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril ortrandolapril.

15 20. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha blocker being doxazosin, prazosin or trimazosin.

21. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the sum of the therapeutic effect achieved by administering said first and second pharmaceutical compositions separately and
20 which second pharmaceutical composition comprises an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said
25 antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

22. A pharmaceutical composition of claim 21 wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic
30 receptor blocker.

23. A pharmaceutical composition of claim 22 comprising the hemicalcium salt of atorvastatin.

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24. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker being verapamil, diltiazem, milbepradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine.

5 25. A pharmaceutical composition of claim 24 wherein said calcium channel blocker is felodipine or nifedipine.

26. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan irbesartan or valsartan.

10 27. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is a diuretic, said diuretic being amiloride or bendroflumethiazide.

28. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic
15 receptor blocker being carvedilol.

29. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril ortrandolapril.

30. A pharmaceutical composition of claim 23 wherein said
20 antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha blocker being doxazosin, prazosin or trimazosin.

31. A pharmaceutical composition of claim 11 wherein said therapeutic effect is antianginal; antilatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

25 32. A pharmaceutical composition of claim 13 wherein said therapeutic effect is antianginal; antilatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

33. A pharmaceutical composition of claim 21 wherein said therapeutic effect is antianginal; antilatherosclerotic; antihypertensive and hypolipidemic; or is
30 effective for cardiac risk management.

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34. A pharmaceutical composition of claim 23 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

5 35. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the therapeutic effect achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or
10 diluent, said first pharmaceutical composition comprising an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

15 36. A pharmaceutical composition of claim 35 wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

37. A pharmaceutical composition of claim 36 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

20 38. A pharmaceutical composition of claim 35 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

25 39. A pharmaceutical composition of claim 37 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

30 40. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the therapeutic effect achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or

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a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

41. A pharmaceutical composition of claim 40 wherein said
5 antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.
42. A pharmaceutical composition of claim 41 comprising the hemicalcium salt of atorvastatin.
- 10 43. A pharmaceutical composition of claim 40 wherein said therapeutic effect is antilanginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.
44. A pharmaceutical composition of claim 42 wherein said therapeutic effect is antilanginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is
15 effective for cardiac risk management.
45. A kit for achieving a therapeutic effect in a mammal comprising:
- a. an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;
- 20 b. an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and
- c. container means for containing said first and second dosage forms, provided that said antihypertensive agent is not amlodipine or a
25 pharmaceutically acceptable acid addition salt thereof.
46. A kit of claim 45 comprising the hemicalcium salt of atorvastatin.
47. A method for treating a mammal in need of therapeutic treatment comprising administering to said mammal
- (a) an amount of a first compound, said first compound being
30 atorvastatin or a pharmaceutically acceptable salt thereof; and
- (b) an amount of a second compound, said second compound being an antihypertensive agent or a pharmaceutically acceptable salt thereof;

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wherein said first compound and said second compound are each optionally and independently administered together with a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

- 5 48. A method of claim 47 comprising the hemicalcium salt of atorvastatin.
49. A method of claim 47 wherein said therapeutic treatment comprises antihypertensive and antihyperlipidemic treatment.
50. A method of claim 47 wherein said therapeutic treatment comprises antianginal treatment.
- 10 51. A method of claim 47 wherein said therapeutic treatment comprises cardiac risk management.
52. A method of claim 47 wherein said therapeutic treatment comprises the treatment of atherosclerosis.

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ANEXO 3

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/53, 31/35	A1	(11) International Publication Number: WO 97/38694 (43) International Publication Date: 23 October 1997 (23.10.97)												
(21) International Application Number: PCT/US97/06127 (22) International Filing Date: 14 April 1997 (14.04.97) (30) Priority Data: <table border="0"><tr><td>60/015,689</td><td>17 April 1996 (17.04.96)</td><td>US</td></tr><tr><td>9612082.9</td><td>10 June 1996 (10.06.96)</td><td>GB</td></tr><tr><td>60/020,977</td><td>24 June 1996 (24.06.96)</td><td>US</td></tr><tr><td>9616804.2</td><td>9 August 1996 (09.08.96)</td><td>GB</td></tr></table> (71) Applicant (for all designated States except US): MERCK & CO., INC. (US/US); 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventor; and (73) Inventor/Applicant (for US only): TOBERT, Jonathan, A. (GB/US); 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		60/015,689	17 April 1996 (17.04.96)	US	9612082.9	10 June 1996 (10.06.96)	GB	60/020,977	24 June 1996 (24.06.96)	US	9616804.2	9 August 1996 (09.08.96)	GB	(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, 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). 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>
60/015,689	17 April 1996 (17.04.96)	US												
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(54) Title: COMBINATION THERAPY FOR REDUCING THE RISKS ASSOCIATED WITH CARDIOVASCULAR DISEASE (57) Abstract The instant invention provides methods for preventing or reducing the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a therapeutically effective amount of an HMG-CoA RI in combination with folic acid or a pharmaceutically acceptable salt or ester thereof to a person who is at risk of developing atherosclerosis or who already has atherosclerotic disease.														

