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Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Doctor,

JAIRO RUBIO ESCOBAR

Superintendente de Industria y Comercio

E. S. D.

SUPERINTENDENCIA Y COMERCIO
Sede: Bogotá, D.C. Tel: 371 4000
Fecha (AMD): 2005-05-23 10:00:00
Trámite: 1. REGISTRO DE MARCAS Y DISEÑOS
Dependencia: 2005 DIVISION DE MARCAS Y DISEÑOS

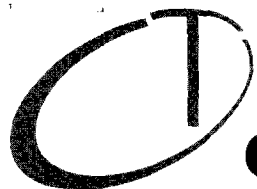
Referencia : Expediente N° 00-029421

Asunto : Remisión de información a la solicitud de patente de
Invención titulada "EFECTOS SINÉRGICOS DE LA
AMLODIPINA Y ATORVASTATINA Ó METABOLITO DE
LA ATORVASTATINA COMO BASE PARA UNA
TERAPIA COMBINADA".

Solicitante: Dr. K. PRESTON MASON

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, con el animo de colaborar con esa Entidad en la decisión que sobre la patentabilidad de la solicitud de la referencia se tomará, me permito solicitarle, muy respetuosamente, dar curso a la siguiente información relativa al arte anterior relevante para que sea tomado en cuenta en el estudio de patentabilidad de la solicitud de patente de Invención de la referencia.

1. PETICIÓN.



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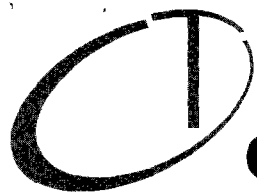
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Derecho de la Competencia, Propiedad
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Ruego al Señor Superintendente, **NEGAR**, en los términos de artículo 48 de la Decisión 486 de 2000 de la CAN, la Solicitud de Patente de Invención denominada **“EFECTOS SINÉRGICOS DE LA AMLODIPINA Y ATORVASTATINA Ó METABOLITO DE LA ATORVASTATINA COMO BASE PARA UNA TERAPIA COMBINADA”**, cuyo solicitante es el **Dr. K. PRESTON MASON**, con base en los siguientes hechos y fundamentos de derecho, relacionados con el incumplimiento de los requisitos fundamentales exigidos para la concesión de Patentes de Invención, según la legislación vigente.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 24 de abril de 2000, reivindicando prioridad bajo las solicitudes de Estado Unidos de América 60/130.659 del 1999-04-23; 60/130.665 del 1999-04-23; 60/145.305 del 1999-07-23; 60/151.121 del 1999-08-27; y, 60/166.592 del 1999-11-19 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 517 del 27 de junio de 2002.
- 2.2. La solicitud colombiana 00-029421 objeto de la presente remisión, se refiere a la combinación de la amlodipina con atorvastatina o un metabolito de la atorvastatina muestra un efecto antioxidante sinérgico sobre la peroxidación lipídica en las lipoproteínas de baja densidad humanas y las vesículas de membrana enriquecidas con ácidos grasos poliinsaturados. La inhibición del daño oxi-radical por esta combinación farmacológica fue observada a niveles terapéuticos de una manera no reproducible por la combinación de amlodipina con otras estatinas o el antioxidante natural, la vitamina E. La base de esta actividad potente es atribuida a las estructuras químicas de estos compuestos y sus interacciones moleculares con moléculas fosfolípidas, tal como se determina mediante análisis de difracción de



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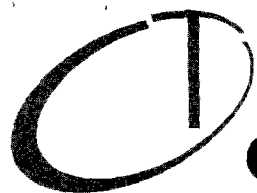
Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

los rayos X. Esta terapia combinada puede ser utilizada para tratar trastornos cardiovasculares, especialmente la enfermedad coronaria, al incrementar la resistencia de las lipoproteínas de baja densidad y de las membranas celulares vasculares contra la modificación oxidativa.

2.3. Lo primero que hay que decir es que esta solicitud de patente no cumple con los requerimientos consagrados en el artículo 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 referido al método de tratamiento definido en el capítulo reivindicatorio de la presente solicitud no puede ser objeto de patente en Colombia. Ellas se refieren directamente a un método terapéutico para el tratamiento humano. Por lo tanto, dichas reivindicaciones referidas al método terapéutico no deben ser objeto de patentabilidad.

2.4. De otra parte el artículo 14 de la Decisión 486 de la CAN consagra 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"*. Así las cosas, 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: US4681893, 1987-07-21.
- D2: WO9911260, 1999-03-11
- D3: US5155120, 1992-10-13
- D4: WO9911259, 1999-03-11



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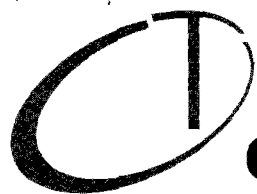
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2.5. Básicamente, la presente solicitud se refiere a la combinación de la amlodipina con atorvastatina

2.6. Ahora bien, es sabido que si un sujeto padece de la presencia exagerada de lípidos (grasas) circulantes en la sangre (hiperlipidemia), es posible que esto le ocasione enfermedades cardíacas, endurecimiento de las arterias o ataque cerebral. En el documento D1, se evidencia la existencia de una medicación antihiperlipidémica. Según dicho documento D1, en casos de hiperlipidemia, es necesaria una medicación para tratar al sujeto y tal terapia puede comprender una composición que incluya una estatina inhibidora de HMG-CoA reductasa con su utilización como un antihiperlipidémico. Ahora bien, con base en el mismo documento D1, es posible derivar que la atorvastatina es una estatina de inhibidor selectivo y competitivo de la hidroximetilglutaril-coenzima A (HMG-CoA) reductasa. Así las cosas, con base en este documento D1, podemos concluir que la atorvastatina y su uso en el tratamiento de la hiperlipidemia y la hipocolesterolemia es conocido hacia el 21 de julio de 1987. Así lo evidencia dicho documento.

2.7. Por su parte, el documento D2 revela combinaciones entre atorvastatina y agentes hipertensivos. Según este documento D2, dicha combinación es utilizada para el tratamiento en sujetos que sufren de angina de pecho y aterosclerosis combinado con hipertensión e hiperlipidemia y para el tratamiento en sujetos que presentan síntomas de riesgos cardíacos. Así las cosas, el uso de combinaciones entre estatinas e antihipertensivos, es conocido con anterioridad y esto se evidencia en el documento D2.

2.8. En materia de antihipertensivos, el documento D3 revela el compuesto de la amlodipina, junto con la acción como bloqueador de los canales de calcio y su utilidad como antihipertensivo y la falla cardíaca congestiva. Según la acción terapéutica indicada en el producto comercializado bajo la marca **NORVASC®**, por **PFIZER**, mismo titular del documento D3, la amlodipina está indicada para el



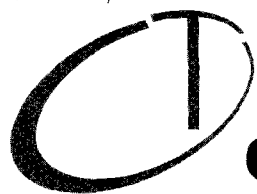
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tratamiento de la hipertensión arterial esencial y en la isquemia del miocardio. Por lo tanto, con base en este documento D3, es posible deducir que el amlodipino y su acción como bloqueador de los canales de calcio y su utilidad como antihipertensivo y la falla cardiaca congestiva es conocido hacia el 13 de octubre de 1992.