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TITLE OF THE INVENTION**COMBINATION THERAPY FOR REDUCING THE RISKS
ASSOCIATED WITH CARDIOVASCULAR DISEASE****5 BACKGROUND OF THE INVENTION**

The instant invention involves a combination therapy comprising the administration of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or HMG-CoA RI) and folic acid or a pharmaceutically acceptable salt or ester thereof for preventing, halting or slowing the progression of atherosclerotic cardiovascular diseases and related conditions and disease events.

There is increasing evidence that high blood levels of homocysteine are associated with an increased risk of coronary heart disease (CHD) and stroke. The mechanism of the association is unknown, but it is well established that folic acid (a B complex vitamin) lowers plasma homocysteine by increasing its catabolism.

It has been clear for several decades that elevated blood cholesterol is a major risk factor for coronary heart disease, and many studies have shown that the risk of CHD events can be reduced by lipid-lowering therapy. Prior to 1987, the lipid-lowering armamentarium was limited essentially to a low saturated fat and cholesterol diet, the bile acid sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of these treatments have limited efficacy or tolerability, or both. Substantial reductions in LDL (low density lipoprotein) cholesterol accompanied by increases in HDL (high density lipoprotein) cholesterol could be achieved by the combination of a lipid-lowering diet and a bile acid sequestrant, with or without the addition of nicotinic acid. However, this therapy is not easy to administer or tolerate and was therefore often unsuccessful except in specialist lipid clinics. The fibrates produce a moderate reduction in LDL cholesterol accompanied by increased HDL cholesterol and a substantial reduction in triglycerides, and because they are well tolerated these drugs have been more widely used. Probuco

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HDL cholesterol, which, because of the strong inverse relationship between HDL cholesterol level and CHD risk, is generally considered undesirable. With the introduction of lovastatin, the first inhibitor of HMG-CoA reductase to become available for prescription in 1987, for the first time physicians were able to obtain large reductions in plasma cholesterol with very few adverse effects.

Recent studies have unequivocally demonstrated that lovastatin, simvastatin and pravastatin, all members of the HMG-CoA reductase inhibitor class, slow the progression of atherosclerotic lesions in the coronary and carotid arteries. Simvastatin and pravastatin have also been shown to reduce the risk of coronary heart disease events, and in the case of simvastatin a highly significant reduction in the risk of coronary death and total mortality has been shown by the Scandinavian Simvastatin Survival Study. This study also provided some evidence for a reduction in cerebrovascular events.

Despite the substantial reduction in the risk of coronary morbidity and mortality achieved by simvastatin, the risk is still substantial in the treated patients. For example, in the Scandinavian Simvastatin Survival Study, the 42% reduction in the risk of coronary death still left 5% of the treated patients to die of their disease over the course of this 5 year study. Further reduction of risk is clearly needed.

The use of folic acid to reduce the risk of cardiovascular disease by reducing homocysteine levels is attractive as this therapy is believed to be almost risk-free (folic acid is a vitamin) and relatively inexpensive. In addition, as the dose of folic acid required to reduce homocysteine is small (typically 1-5 mg daily) and, like HMG-CoA reductase inhibitors, may be given once daily, the active agents can be readily combined in a single tablet, capsule or other dosage form having the same or similar size as the inhibitor of HMG-CoA reductase alone. This would provide patient convenience, an important consideration

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especially in patients who already have coronary heart disease, as such patients generally have several different drugs to take.

SUMMARY OF THE INVENTION

5 The instant invention involves a novel combination therapy comprised of a therapeutically effective amount of an HMG-CoA reductase inhibitor in combination with folic acid or a pharmaceutically acceptable salt or ester thereof.

10 One object of the instant invention is to administer the above-described combination therapy to people who do not yet show clinical signs of atherosclerosis, but who are at risk of developing atherosclerosis and associated diseases. Clinical manifestations of atherosclerosis include atherosclerotic cardiovascular disease such as coronary heart disease (also known as ischemic heart disease),
15 cerebrovascular disease, and peripheral vessel disease. Toward this end, the instant invention provides methods for preventing or reducing the risk of developing atherosclerotic cardiovascular disease, coronary heart disease, cerebrovascular disease and peripheral vessel disease, and preventing or reducing the risk of occurrence, or recurrence where the
20 potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication, by administering the above-described combination therapy to said at-risk persons.

 A second object of the instant invention is to provide the above-described combination therapy to people who have clinical signs
25 of atherosclerosis. Toward this end, the instant invention provides methods for halting or slowing the progression of atherosclerotic cardiovascular disease, coronary heart disease, ischemic heart disease, cerebrovascular disease and peripheral vessel disease, and preventing or reducing the risk of occurrence, or recurrence where the potential
30 exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication, by administering the above-described combination therapy to said persons who have clinically manifest atherosclerotic disease.

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A third object of the instant invention involves the above-described methods further comprising the administration of one or more additional active agents, for example, a bile acid sequestrant, cholesterol absorption inhibitor, squalene synthase inhibitor, and/or niacin, either in separate or combined dosage formulations. A fourth object is to provide pharmaceutical compositions which can be used in the above-described methods. Additional objects will be evident from the following detailed description.