2.9. Ahora bien, si un sujeto sufre de hiperlipidemia y hipocolesterolemia en conjunto con hipertensión arterial esencial e isquemia del miocardio, será obvio que un especialista en el arte, debe recomendar administrar al sujeto medicamentos que incluyan amlodipino y atorvastatina, según un esquema previamente evaluado. Por lo tanto, debe ser claro, que a la luz de los documentos D1, D2 y D3 en combinación, es posible deducir lo que pretende la invención objeto de protección. El nivel de obviedad, sin lugar a dudas puede estar basado en que los medicamentos independientes tienen sus aplicaciones concretas, debidamente estudiadas y referenciadas desde 1987 para la atorvastatina y 1992 para amlodipino, de manera tal que una persona versada en la materia recomendaría la administración de amlodipino para tratar la hipertensión arterial esencial e isquemia del miocardio y recomendaría la administración de atorvastatina para tratar la hiperlipidemia y hipocolesterolemia. Ahora bien, si el paciente padece en combinación de estos males, pues será mucho más obvio que se le recomendaría administrar una dosis de amlodipino y una dosis de atorvastatina al mismo paciente. En consecuencia, la solicitud objeto de patentabilidad, bajo la óptica de los documentos D1, D2 y D3, carece de nivel inventivo, toda vez que cualquier persona versada puede derivar un uso de medicamentos que incluyan estas sustancias combinadas para tratar los males indicados también combinados.

2.10. Ahora bien, el documento D4, revela combinaciones farmacéuticas de amlodipina o de una sal de adición de ésta, farmacéuticamente aceptable, y de atorvastatina o de una sal de ésta farmacéuticamente aceptable así como kits que



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contienen estas combinaciones y a procedimientos de utilización de estas combinaciones para tratar sujetos que padecen angina de pecho, aterosclerosis, hipertensión e hiperlipidemia combinadas y para tratar sujetos que presentan síntomas de riesgos cardiacos. Este documento D4 se refiere también a combinaciones aditivas y sinérgicas de amlodipina y de atorvastatina que sirven para tratar sujetos que padecen de angina de pecho, de aterosclerosis, de hipertensión y de hiperlipidemia combinadas y sujetos que presentan síntomas de riesgos cardiacos. Así las cosas, una combinación dentro de un mismo medicamento que comprenda amlodipina y atorvastatina combinado, es conocido en la técnica desde 11 de marzo de 1999.

2.11. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 00-029421 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los tres requisitos necesarios para su protección.

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

2.12.1. **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, 23 de abril de 1999, ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D4, un medicamento que comprenda amlodipina y atorvastatina combinado sobre el cual busca protección en el capítulo reivindicatorio.

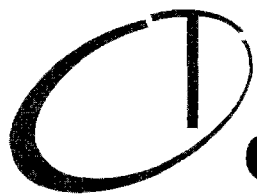
2.12.2. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- "Se considerará que una

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 prioridad, 23 de abril de 1999, a partir de los documentos D1, D2, y D3 en combinación, es posible deducir un medicamento que comprenda amlodipina y atorvastatina combinado según lo definido en las reivindicaciones de la presente solicitud.

2.12.3. 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 anteriormente, algunas cláusulas reclaman un método de tratamiento. Éstos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los métodos de tratamiento, no cumplen con el requisito de la aplicación industrial.

2.13. 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 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.



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- 2.14. 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.
- 2.15. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“EFECTOS SINÉRGICOS DE LA AMLODIPINA Y ATORVASTATINA Ó METABOLITO DE LA ATORVASTATINA COMO BASE PARA UNA TERAPIA COMBINADA”**, cuyo solicitante es el **Dr. K. PRESTON MASON**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 517.

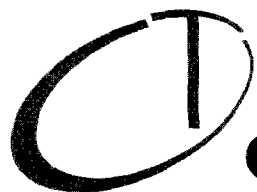
3. PRUEBAS

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

- D1: US4681893, 1987-07-21.
- D2: WO9911260, 1999-03-11
- D3: US5155120, 1992-10-13
- D4: WO9911259, 1999-03-11

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:



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- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 48 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

- D1: US4681893, 1987-07-21.
- D2: WO9911260, 1999-03-11
- D3: US5155120, 1992-10-13
- D4: WO9911259, 1999-03-11

6. NOTIFICACIONES

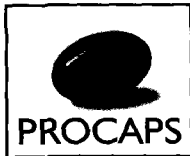
Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la calle 119ª N° 53-99 de esta ciudad de Bogotá.

Señor Superintendente,

LUIS FERNANDO RINCÓN-CUELLAR

C.C. 79'532.186 de Bogotá

T.P.A. 113.438 del C.S. de la J.



PODER ESPECIAL

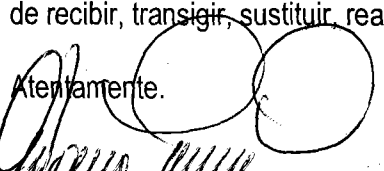
Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
Ciudad

Referencia: Poder- Remisión de información a la solicitud de patente N° 00-029421.

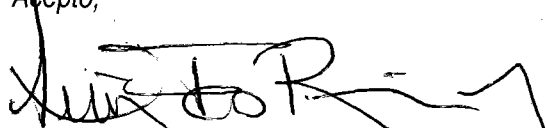
Yo, WALTER TANAKA TATEKAWA, mayor de edad, identificado con la cédula de ciudadanía No. 16.251.923, domiciliado y residente en la ciudad de Barranquilla, actuando en nombre y representación de la sociedad PROCAPS S.A., con NIT 890.106.527-5, manifiesto que confiero poder especial, amplio y suficiente 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 una remisión de información en relación a la patentabilidad de la solicitud de la referencia titulada "**EFFECTOS SINÉRGICOS DE LA AMLODIPINA Y ATORVASTATINA Ó METABOLITO DE LA ATORVASTATINA COMO BASE PARA UNA TERAPIA COMBINADA**", cuyo solicitante es el **Dr. K. PRESTON MASON**.

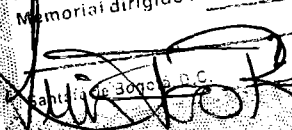
Mi apoderado cuenta con amplias facultades para el ejercicio del presente poder, en especial las de recibir, transigir, sustituir, reasumir y desistir.

Atentamente.


WALTER TANAKA TATEKAWA
REPRESENTANTE LEGAL
PROCAPS S.A.,
C.C. 16.251.923 de Palmira *patras*

Acepto,


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

DECLARACION DE RECONOCIMIENTO
Y PRESENTACION
Ante el Notario Once del Circuito de Santa Fe de Bogotá, compareció
Luis Fernando Rincon Cuellar
Quien exhibió la C.C. No. **79.532.186**
expedida en **BT** **113.438**
y declaró que la firma y huella que aparecen en
el presente memorial son suyos y que el contenido del mismo es cierto.
Memorial dirigido a **Dr. K. Preston Mason**
8 SET 2005
Firma del Declarante 
Autorizó la anterior Declaración
REPUBLICA DE COLOMBIA
NOTARIA DEL CIRCUITO DE SANTA FE DE BOGOTA
NOTARIO ONCE DEL CIRCUITO DE SANTA FE DE BOGOTA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE



***** Pag.01
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
06*****
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 bajo
el No. 6,070 del libro respectivo, fue constituida la sociedad
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA
"PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura 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 bajo

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

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

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
416	3/ 3/2005	Notaria 2. de Barranquilla	116,364	3/10/2005
1,613	7/28/2005	Notaria 2. de Barranquilla	119,322	8/18/2005

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
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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 los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, de-

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

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

C E R T I F I C A

CAPITAL:	Nro. Acciones	Valor Accion
AUTORIZADO:		
\$*****2,000,000,000.00	2,000,000.00	1,000.00
SUSCRITO:		
\$*****1,220,000,000.00	1,220,000.00	1,000.00
PAGADO:		
\$*****1,220,000,000.00	1,220,000.00	1,000.00

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde 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 *****



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

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente. -----

C E R T I F I C A

Que 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, correspon a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, hechos los siguientes nombramientos: -----

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



***** Pag.04

CAMARA DE COMERCIO
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PROCAPS S.A. -----

Cargo	Nombre	Identificacion
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: -----

PROCAPS S.A. -----

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, otorgada 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. GRUPO 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. GRUPO 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 DIAZ GRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requerira 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

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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

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

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

PROCAPS S.A. -----

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2.004, bajo el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribir en el giro normal de sus negocios y operaciones sociales. Por lo anterior, el señor ANTONIO VARELA DIAZ, queda facultado para firmar las declaraciones comabiarias y demas documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo acto necesario de tal forma que pueda cumplir con el mandato dado.-

C E R T I F I C A

Que segun documento privado del 22 de Febrero de 2005, inscrito en esta Camara de Comercio el 28 de Marzo de 2.005, bajo el No. 2.820 del libro respectivo, consta que WALTER TANAKA TATEKAWA C.C. 16.251-923 de Palmira, quien actua como representante legal de la sociedad PROCAPS S.A, otorga Poder Especial, Amplio y Suficiente al señor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los tramites o registros de comercio exterior ante la direccion de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces, y para que responda todo tipo de requerimientos y/o solicitudes de informacion de las autoridades aduaneras en los ordenes distrital, departamental y nacional.-----

C E R T I F I C A

Que por Escritura Publica No.1.613 del 28 de Junio del 2.005, otorgada en la Notaria Segunda de Barranquilla, inscrita en esta Camara de Comercio el 18 de agosto del 2.005 bajo el No.2.913 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C.No.7.463.928, en su condicion de Presidente y Representante Legal de la sociedad PROCAPS S.A., 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 suministro de mercancías y servicios con entidades oficiales, hasta por la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS DE AMERICA (US\$800.000), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GRUPO A: MIRIAM RODRIGUEZ DIAZ, C.C.No. 41.473.569. GRUPO B: NELSON SUAREZ CHAVEZ, C.C.No.79.417.971.-----

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 *****



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CAMARA DE COMERCIO
DE BARRANQUILLA

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

C E R T I F I C A

Que su ultima Renovacion fue el: 23 de Marzo de 2,005. -----

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

maribel

NO CAUSA IMPUESTO DE TIMBRE

EL SECRETARIO
MARIBEL REYES OVIEDO

NO ES VALIDO POR ESTA CARA

NO ES VALIDO POR ESTA CARA

NO ES VALIDO POR ESTA CARA

D1.US461893, 1987-07-21



United States Patent [19]

Roth

[11] Patent Number: 4,681,893

[45] Date of Patent: Jul. 21, 1987

[54] TRANS-6-[2-(3- OR
4-CARBOXAMIDO-SUBSTITUTED
PYRROL-1-YL)ALKYL]-4-HYDROXYPY-
RAN-2-ONE INHIBITORS OF
CHOLESTEROL SYNTHESIS

[75] Inventor: Bruce D. Roth, Ann Arbor, Mich.

[73] Assignee: Warner-Lambert Company, Morris
Plains, N.J.

[21] Appl. No.: 868,867

[22] Filed: May 30, 1986

[51] Int. Cl.⁴ A61K 31/40; A61K 31/35;
C07D 207/327

[52] U.S. Cl. 514/422; 514/423;
546/256; 546/275; 548/517; 548/537

[58] Field of Search 548/517, 537; 514/422,
514/423

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4,255,444	3/1981	Oka et al.	549/292 X
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Brown, et al.; New England Jour. of Med., vol. 305, No. 9, pp. 515-517, (1981).

Brown, et al.; J. Chem. Soc. Perkin I, (1976), pp. 1165-1170.

Journal of the Americas Medical Assoc.; (1984), vol. 251, pp. 351-364, 365-374.

Primary Examiner—Joseph Paul Brust

Attorney, Agent, or Firm—Jerry F. Janssen

[57]

ABSTRACT

Certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase and are thus useful hypolipidemic or hypocholesterolemic agents. Pharmaceutical compositions containing such compounds, and a method of inhibiting the biosynthesis of cholesterol employing such pharmaceutical compositions are also disclosed.

9 Claims, No Drawings

**TRANS-6-[2-(3- OR
4-CARBOXAMIDO-SUBSTITUTED
PYRROL-1-YL)ALKYL]-4-HYDROXYPYRAN-
2-ONE INHIBITORS OF CHOLESTEROL
SYNTHESIS**

BACKGROUND OF THE INVENTION

The present invention is related to compounds and pharmaceutical compositions useful as hypocholesterolemic and hypolipidemic agents. More particularly, this invention concerns certain trans-6-[2-(3- or 4-carboxamidosubstitutedpyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase), pharmaceutical compositions containing such compounds, and a method of inhibiting the biosynthesis of cholesterol employing such pharmaceutical compositions.

High levels of blood cholesterol and blood lipids are conditions involved in the onset of arteriosclerosis. It is well known that inhibitors of HMG-CoA reductase are effective in lowering the level of blood plasma cholesterol, especially low density lipoprotein cholesterol (LDL-C), in man (cf. M. S. Brown and J. L. Goldstein, *New England Journal of Medicine*, 305, No. 9, 515-517 (1981). It has now been established that lowering LDL-C levels affords protection from coronary heart disease (cf. *Journal of the American Medical Association*, 251, No. 3, 351-374 (1984).

Moreover, it is known that certain derivatives of mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) and the corresponding ring-closed lactone form, mevalonolactone, inhibit the biosynthesis of cholesterol (cf. F. M. Singer et al., *Proc. Soc. Exper. Biol. Med.*, 102: 370 (1959) and F. H. Hulcher, *Arch. Biochem. Biophys.*, 146: 422 (1971)).

U.S. Pat. Nos. 3,983,140; 4,049,495 and 4,137,322 disclose the fermentative production of a natural product, now called compactin, having an inhibitory effect on cholesterol biosynthesis. Compactin has been shown to have a complex structure which includes a mevalonolactone moiety (Brown et al., *J. Chem. Soc. Perkin I* (1976) 1165).

U.S. Pat. No. 4,255,444 to Oka et al. discloses several synthetic derivatives of mevalonolactone having antilipidemic activity.

U.S. Pat. Nos. 4,198,425 and 4,262,013 to Mitsue et al. disclose aralkyl derivatives of mevalonolactone which are useful in the treatment of hyperlipidemia.

U.S. Pat. no. 4,375,475 to Willard et al. discloses certain substituted 4-hydroxytetrahydropyran-2-ones which, in the 4(R)-trans-stereoisomeric form, are inhibitors of cholesterol biosynthesis.

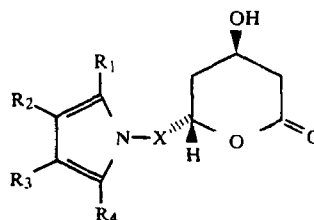
Published PCT application No. WO 84/01231 discloses certain indole analogs and derivatives of mevalonolactone having utility as hypolipoproteinemic and antiatherosclerotic agents.