10 DETAILED DESCRIPTION OF THE INVENTION

The instant invention provides methods for preventing or reducing the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a therapeutically effective amount of an HMG-CoA RI in combination with folic acid or a pharmaceutically acceptable salt or ester thereof to a person who is at risk of developing atherosclerosis or who already has atherosclerotic disease.

Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease."

The combination comprised of an HMG-CoA RI and folic acid or folate may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular

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accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease event are those for whom the potential for recurrence of such an event exists.

Accordingly, the instant invention also provides a method for preventing or reducing the risk of occurrence, or recurrence where the potential exists, of an atherosclerotic disease event comprising the administration of a therapeutically effective amount of an HMG-CoA reductase inhibitor in combination with folic acid or folate to a person at risk of developing atherosclerotic disease. The instant combination therapy can also be administered to a person who already has atherosclerotic disease for preventing or reducing the risk of occurrence, or recurrence where the potential exists, of an atherosclerotic disease event.

Persons to be treated with the instant combination therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician practicing in the relevant fields of medicine. Such known risk factors include but are not limited to hypertension, smoking, diabetes, low levels of high density lipoprotein (HDL) cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: National Cholesterol Education Program, Second report of the Expert Panel on *Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II)*, National Institute of Health, National Heart Lung and Blood Institute, NIH Publication No. 93-3095, September 1993; *abbreviated version*: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, *Summary of the second report of the national cholesterol education program (NCEP) Expert Panel on Detection, Evaluation, and*

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Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), JAMA, 1993, 269, pp. 3015-23. People who are identified as having one or more of the above-noted risk factors are intended to be included in the group of people considered at risk for developing atherosclerotic disease. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within the group of people considered to be at risk for having an atherosclerotic disease event.

A compound which inhibits HMG-CoA reductase is used in combination with folic acid or folate to practice the instant invention. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®), simvastatin (ZOCOR®), pravastatin (PRAVACHOL®), fluvastatin (LESCOL®), atorvastatin and rivastatin (also known as cerivastatin). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996). The term HMG-CoA reductase inhibitor is intended to include all pharmaceutically acceptable salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts and esters is included within the scope of this invention.

Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. Preferably, the HMG-CoA RI is selected from lovastatin and simvastatin.

Folic acid or a pharmaceutically acceptable salt or ester thereof is administered in combination with the HMG-CoA reductase inhibitor. Pharmaceutically acceptable salts of folic acid are well known to those skilled in the art and include, for example, the sodium salt and the methylglucamine salt. The acid moiety also lends itself to the preparation of pharmaceutically acceptable esters, and such esters are likewise included in the scope of the invention. The term "folate" is

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used herein to refer to the pharmaceutically acceptable salts and esters of folic acid.

Herein, the term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base.

Ester derivatives of the described compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

The instant method involves the administration of an HMG-CoA reductase inhibitor in combination with folic acid or a folate. This combination therapy includes administration of a single pharmaceutical dosage formulation which contains both the HMG-CoA reductase inhibitor and the folic acid or folate, as well as administration of each active agent in its own separate pharmaceutical dosage formulation. Where separate dosage formulations are used, the HMG-CoA reductase inhibitor and the folic acid or folate can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially. It is preferred that the HMG-CoA reductase inhibitor and the folic acid or folate be co-administered concurrently on a once-a-day dosing schedule. A single dosage formulation comprised of both an HMG-CoA reductase inhibitor and the folic acid or folate is preferred. A single dosage formulation will provide convenience for the patient, which is an important consideration especially for patients who already have coronary heart disease and may be in need of multiple medications.

The term "therapeutically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The dosage regimen utilizing an HMG-CoA RI in combination with folic acid or folate is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the

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route of administration; the renal and hepatic function of the patient; and the particular compound or salt or ester thereof employed. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective dosage amounts to be given to a person in need of the instant combination therapy. Dosage information for HMG-CoA RI's and for folic acid is well known in the art, since several HMG-CoA RI's and nutritional supplements containing folic acid are marketed in the U.S.

10 In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor are intended to be the same or similar to those amounts which are employed for anti-hypercholesterolemic treatment and which are described in the *Physicians' Desk Reference* (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in 15 particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. Preferably, the oral dosage amount of HMG-CoA RI is from about 1 to 200 mg/day, and more preferably from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the 20 specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA RI which has sufficiently greater potency may be given in sub-milligram daily dosages.

As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg; for 25 lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; and for pravastatin sodium, 10 mg, 20 mg, and 40 mg.

The therapeutically effective amount of folic acid to be used in the instant method is intended to be a dosage amount 30 sufficient to reduce the plasma level of homocysteine below the pre-treatment plasma level of homocysteine in the person receiving the combination therapy. Examples of dosage amounts of folic acid are described in the PDR. For example, see at page 119 of the 1996 PDR the heading "Folic Acid" and the reference pages cited therein.