SUMMARY OF THE INVENTION

In accordance with the present invention, there are provided certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened hydroxy-acids derived therefrom which are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the en-

zyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase).

In particular, in its broadest aspect the present invention provides compounds of structural formula I



wherein X is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{C}-$
 H_2- or $-\text{CH}_2\text{CH}(\text{CH}_3)-$.

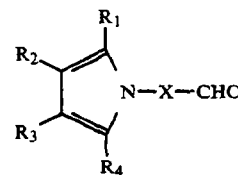
R₁ is 1-naphthyl; 2-naphthyl; cyclohexyl; norborne-
nyl; 2-, 3-, or 4-pyridinyl; phenyl, phenyl substituted
with fluorine, chlorine, bromine, hydroxyl; trifluoro-
methyl; alkyl of from one to four carbon atoms, alkoxy
of from one to four carbon atoms, or alkanoyloxy of
from two to eight carbon atoms.

Either R₂ or R₃ is $-\text{CONR}_5\text{R}_6$ where R₅ and R₆ are
independently hydrogen; alkyl of from one to six car-
bon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substi-
tuted with fluorine, chlorine, bromine, cyano, trifluoro-
methyl, or carboalkoxy of from three to eight carbon
atoms; and the other of R₂ or R₃ is hydrogen; alkyl of
from one to six carbon atoms; cyclopropyl; cyclobutyl;
cyclopentyl; cyclohexyl; phenyl; or phenyl substituted
with fluorine, chlorine, bromine, hydroxyl; trifluoro-
methyl; alkyl of from one to four carbon atoms, alkoxy
of from one to four carbon atoms, or alkanoyloxy of
from two to eight carbon atoms.

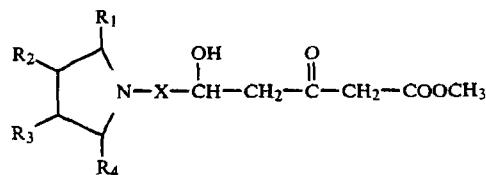
R₄ is alkyl of from one to six carbon atoms; cyclopro-
pyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoro-
methyl.

Also contemplated as falling within the scope of the
present invention are the hydroxy acids, and pharma-
ceutically acceptable salts thereof, derived from the
opening of the lactone ring of the compounds of struc-
tural formula I above.

In another aspect of the present invention, there is
provided a method of preparing the compounds of
structural formula I above which comprises the steps of
(a) first reacting a substituted [(pyrrol-1-yl)alkyl]alde-
hyde compound of the formula

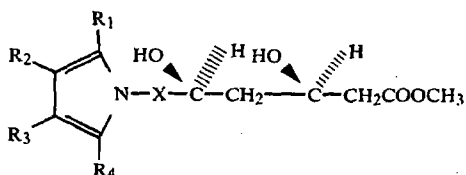


with the dilithio or sodio-lithio salt of methyl aceto-
acetate to form a compound of the structure



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- (b) reducing the product of step (a) with a trialkylborane compound such as tributylborane in the presence of sodium borohydride in an inert solvent;
 (c) oxidizing the product of step (b) with alkaline aqueous hydrogen peroxide solution to produce a compound of the formula



and

- (d) cyclizing the product step (c) to a lactone of formula I above by heating in an inert solvent such as toluene or, alternatively converting the product of step (c) to a pharmaceutically acceptable salt by conventional methods.

In yet another aspect, the present invention provides pharmaceutical compositions useful as hypolipidemic or hypocholesterolemic agents comprising a hypolipidemic or hypocholesterolemic effective amount of a compound in accordance with this invention as set forth above, in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering an effective amount of a pharmaceutical composition as defined above.

DETAILED DESCRIPTION

The compounds of the present invention comprise a class of trans-6-[2-(3- or 4-carboxamidosubstituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones in which the pyran-2-one moiety is attached, through an alkyl chain, to the substituted pyrrole nucleus at the nitrogen, or 1-position, of the pyrrole. The alkyl group may be methylene, ethylene, propylene, or methylethylene. The preferred alkyl chain linking the substituted pyrrole nucleus and the 4-hydroxypyran-2-one ring is ethylene.

The compounds of structural formula I above possess two asymmetric carbon centers, one at the 4-hydroxy position of the pyran-2-one ring, and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. This asymmetry gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans- and S-trans-isomers. This invention contemplates only the trans- form of the compounds of formula I above.

In the compounds of the present invention, position 2 of the substituted pyrrole nucleus is substituted with 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms. Preferred substituent groups at the 2-position of the pyrrole nucleus are phenyl and substituted phenyl.

In the compounds of this invention, position 5 of the pyrrole nucleus is substituted with alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl. Preferred substituents

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are alkyl or trifluoromethyl with isopropyl being particularly preferred.

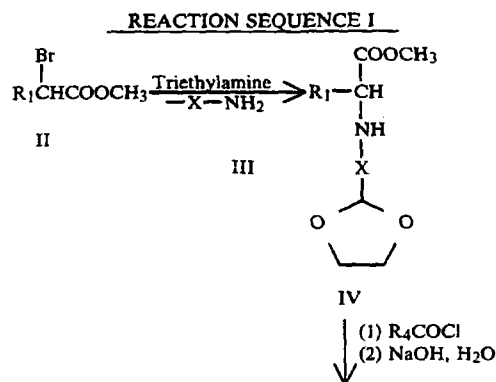
- The preferred reaction sequence which is used to prepare compounds of the present invention involves the cycloaddition of a disubstituted acetylene, in which one substituent is carboxamido or N-substituted carboxamido, to an appropriately substituted N-acylaminocarboxylic acid to form a substituted pyrrole. This addition may occur in either of two ways, leading to a substituted pyrrole addition product in which the carboxamido substituent resides on either carbon 3 or 4 of the pyrrole nucleus.

Thus, in compounds of the present invention, the substituent at either position 3 or 4 of the pyrrole nucleus is $-\text{CONR}_5\text{R}_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms and the other of the two positions is unsubstituted or is substituted with alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

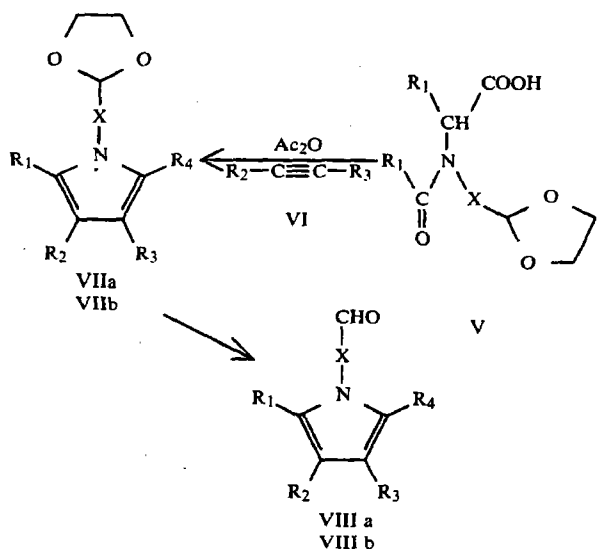
Preferred groups for R_5 and R_6 are hydrogen, phenyl, or substituted phenyl. In a particularly preferred group of compounds within the present invention, R_5 is hydrogen and R_6 is phenyl or substituted phenyl.

The compounds of this invention are prepared by the general reaction scheme outlined in Reaction Sequence I which takes advantage of the chemistry of mesionic compounds of the type described originally by R. Huisgen et al., *Ang. Chem. Int. Ed.*, 3: 136 (1964).

The known, or readily prepared, α -haloesters of structural formula II are reacted with the known 2-[1-(2-aminoalkyl)]-1,3-dioxalane, III, in the presence of an acid scavenger such as triethylamine to produce the N-alkyl- α -aminoesters, IV. The aminoesters, IV are



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-continued
REACTION SEQUENCE I

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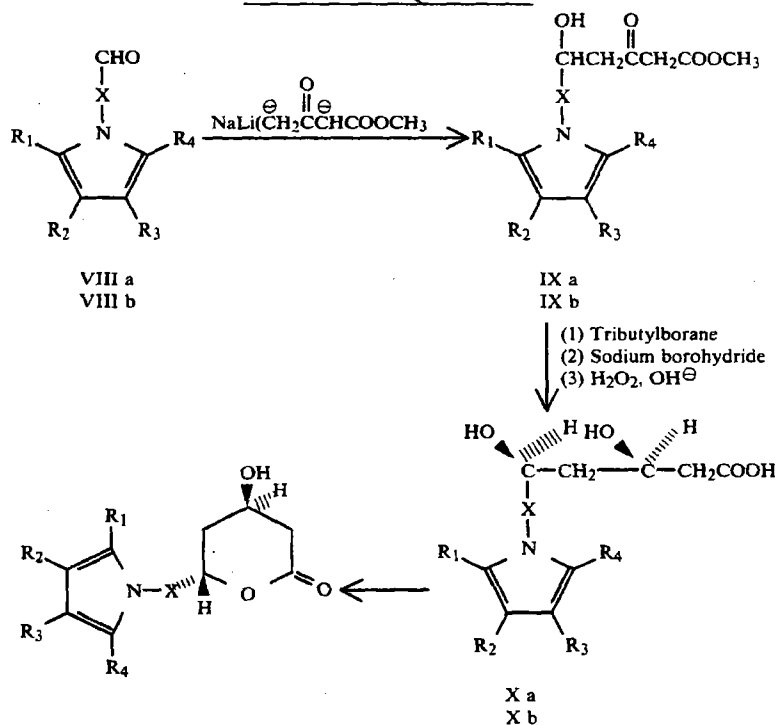
known in the art, and subsequently further purified, if desired, by recrystallization. On the other hand, in the case where R_4 is 1-methylethyl, the cyclo-addition reaction yields predominantly one product which can be purified by recrystallization alone.

Hydrolysis of the acetal function of compounds VIIa and VIIb in aqueous acid solution affords the aldehydes VIIIa and VIIIb. The aldehydes, VIII, are further converted to compounds of the present invention by the processes depicted in Reaction Sequence 2.

The aldehyde compounds, VIII, are reacted with the dilithium or lithio-sodio salt of methyl acetoacetate to produce the corresponding 7-(substituted-pyrrolyl)-5-hydroxy-3-oxoheptanoates, IX. The heptanoates, IX, are dissolved in a polar solvent such as tetrahydrofuran, through which a small amount of air has been bubbled. A slight excess of a trialkylborane, such as tributylborane, is added to the mixture which is then cooled to a temperature of preferably between about 0°C . and -78°C . after which sodium borohydride is added.

The mixture is stirred for about one to two hours and then oxidized by the addition of basic aqueous hydrogen peroxide solution. The reaction produces the 7-(substituted-pyrrolyl)-3,5-dihydroxyheptanoic acids,

REACTION SEQUENCE II



acylated with an acid halide and subsequently hydrolyzed in aqueous base solution to produce the N-acyl-N-alkyl aminoacids, V.

The N-acyl-N-alkyl aminoacids, V, are reacted with the appropriately substituted carboxamido acetylenic compounds, VI, in the presence of an acid anhydride to produce a mixture of the isomeric substituted pyrrole compounds VIIa and VIIb. Depending upon the substituents present, this cyclo-addition reaction affords differing ratios of the two products. For example, in the situation where R_4 is trifluoromethyl, the reaction yields roughly equimolar amounts of the two isomeric products. In such situations, the two isomeric products are separated by chromatographic techniques well

X, in which the product contains a predominance of the desired R^*,R^* configuration at carbon atoms three and five which bear the hydroxy groups.

The acids may be converted to a corresponding pharmaceutically acceptable salt by conventional means, if desired, or cyclized to the trans-6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones, I, by dehydration in an inert solvent such as refluxing toluene with azeotropic removal of water. This cyclization step has been found to produce material containing from 85-90% of the desired trans-configuration of the 4-hydroxy group relative to the 6-(substituted-pyrrol-1-yl)alkyl group on the pyran-2-one lactone ring.

The ring-opened hydroxy acids of structural formula II above are intermediates in the synthesis of the lactone compounds of formula I and may be used in their free acid form or in the form of a pharmaceutically acceptable metal or amine salt in the pharmaceutical method of the present invention. These acids react to form pharmaceutically acceptable metal and amine salts. The term "pharmaceutically acceptable metal salt" contemplates salts formed with the sodium, potassium, calcium, magnesium, aluminum, iron, and zinc ions. The term "pharmaceutically acceptable amine salt" contemplates salts with ammonia and organic nitrogenous bases strong enough to form salts with carboxylic acids. Bases useful for the formation of pharmaceutically acceptable nontoxic base addition salts of compounds of the present invention form a class whose limits are readily understood by those skilled in the art.

The free acid form of compounds of the present invention may be regenerated from the salt form, if desired, by contacting the salt with a dilute aqueous solution of an acid such as hydrochloric acid.

The base addition salts may differ from the free acid forms of the compounds of this invention in such physical characteristics as solubility and melting point, but are otherwise considered equivalent to the free acid form for the purposes of this invention.

The compounds of the present invention may exist in solvated or unsolvated form. In general, the solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for the purposes of this invention.

The compounds of this invention are useful as hypocholesterolemic or hypolipidemic agents by virtue of their ability to inhibit the biosynthesis of cholesterol through inhibition of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase).

The ability of compounds of the present invention to inhibit the biosynthesis of cholesterol was measured by two methods. A first method (designated CSI screen) utilized the procedure described by R. E. Dugan et al., *Archiv. Biochem. Biophys.*, (1972), 152, 21-27. In this method, the level of HMG-CoA enzyme activity in standard laboratory rats is increased by feeding the rats a chow diet containing 5% cholestyramine for four days, after which the rats are sacrificed.

The rat livers are homogenized, and the incorporation of cholesterol-¹⁴C-acetate into nonsaponifiable

lipid by the rat liver homogenate is measured. The micromolar concentration of compound required for 50% inhibition of sterol synthesis over a one-hour period is measured, and expressed as an IC₅₀ value.

A second method (designated COR screen) employed the procedure detailed by T. Kita, et al., *J. Clin. Invest.*, (1980), 66: 1094-1100. In this method, the amount of ¹⁴C-HMG-CoA converted to ¹⁴C-mevalonate in the presence of a purified enzyme preparation of HMG-CoA reductase was measured. The micromolar concentration of compound required for 50% inhibition of cholesterol synthesis was measured and recorded as an IC₅₀ value.