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For example, the daily dosage amount of folic acid or folate employed in the instant combination therapy can be from about 0.1 to 20 mg/day. In particular, the dosage is from about 0.1 to 10 mg/day, more particularly from about 0.1 to 5 mg/day, and most particularly from about 1 to 5 mg/day, based on the free acid weight. For example, the daily dosage amount of folic acid or folate may be selected from 1 mg, 2 mg and 5 mg, based on the free acid weight.

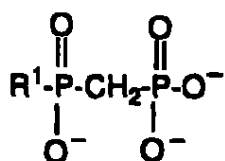
Additional active agents may be combined with the HMG-CoA RI and folic acid or folate in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration. One or more additional active agents may be administered with the HMG-CoA RI and folic acid or folate. The additional active agent or agents can be cholesterol lowering compounds. Examples of additional active agents which may be employed include HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, and gemfibrozil; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; vitamin B6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B12 (also known as cyanocobalamin); aspirin; beta-blockers; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

Examples of HMG-CoA synthase inhibitors include: the beta-lactone derivatives disclosed in U.S. Patent No. 4,806,564, 4,816,477, 4,847,271, and 4,751,237; the beta lactam derivatives disclosed in U.S. 4,983,597 and the substituted oxacyclopropane analogues disclosed in European Patent Publication EP O 411 703. The squalene synthetase inhibitors suitable for use herein include, but are not limited to, those disclosed by Biller *et al.*, *J. Med. Chem.*, 1988 Vol. 31, No. 10, pp. 1869-1871, including isoprenoid (phosphinylmethyl)-phosphonates such as those of the formula

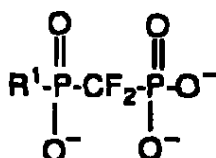
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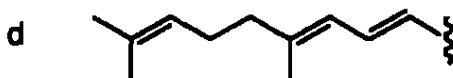
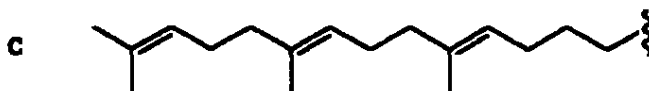
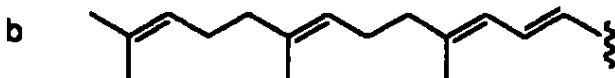
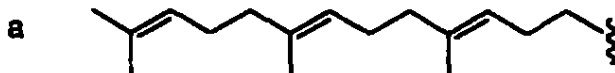
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wherein R¹ is:

including the triacids thereof, triesters thereof and tripotassium and trisodium salts thereof as well as other squalene synthetase inhibitors disclosed in pending U.S. Patent No. 4,871,721 and 4,924,024 and in Biller *et al.*, *J. Med.Chem.*, 1988, Vol. 31, No. 10, pp. 1869 to 1871.

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano *et al.*, *J. Med. Chem.*, 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, *J. Am. Chem. Soc.* 1976, 98, 1291-1293, phosphinylphosphonate reported by McClard, R. W. *et al.*, *J.A.C.S.*, 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, *Dept. Med. Chem. U.*

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of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary.

Further, the benzodiazepine squalene synthase inhibitors described in EP O 567 026 to Takeda Chemical Industries, and the
5 quinuclidinyl squalene synthase inhibitors described in PCT publications WO 94/03451, WO 93/09115, WO 93/21183, WO 93/21184, WO 93/24486, and U.S. 5,135,935, may be co-administered with the HMG-CoA RI plus folic acid or folate
10 type squalene synthase inhibitors as described in U.S. Patents 5,284,758; 5,283,256; 5,262,435; 5,260,332; 5,264,593; 5,260,215; 5,258,401; 5,254,727; 5,256,689; 5,132,320; 5,278,067, and PCT Publications WO 92/12156; WO 92/12157; WO 92/12158; WO 92/12159; WO 92/12160; WO 93/18040; WO 93/18039; WO
15 93/07151; and European Patent Publications EP O 512 865, EP O 568 946; EP O 524,677 and EP O 450 812, as well as the acyclic tricarboxylic acid compounds of U.S. patent 5,254,727, may be employed.

20 Illustrative examples of squalene epoxidase inhibitors are disclosed in European Patent Publication EP O 318 860 and in Japanese Patent Publication JO2 169-571A. LDL-receptor gene inducer molecules are disclosed in U.S. Patent No. 5,182,298.

Examples of bile acid sequestrants which may be employed in the present method include cholestyramine, colestipol,
25 and poly[methyl-(3-trimethylaminopropyl)imino-trimethylene dihalide] and those disclosed in WO95/34585 to Geltex Pharmaceuticals, Inc. and EP O 622 078 assigned to Hisamitsu Pharmaceutical Co., Inc.

30 Examples of cholesterol absorption inhibitors which may be employed in the present method include those described in WO 95/18143 and WO 95/18144 both assigned to Pfizer Inc., and WO 94/17038, WO 95/08532 and WO 93/02048 each assigned to Schering Corp.

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The additional active agents described above which may be employed along with the HMG-CoA RI and folic acid or folate combination therapy can be used, for example, in amounts as indicated in the PDR or in amounts as indicated in the reference disclosures, as appropriate.