The activity of several representative examples of compounds in accordance with the present invention appears in Table 1, and is compared with that of the prior art compound, compactin.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted, and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5 to about 70% by weight of the active ingredient. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is

TABLE 1

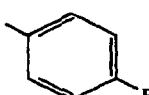
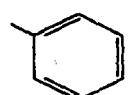
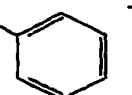
Compound	X	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (Micromoles/liter)	
						CSI	COR
1	—CH ₂ CH ₂ —			—CONH— 	—CH(CH ₃) ₂	0.035	0.050

TABLE 1-continued

Compound	X	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (Micromoles/liter)	
						CSI	COR
2	—CH ₂ CH ₂ —		—CONH—		—CF ₃	0.40	0.40
3	—CH ₂ CH ₂ —			—CONH—	—CF ₃	0.018	0.020
Compactin (Prior art)						0.026	0.028

surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions suitable for oral or parenteral administration, or suspensions and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol may be mentioned as examples of liquid preparations suitable for parenteral administration.

Sterile solutions may be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

In therapeutic use as hypolipidemic or hypocholesterolemic agents, the compounds utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from 40 mg to 600 mg per day. For a normal human adult of approximately 70 kg

or body weight, this translates to a dosage of from about 0.5 mg/kg to about 8.0 mg/kg of body weight per day.

The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of optimum dosages for a particular situation is within the skill of the art.

The following examples illustrate particular methods for preparing compounds in accordance with this invention. These examples are illustrative and are not to be read as limiting the scope of the invention as it is defined by the appended claims.

EXAMPLE 1

Preparation of

trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-pyrrole-3-carboxamide

Step A: Preparation of α -[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester

A solution of 26 g (220 mmol) of 2-[1-(2-aminoethyl)]-1,3-dioxalane in 50 ml of acetonitrile was added at room temperature with stirring to a solution of 200 mmol of α -bromo-4-fluorobenzeneacetic acid, ethyl ester (J. W. Epstein et al., *J. Med. Chem.*, 24: 481-490 (1981)) and 42 ml (300 mmol) of triethylamine in 350 ml of acetonitrile. The resulting mixture was stirred at room temperature overnight and then poured into 500 ml of diethyl ether. The resulting suspension was extracted with 300 ml of water and then twice with 300-ml portions of 2M hydrochloric acid. The combined extracts were made basic with 25% aqueous sodium hydroxide solution and extracted twice with 500-ml portions of ethyl acetate. The ethyl acetate extracts were combined, washed successively with water and brine, and then dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the residue concentrated to yield 49.5 g of α -[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester.

The 90 MHz proton magnetic resonance spectrum of the product in deuteriochloroform exhibited signals at 1.18 (triplet, 3H, J=7 Hz); 1.85 (multiplet, 2H); 2.20

(broad singlet, 1H); 2.6 (multiplet, 2H); 3.85 (multiplet, 4H); 4.1 (quartet, 2H, $J=7$ Hz); 4.22 (singlet, 1H); 4.83 (triplet, 1H, $J=4.5$ Hz); and 6.8–7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step B. Preparation of α -[[2-(1,3-dioxolan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester. Thirty grams (100 mmol) of α -[[2-(1,3-dioxolan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester from Step A were dissolved in 200 ml of dichloromethane together with 28.6 ml (205 mmol) of triethylamine and the resulting mixture was cooled to 0° C. under dry nitrogen. A solution of 11 ml (105 mmol) of isobutyl chloride in 50 ml of dichloromethane was slowly added with stirring. After addition was complete, the mixture was stirred for an additional 60 minutes and then poured into 100 ml of diethyl ether. The ether solution was washed successively with portions of water, 2M hydrochloric acid, sodium bicarbonate solution, and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvents yielded 35 g of α -[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid, ethyl ester.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the product exhibited signals at 1.2 (multiplet, 9H); 1.7 (multiplet, 2H); 2.85 (multiplet, 1H); 3.35 (multiplet, 2H); 3.80 (multiplet, 4H); 4.20 (quartet, 2H, $J=7$ Hz); 4.60 (triplet, 1H, $J=4.5$ Hz); 5.81 (singlet, 1H); and 6.8–7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step C. Preparation of α -[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid. A solution of 35 g (95.3 mmol) of the ester from Step B and 12 g (300 mmol) of sodium hydroxide in 480 ml of 5:1 methanol water was heated under reflux and stirred for two hours. The solution was cooled to room temperature, concentrated, and diluted by the addition of 500 ml of water. The resulting solution was extracted with ether and the aqueous layer was acidified with ice-cold 6M hydrochloric acid and then extracted twice with 300-ml portions of ethyl acetate.

The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, and evaporated to yield 30 g of crude α -[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid which was used without further purification.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the product exhibited signals at 1.11 (doublet, 6H, $J=7$ Hz); 1.4–1.9 (multiplet, 2H); 2.85 (multiplet, 1H); 3.32 (multiplet, 2H); 3.75 (multiplet, 4H); 4.52 (triplet, 1H, $J=4.5$ Hz); 5.73 (singlet, 1H); and 6.8–7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step D. Preparation of N,3-diphenylpropynamide

A solution of 171 mmol of dicyclohexylcarbodiimide in 250 ml of dichloromethane was added dropwise over a two hour period at 0° C. to a suspension of 171 mmol of propionic acid, 179.6 mmol of aniline, and 5 mmol of 4-dimethylaminopyridine in 400 ml of dichloromethane. After addition was complete, the mixture was stirred for an additional 30 minutes and then diluted with diethyl ether. The resulting mixture was filtered through silica gel, concentrated, and the residue recrystallized to provide 30.5 g of N,3-diphenyl-2-propynamide, mp 122°–123° C.

Analyzed for $C_{15}H_{13}NO$: Calc.: C, 80.69%; H, 5.87%; N, 6.27%; Found: C, 80.54%; H, 5.58%; N, 6.52%.

The infrared spectrum of a KBr pellet of the compound showed principal peaks at 2215, 1630, 1595, 1549, 1490, 1445, 1330, 756, and 691 reciprocal centimeters.

Step E. Preparation of 1-[2-(1,3-dioxolan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide

A solution of 95 g (280 mmol) of α -[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid, prepared as described in Step C above, and 98 g (439 mmol) of N,2-diphenylpropenoic carboxamide, prepared as described in Step D above, was heated at 90° C. with stirring for four hours, (Vigorous gas evolution occurred for two hours.) After this time, the mixture was cooled to room temperature and chromatographed twice on silica gel, eluting with 4:1 hexane:ethyl acetate to separate the product ($R_f=0.35$) from the starting material ($R_f=0.5$).

Recrystallization of the product from isopropyl ether provided 59.5 g (119.3 mmol) of 1-[2-(1,3-dioxolan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, mp 159°–162° C.

Analyzed for $C_{31}H_{31}FN_2O_3$: Calc.: C, 74.68%; H, 6.27%; N, 5.62%; Found: C, 75.04%; H, 6.12%; N, 5.89%.

Step F. Preparation of 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide

A solution of 59 g (118.3 mmol) of 1-[2-(1,3-dioxolan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, from Step E above, and 0.4 ml of concentrated hydrochloric acid in 1200 ml of anhydrous ethanol was heated under reflux with stirring for 24 hours. After this time the mixture was cooled to room temperature, concentrated, and the residue taken up in 1200 ml of 3:1 acetone:water and 5 g of p-toluenesulfonic acid was added. This mixture was heated under reflux with stirring for two days after which time the solution was cooled to room temperature and partitioned between 1 liter of diethyl ether and 200 ml of brine solution.