Pharmaceutical formulations for both HMG-CoA RI's and for folic acid or folates are well-known to those skilled in the art, as evidenced by the information provided in the 1996 PDR. Methods for preparing various pharmaceutical compositions comprising the combination of an HMG-CoA RI and folic acid or folate are likewise well known to those skilled in the art. For example, see *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA.

For example, the active agents employed in the instant combination therapy can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. The instant invention includes the use of both oral rapid-release and time-controlled release pharmaceutical formulations. Oral formulations are preferred.

In the methods of the present invention, the HMG-CoA RI and the folic acid or folate may be formulated together with or without an additional active agent, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with a non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, modified sugars, modified starches, methyl cellulose and its derivatives, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and other reducing and non-reducing sugars, magnesium stearate, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium

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stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, 5 disintegrating agents and coloring and flavoring agents can also be incorporated into the mixture. Stabilizing agents such as antioxidants (BHA, BHT, propyl gallate, sodium ascorbate, citric acid) can also be added to stabilize the dosage forms. Other suitable components include 10 gelatin, sweeteners, natural and synthetic gums such as acacia, tragacanth or alginates, carboxymethylcellulose, polyethylene glycol, waxes and the like.

Although the active agents of the present method may be administered in divided doses, for example two or three times daily, a single daily dose of each of the HMG-CoA RI and the folic acid or folate 15 is preferred, with a single daily dose of both agents in a single pharmaceutical composition being most preferred.

As such, a therapeutically effective amount of an HMG-CoA RI and folic acid or a pharmaceutically acceptable salt or ester thereof can be used together for the preparation of a medicament useful 20 for preventing or reducing the risk of developing atherosclerotic disease, halting or slowing the progression of atherosclerotic disease once it has become clinically manifest, and preventing or reducing the risk of occurrence, or recurrence where the potential exists, of an atherosclerotic disease event. For example, the medicament may be 25 comprised of folic acid or folate in combination with about 1 mg to 200 mg of an HMG-CoA RI, or more particularly about 5 mg to 160 mg of the HMG-CoA RI. More specific amounts of HMG-CoA RI which may be used in the medicament preparation include 1 mg, 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg, as well as sub-milligram amounts of 30 HMG-CoA RI's which have sufficient potency at such levels. As a further example, the medicament may be comprised of an HMG-CoA RI in combination with about 0.1 to 20 mg of folic acid or folate. In particular, the amount of folic acid or folate used in the preparation of the medicament may be from about 0.1 to 10 mg, or more particularly

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from about 0.1 to 5 mg, and most particularly from about 1 to 5 mg, based on the free acid weight. For example, the medicament may be comprised of 1 mg, 2 mg or 5 mg of folic acid or folate, based on the free acid weight.

5 The above-described medicament may also be prepared with one or more additional active agents such as an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, a squalene synthetase inhibitor, an ACAT inhibitor, probucol, niacin, a fibrate, a cholesterol absorption inhibitor, a bile acid sequesterant, an LDL receptor inducer, vitamin B₆
10 and the pharmaceutically acceptable salts thereof, vitamin B₁₂, aspirin, beta-blockers, vitamin C, vitamin E and beta carotene.

 An example of an oral dosage formulation comprising both an HMG-CoA RI and folic acid which is suitable for use in practicing the instant method invention is as follows:

15

<u>Ingredient</u>	<u>Amount</u>
simvastatin	1 - 200 mg.
folic acid or folic acid equivalent	0.05 - 20 mg.
diluent binder disintegrant lubricant	excipients qs. 200 - 400 mg.

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More specific examples of oral dosage formulations are as follows.

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EXAMPLE 1

	<u>Ingredient</u>	<u>Amount</u>
	Simvastatin	5.0 mg
5	BHA	0.02mg
	Ascorbic acid	2.50 mg
	Citric acid	1.25 mg
	Microcrystalline cellulose	5.0 mg
	Pregel starch	10.0 mg
10	Magnesium stearate	0.5 mg
	Lactose	74.73 mg
	Folic acid	1.0 mg

- 15 All the ingredients except magnesium stearate are blended together in a suitable mixer. The powder mixture is then granulated with adequate quantities of granulating solvent(s). The wet granulated mass is dried in a suitable dryer. The dried granulation is sized through a suitable screen. The sized granulation is mixed with magnesium
- 20 stearate before tableting. The tablets may be coated if deemed necessary. Additional ingredients that may be added to the above include suitable color and mixtures of colors.

EXAMPLE 2

25	<u>Ingredient</u>	<u>Amount</u>
	Simvastatin	5.0 mg
	BHA	0.04 mg
	Citric acid	2.5 mg
30	Microcrystalline cellulose	10.0 mg
	Pregel starch	20.0 mg
	Magnesium stearate	1.0 mg
	Lactose	148.46 mg
	Folic acid	5.0 mg
35	Hydrolized gelatin	8.0 mg

The process of manufacture is essentially the same as in Example 1, above.