The organic phase was separated, washed successively with sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate and concentrated. The oil which resulted was dissolved in the minimum amount required of hot isopropyl ether. The crystals which formed upon cooling were collected by filtration to yield 36.8 g of 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide. A further crop of 9.8 g of crystals were obtained from the mother liquor.

Analyzed for $C_{29}H_{27}FN_2O_3$: Calc.: C, 76.63%; H, 5.99%; N, 6.16%; Found: C, 76.48%; H, 6.20%; N, 6.14%.

Step G. Preparation of 2-(4-fluorophenyl)- δ -hydroxy-5-(1-methylethyl)- β -oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester

A solution of methyl acetoacetate (26.4 ml, 243 mmol) in 250 ml of anhydrous tetrahydrofuran was added dropwise to a stirred suspension of hexane-washed sodium hydride (6.4 g, 267 mmol) in 200 ml of tetrahydrofuran at 0° C. When gas evolution was complete, 97.2 ml of 2.5M n-butyl lithium was added dropwise over a period of 60 minutes.

The resulting solution was stirred for 30 minutes at 0° C. and then cooled to –78° C. after which a solution of

36.8 g (80.9 mmol) of 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, from Step F above, in 100 ml of tetrahydrofuran was added over a period of thirty minutes. The resulting solution was stirred for 30 minutes at -78°C . and then warmed to 0°C . where it was held for an additional 60 minutes.

The mixture was then acidified by the dropwise addition of 300 ml of ice-cold 3M hydrochloric acid, diluted with ether, washed successively with water and brine, dried over anhydrous magnesium sulfate, and concentrated. Flash chromatography of the residue yielded 37.9 g of 2-(4-fluorophenyl)- δ -hydroxy-5-(1-methylethyl)- β -oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester.

The 90 MHz proton magnetic resonance spectrum of the product exhibited signals at 1.50 (doublet, 6H, $J=7$ Hz); 1.8 (multiplet, 2H); 2.45 (doublet, 2H, $J=7$ Hz); 2.8 (broad, 1H); 3.33 (singlet, 2H); 3.5 (multiplet, 1H); 3.67 (singlet, 3H); 3.8–4.0 (multiplet, 2H); and 6.8–7.3 (multiplet, 14H) parts per million downfield from tetramethylsilane.

Step H. Preparation of R^*,R^* -2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid and trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide

Air (60 ml) was bubbled via a syringe through a solution of 2-(4-fluorophenyl)- δ -hydroxy-5-(1-methylethyl)- β -oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester (48 g, 84.1 mmol) and 92.5 ml of 1M tributylborane in 100 ml of anhydrous tetrahydrofuran. The mixture was stirred overnight at room temperature and then cooled to -78°C . Sodium borohydride (3.85 g, 101.8 mmol) was added to the cooled mixture in one portion. The mixture was allowed to warm slowly to 0°C . over a period of three hours, during which there was vigorous gas evolution.

The dry ice-acetone bath applied to the reaction vessel was replaced by an ice bath and 18.3 ml of glacial acetic acid were added dropwise, followed by 204 ml of 3M aqueous sodium hydroxide solution and 30.5 ml of 30% aqueous hydrogen peroxide solution.

The mixture was vigorously stirred while being allowed to warm to room temperature overnight. The mixture was then partitioned between diethyl ether and water and the aqueous layer was separated, acidified, and extracted with ethyl acetate.

The ethyl acetate extract was washed with brine, dried, and evaporated to yield crude R^*,R^* -2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid which was used without further purification.

The crude acid was taken up in toluene and lactonized by heating under reflux for six hours. This mixture was chromatographed to provide 30 g of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide as a foamy solid, mp 90° – 97°C .

Analyzed for $\text{C}_{33}\text{H}_{33}\text{FN}_2\text{O}_4$: Calc.: C, 73.31%; H, 6.15%; N, 5.18%; Found: C, 73.46%; H, 6.31%; N, 5.28%.

This material was found by HPLC analysis to comprise a 9:1 molar ratio of the cis- and trans-isomeric forms of the product. Recrystallization from toluene-ethyl acetate yield the essentially pure trans-form, mp 148° – 149°C .

EXAMPLE 2

Preparation of

R^*,R^* -2-(4-fluoro-phenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, sodium salt

A mixture of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (10 g, 18.5 mmol) and 0.74 g (18.5 mmol) of sodium hydroxide in 90 ml of a 1:2 mixture of tetrahydrofuran-water was cooled to 0°C . This mixture was allowed to warm slowly to 25°C ., after which time it was concentrated and the residual solid dried under vacuum.

The infrared spectrum of the product exhibited principal absorption peaks at 3400, 1651, 1598, 1565, 1511, 1438, 1412, 1316, 1224, 1159, 844, 754, and 702 reciprocal centimeters.

The 90 MHz proton magnetic resonance spectrum of a hexadeutero dimethylsulfoxide solution of the product exhibited signals at 1.34 (doublet, $J=7$ Hz, 6H); 1.5 (multiplet, 4H); 1.80 (doublet of doublets, $J=15$, 8 Hz, 1H); 1.99 (doublet of doublets, $J=15$, 4 Hz, 1H); 3–4 (multiplet, 8H); 6.9–7.3 (multiplet, 12H); 7.50 (doublet, $J=8$ Hz, 2H); and 9.85 (singlet, 1H) parts per million downfield from tetramethylsilane.

EXAMPLES 3 AND 4

Preparation of

trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide and trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)pyrrole-3-carboxamide

Step A. Preparation of α -[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid.

α -[[2-(1,3-Dioxolan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester (36.5 g, 122.8 mmol, prepared as described above in Example 1, Step A) was dissolved in 1500 ml of a 5:1 mixture of methanol-water together with 7.6 g of sodium hydroxide. This mixture was heated under reflux for a period of two and one-half hours after which time the solvents were removed under vacuum.

The solid residue was taken up in 325 ml of water and a mixture of 14 ml of glacial acetic in 28 ml of water was added with stirring. After stirring for a time, an additional 3 ml of glacial acetic acid were added and the mixture was chilled for 75 minutes. The solids were collected by filtration, washed with water and then ethyl acetate and dried to yield α -[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, mp 218° – 220°C .

Step B. Preparation of a mixture of 5-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide and 2-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-5-(trifluoromethyl)-1H-pyrrole-3-carboxamide

α -[[2-(1,3-Dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid (6.06 g, 22.5 mmol) was dissolved in 45 ml of trifluoroacetic anhydride and 7.47 g (33.8 mmol) of N,3-diphenyl-2-propynamide (prepared as described above in Example 1, Step D) was added. The resulting mixture was heated under reflux for a period of five and one-half hours. The mixture was then cooled, and 1.74

ml of trifluoroacetic acid were added and the mixture was stirred overnight.

The excess trifluoroacetic anhydride was removed under vacuum, and water was added, followed by sufficient acetone to give a homogenous solution. This solution was stirred at room temperature for three hours. The mixture was seeded with N,3-diphenyl-2-propynamide, and a precipitate formed. After three hours, this precipitate was removed by filtration.

The acetone was removed from the filtrate under vacuum and the solid residue was taken up in ether, washed successively with two portions of water, two portions of sodium bicarbonate solution, and two portions of brine and dried over anhydrous magnesium sulfate. The ether was removed under vacuum to yield a crude mixture of the two title compounds.