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EXAMPLE 3

	<u>Ingredient</u>	<u>Amount</u>
	Simvastatin ✓	80.0 mg
5	BHA	0.16 mg
	Ascorbic acid	20.0 mg
	Citric acid	10.0 mg
	Microcrystalline cellulose	40.0 mg
	Pregel starch	80.0 mg
10	Lactose	550.0 mg
	Folic acid	10.0 mg
	Colorant	5.0 mg
	Magnesium stearate	4.8 mg

- 15 The process of manufacture is essentially the same as in Example 1, above.

- 20 While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the
- 25 mammal being treated for any of the indications for the active agents used in the instant invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or
- 30 whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as
- 35 broadly as is reasonable.

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WHAT IS CLAIMED IS:

1. A method for preventing or reducing the risk of developing atherosclerotic disease comprising the administration of a therapeutically effective amount of an HMG-CoA reductase inhibitor in combination with folic acid or a pharmaceutically acceptable salt or ester thereof to a person at risk of developing atherosclerotic disease.
2. The method of Claim 1 wherein the atherosclerotic disease is selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.
3. The method of Claim 2 wherein the cardiovascular disease is coronary heart disease.
4. The method of Claim 1 wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin and the pharmaceutically acceptable salts and esters thereof.
5. The method of Claim 4 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.
6. The method of Claim 1 wherein the pharmaceutically acceptable salt of folic acid is selected from the sodium salt and the methylglucamine salt.
7. The method of Claim 1 further comprising the administration of a therapeutically effective amount of an active agent selected from an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, a squalene synthetase inhibitor, an ACAT inhibitor, probucol, niacin, a fibrate, a cholesterol absorption inhibitor, a bile acid sequestrant, an LDL receptor inducer, vitamin B6 and the

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pharmaceutically acceptable salts thereof, vitamin B12, aspirin, a beta-blocker, vitamin C, vitamin E and beta carotene.

5 8. A method for halting or slowing the progression of atherosclerotic disease comprising the administration of a therapeutically effective amount of an HMG-CoA reductase inhibitor in combination with folic acid or a pharmaceutically acceptable salt or ester thereof to a person who has atherosclerotic disease.

10 9. The method of Claim 8 wherein the atherosclerotic disease is selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

15 10. The method of Claim 9 wherein the cardiovascular disease is coronary heart disease.

20 11. The method of Claim 8 wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin and the pharmaceutically acceptable salts and esters thereof.

 12. The method of Claim 11 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

25 13. The method of Claim 8 wherein the pharmaceutically acceptable salt of folic acid is selected from the sodium salt and the methylglucamine salt.

30 14 The method of Claim 8 further comprising the administration of a therapeutically effective amount of an active agent selected from an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, a squalene synthetase inhibitor, an ACAT inhibitor, probucol, niacin, a fibrate, a cholesterol absorption inhibitor, a bile acid sequesterant, an LDL receptor inducer, vitamin B6 and the

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pharmaceutically acceptable salts thereof, vitamin B12, aspirin, a beta-blocker, vitamin C, vitamin E and beta carotene.

5 15. A method for preventing or reducing the risk of
occurrence, or recurrence where the potential exists, of an
atherosclerotic disease event comprising the administration of a
therapeutically effective amount of an HMG-CoA reductase inhibitor in
combination with folic acid or a pharmaceutically acceptable salt or
10 ester thereof to a person at risk of having an atherosclerotic disease
event.

 16. The method of Claim 15 wherein the person
receiving the administration has atherosclerotic disease.

15 17. The method of Claim 15 wherein the person
receiving the administration is at risk of developing atherosclerotic
disease.

 18. The method of Claim 15 wherein the atherosclerotic
20 disease event is selected from a coronary heart disease event, a
cerebrovascular event and intermittent claudication.

 19. The method of Claim 18 wherein the coronary heart
disease event is selected from coronary heart disease death, myocardial
25 infarction, and coronary revascularization procedures.

 20. The method of Claim 18 wherein the cerebrovascular
event is selected from a cerebrovascular accident and a transient
ischemic attack.

30 21. The method of Claim 15 wherein the HMG-CoA
reductase inhibitor is selected from lovastatin, simvastatin, pravastatin,
fluvastatin, atorvastatin, rivastatin and the pharmaceutically acceptable
salts and esters thereof.

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22. The method of Claim 21 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

5 23. The method of Claim 15 wherein the pharmaceutically acceptable salt of folic acid is selected from the sodium salt and the methylglucamine salt.

10 24. The method of Claim 15 further comprising the administration of a therapeutically effective amount of an active agent selected from HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, a squalene synthetase inhibitor, an ACAT inhibitor, probucol, niacin, a fibrate, a cholesterol absorption inhibitor, a bile acid sequesterant, an LDL receptor inducer, vitamin B6 and the
15 pharmaceutically acceptable salts thereof, vitamin B12, aspirin, a beta-blocker, vitamin C, vitamin E and beta carotene.

20 25. A pharmaceutical composition comprising a therapeutically effective amount of an HMG-CoA reductase inhibitor, a therapeutically effective amount of folic acid or a pharmaceutically acceptable salt or ester thereof, and a pharmaceutically acceptable carrier.

25 26. The composition of Claim 25 wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin and the pharmaceutically acceptable salts and esters thereof.

30 27. The composition of Claim 26 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

28. The composition of Claim 25 wherein the pharmaceutically acceptable salt of folic acid is selected from the sodium salt and the methylglucamine salt.

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29. The composition of Claim 25 further comprising a therapeutically effective amount of an active agent selected from an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, a squalene synthetase inhibitor, an ACAT inhibitor, probucol, niacin, a fibrate, a cholesterol absorption inhibitor, a bile acid sequesterant, an LDL receptor inducer, vitamin B6 and the pharmaceutically acceptable salts thereof, vitamin B12, aspirin, a beta-blocker, vitamin C, vitamin E and beta carotene.
30. The use of an HMG-CoA reductase inhibitor together with folic acid or a pharmaceutically acceptable salt or ester thereof for the preparation of a medicament useful for preventing or reducing the risk of developing atherosclerotic disease.
31. The use of an HMG-CoA reductase inhibitor together with folic acid or a pharmaceutically acceptable salt or ester thereof for the preparation of a medicament useful for halting or slowing the progression of atherosclerotic disease.
32. The use of an HMG-CoA reductase inhibitor together with folic acid or a pharmaceutically acceptable salt or ester thereof for the preparation of a medicament useful for preventing or reducing the risk of occurrence, or recurrence where the potential exists, of an atherosclerotic disease event.
33. A process for preparing the pharmaceutical composition as claimed in any one of Claims 25 to 28 comprising admixing an HMG-CoA reductase inhibitor and folic acid or a pharmaceutically acceptable salt or ester thereof with a pharmaceutically acceptable carrier.
34. A process for preparing the pharmaceutical composition as claimed in Claim 29 comprising admixing an HMG-CoA

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reductase inhibitor, folic acid or a pharmaceutically acceptable salt or ester thereof, and one or more additional active agents selected from an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, a squalene synthetase inhibitor, an ACAT inhibitor, probucol, niacin, a fibrate, a cholesterol absorption inhibitor, a bile acid sequesterant, an LDL receptor inducer, vitamin B6 and the pharmaceutically acceptable salts thereof, vitamin B12, aspirin, a beta-blocker, vitamin C, vitamin E and beta carotene, with a pharmaceutically acceptable carrier.

10 35. The use of an HMG-CoA reductase inhibitor for the preparation of a medicament for the combined use with folic acid or a pharmaceutically acceptable salt or ester thereof for preventing or reducing the risk of developing atherosclerotic disease, for halting or slowing the progression of atherosclerotic disease, or for preventing or
15 reducing the risk of occurrence, or recurrence where the potential exists, of an atherosclerotic disease event.

 36. The use of folic acid or a pharmaceutically acceptable salt or ester thereof for the preparation of a medicament for the
20 combined use with an HMG-CoA reductase inhibitor for preventing or reducing the risk of developing atherosclerotic disease, for halting or slowing the progression of atherosclerotic disease, or for preventing or reducing the risk of occurrence, or recurrence where the potential
25 exists, of an atherosclerotic disease event.

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ANEXO 4



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The effects of combined treatment with beta 1-selective receptor antagonists and lipid-lowering drugs on fat metabolism and measures of fatigue during moderate intensity exercise: a placebo-controlled study in healthy subjects.

Eagles C.J, Kendall M.J.

Department of Medicine, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK.

AIMS: We examined the effects of different combinations of beta 1-selective adrenoceptor blockers and lipid-lowering drugs, on fat metabolism and fatigue during moderate intensity exercise in 14 healthy young volunteers. **METHODS:** The study was a randomized crossover design, each subject completing 5, 90 min walks at 50% of predetermined maximal oxygen uptake (VO_2 max), one following each 3 day treatment period with either: atenolol 100 mg and bezafibrate 400 mg, atenolol 100 mg and fluvastatin 40 mg, metoprolol CR 100 mg and bezafibrate 400 mg, metoprolol CR 100 mg and fluvastatin 40 mg, or placebo. **RESULTS:** Plasma free fatty acid (FFA) concentration during exercise was significantly reduced on all treatments, in comparison with placebo, $P = 0.0001$. Following 90 min of exercise FFA levels were as follows: placebo 573 $\mu\text{mol l}^{-1}$ (105-1041), metoprolol CR + fluvastatin 277 $\mu\text{mol l}^{-1}$ (0-647), metoprolol CR + bezafibrate 182 $\mu\text{mol l}^{-1}$ (0-396), atenolol + fluvastatin 211 $\mu\text{mol l}^{-1}$ (0-511), and atenolol + bezafibrate 123 $\mu\text{mol l}^{-1}$ (0-352). Total fat oxidation during exercise was also reduced on all treatments in comparison with placebo: 38.1% (2-74), compared with 29.1% (0-61) on metoprolol CR + fluvastatin, $P = 0.02$, 26.2% (2-51) on metoprolol CR + bezafibrate, $P = 0.002$, 25.5% (3-48) on atenolol + fluvastatin, $P = 0.009$, and 22.8% (0-47) on atenolol + bezafibrate treatment, $P = 0.0002$. Plasma ammonia concentration was elevated on all treatments during exercise in comparison with placebo. After 90 min of exercise, plasma ammonia levels were as follows: placebo 37 $\mu\text{mol l}^{-1}$ (0-84), metoprolol CR + fluvastatin 56 $\mu\text{mol l}^{-1}$ (2-110), metoprolol CR + bezafibrate 79 $\mu\text{mol l}^{-1}$ (0-167), atenolol + fluvastatin 90 $\mu\text{mol l}^{-1}$ (10-170), and atenolol + bezafibrate 100 $\mu\text{mol l}^{-1}$ (26-174). In comparison with placebo, metoprolol CR + fluvastatin had the least adverse impact on measures of perceived exertion and the 'feeling scale' during exercise. Metoprolol CR + bezafibrate, atenolol + fluvastatin, and atenolol + bezafibrate treatments had greater adverse effects, particularly on perceived 'cardiorespiratory effort' and 'feeling scale' scores. **CONCLUSIONS:** In healthy volunteers, combinations of beta 1-selective blockers and lipid-lowering drugs were associated with significant reductions in fat metabolism, increased plasma ammonia levels, and raised the perception of effort during exercise, in comparison with placebo. Metoprolol CR + fluvastatin had the least effect, combinations metoprolol CR + bezafibrate and atenolol + fluvastatin had

intermediate effects, and atenolol + bezafibrate had the most adverse effect.

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Treatment of hypertensive and hypercholesterolaemic patients in general practice. The effect of captopril, atenolol and pravastatin combined with life style intervention.

Foss OP, Graff-Iversen S, Istad H, Soyland E, Tjeldflaat L, Graving B.

Department of Clinical Chemistry, Ullevaal Hospital, Oslo, Norway.

OBJECTIVE: To elucidate the effect on blood pressure and blood lipids of an angiotensin converting enzyme inhibitor (captopril), and a beta-receptor blocking agent (atenolol), given alone or in combination with a cholesterol reducing drug, the beta-hydroxy-methylglutaryl-coenzyme A reductase inhibitor pravastatin, in patients who were also encouraged to improve their lifestyle. **DESIGN:** A longitudinal study consisting of three phases. I: Lifestyle intervention alone. II: Continued lifestyle intervention combined with captopril or atenolol. III: Continued lifestyle intervention combined with the same drugs as in phase II and in addition pravastatin or placebo. **SETTING:** Fifty-four general practice surgeries in Norway. **PARTICIPANTS:** Hypertensive patients, 210 females and 160 males, treated or untreated with antihypertensive drugs with a sitting diastolic blood pressure between 95 and 115 mmHg and a serum total cholesterol between 6.5 mmol/l (7.0 for those age 60-67 years) and 9.0 mmol/l. **RESULTS:** The antihypertensive effect of captopril and atenolol was not influenced by concurrent administration of pravastatin. The effect of pravastatin was not limited by concurrent medication with captopril or atenolol. Improvement in lifestyle seemed to reduce the need for supplementary treatment with diuretics. **CONCLUSION:** Pravastatin can be used in combination with captopril or atenolol in the treatment of hypertensive and hypercholesterolaemic patients.

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Lovastatin and coadministered antihypertensive/cardiovascular agents.**Pool JL, Shear CL, Downton M, Schnaper H, Stinnett S, Dujovne C, Bradford RH, Chremos AN.**

Department of Medicine, Baylor College of Medicine, Houston, Tex.

Hypertension and hypercholesterolemia frequently coexist and may require concomitant drug treatments. The efficacy and safety profile of lovastatin given in the presence of antihypertensive medication was evaluated using patient subgroups identified in the Expanded Clinical Evaluation of Lovastatin (EXCEL) Study. The EXCEL study examined 8,245 patients with moderate hypercholesterolemia randomly assigned either to a group treated with lovastatin (20-80 mg daily) or to a group given placebo for 48 weeks. After adjustment for patient characteristics, pairwise comparisons were made between patients taking no antihypertensive agents ($n = 3,772$) and those taking either calcium antagonists ($n = 446$), selective beta 1-adrenergic receptor blockers ($n = 326$), nonselective beta-adrenergic receptor blockers ($n = 219$), potassium-sparing diuretics ($n = 187$), thiazide diuretics ($n = 126$), or angiotensin converting enzyme inhibitors ($n = 171$). The placebo-corrected dose-dependent effect of lovastatin on the percent change from baseline in low-density lipoprotein cholesterol was not attenuated in any subgroup and was slightly enhanced in the calcium antagonist subgroup (-29% to -44%, $p = 0.06$) when compared with patients taking no antihypertensive agents (-24% to -40%); this difference, however, was only of borderline significance. Patterns of lovastatin-induced increase in high-density lipoprotein cholesterol and decrease in triglycerides were not consistently different among the subgroups. Examination of mean changes in serum transaminases, mean changes in creatine kinase, and the proportion of patients discontinuing therapy for clinical adverse experiences did not indicate the presence of an interaction. (ABSTRACT TRUNCATED AT 250 WORDS)

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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 Luis Fernando Rincón Cuellar, en su calidad de apoderado de Procaps 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
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 12 NOV. 2004.

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