This mixture was separated by column chromatography on 600 g of silica gel, eluting with a 4:1 mixture of hexane-ethyl acetate.

The first fraction eluted was 5-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide.

The 90 MHz proton magnetic resonance spectrum of a deuteriochloroform solution of this material exhibited signals at 2.73 (triplet, $J=7$ Hz, 2H); 4.21 (triplet, $J=7$ Hz, 2H); 6.7-7.3 (multiplet, 5H); 7.40 (singlet, 5H), and 9.43 (singlet, 1H) parts per million downfield from tetramethylsilane.

The second compound eluted from the column was 2-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-5-(trifluoromethyl)-1H-pyrrole-3-carboxamide.

The 90 MHz proton magnetic resonance spectrum of a deuteriochloroform solution of this material exhibited signals at 2.67 (triplet, $J=7$ Hz, 2H); 4.25 (triplet, $J=7$ Hz, 2H); 7.0-7.3 (multiplet, 14H); and 9.43 (singlet, 1H) parts per million downfield from tetramethylsilane.

Step C. Preparation of trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide and trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide

Employing the general methods detailed in Example 1, Steps G and H, the title compounds were prepared from the aldehyde compounds of this example, Step B.

The elemental analyses of the two title compounds were:

For trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide:

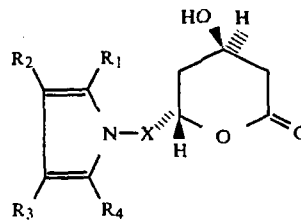
Analyzed for $C_{31}H_{26}N_2O_4$: Calc.: C, 65.72%; H, 4.63%; N, 4.94%; Found: C, 65.82%; H, 4.91%; N, 4.69%.

The trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide was found, upon recrystallization from toluene to contain 0.25 mols of toluene as solvent of crystallization, mp 106°-111° C.

Analyzed for $C_{31}H_{26}N_2O_4 \cdot 0.25C_7H_8$: Calc.: C, 66.72%; H, 4.79%; N, 4.72%; Found: C, 66.81%; H, 4.86%; N, 4.60%.

I claim:

1. A compound of structural formula I



wherein

X is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, or $-\text{CH}_2\text{CH}(\text{CH}_3)-$;

R₁ is

1-naphthyl;
2-naphthyl;
cyclohexyl;
norbornenyl;
phenyl;

phenyl substituted with

fluorine,
chlorine,
bromine,
hydroxyl,
trifluoromethyl,
alkyl of from one to four carbon atoms,
alkoxy of from one to four carbon atoms, or
alkanoyloxy of from two to eight carbon atoms;

either of R₂ or R₃ is $-\text{CONR}_5\text{R}_6$ where R₅ and R₆ are independently

hydrogen;
alkyl of from one to six carbon atoms;
phenyl;

phenyl substituted with

fluorine,
chlorine,
bromine,
cyano,
trifluoromethyl, or
carboalkoxy of from three to eight carbon atoms;

and the other of R₂ or R₃ is

hydrogen;
alkyl of from one to six carbon atoms;

cyclopropyl;

cyclobutyl;

cyclopentyl;

cyclohexyl;

phenyl; or

phenyl substituted with

fluorine,
chlorine,
bromine,
hydroxyl,
trifluoromethyl,
alkyl of from one to four carbon atoms,
alkoxy of from one to four carbon atoms, or
alkanoyloxy of from two to eight carbon atoms;

R₄ is

alkyl of from one to six carbon atoms;

cyclopropyl;

cyclobutyl;

cyclopentyl;

cyclohexyl; or

trifluoromethyl;

or a hydroxy acid or pharmaceutically acceptable salts thereof, corresponding to the opened lactone

ring of the compounds of structural formula I above.

2. A compound as defined by claim 1 wherein X is $-\text{CH}_2\text{CH}_2-$.

3. A compound as defined by claim 2 wherein R_1 is phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

4. A compound as defined by claim 2 wherein R_4 is alkyl of from one to six carbon atoms.

5. A compound as defined by claim 1 having the name trans-($\pm$)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

6. A compound as defined by claim 1 having the name trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-trifluoromethyl-1H-pyrrole-3-carboxamide.

7. A compound as defined by claim 1 having the name trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-trifluoromethyl-1H-pyrrole-3-carboxamide.

8. A pharmaceutical composition, useful as a hypocholesterolemic agent, comprising a hypocholesterolemic effective amount of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

9. A method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering a pharmaceutical composition as defined by claim 8.

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(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, Lon- don 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, GE, 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 those 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.		

D2.WO9911260, 1999-03-11

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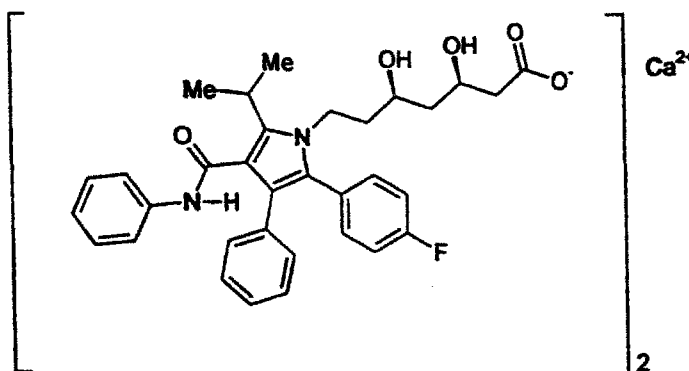
COMBINATION THERAPY COMPRISING ATORVASTATIN AND AN ANTIHYPERTENSIVE AGENT

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.

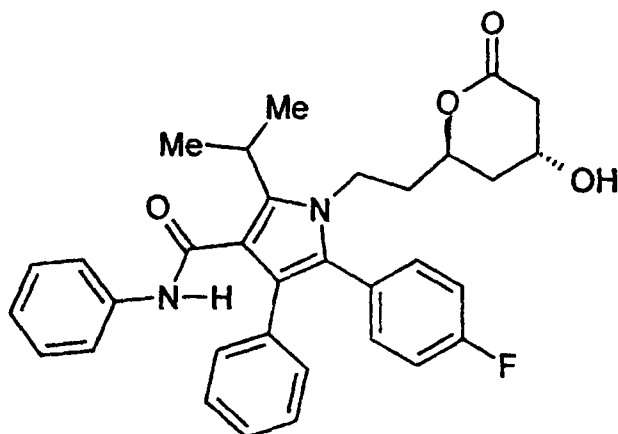
BACKGROUND OF THE INVENTION

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:



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

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. 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 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 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 disease: the Scandinavian Simvastatin Survival Study (4S), Lancet, 1994, 344, 1383-

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).

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.

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.

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.

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

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.

Kramsch 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

blocker on the progression of coronary atherosclerosis, Circulation, 1990, 82, 1940-53.) U.S. 4,681,893 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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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, mibefradil, 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, quinapril 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.

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.

10 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, prazosin or trimazosin.

15 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 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.

25 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 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

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 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, quinapril 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
20 composition of Composition BB wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha-adrenergic receptor blocker being doxazosin, prazosin or trimazosin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition C", for use with a second pharmaceutical
25 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 an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or
30 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 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 antianginal; 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 antianginal; 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 antianginal; 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 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 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
15 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.
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This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition DA", of Composition D wherein said
25 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 DB", of Composition DA wherein said second
30 pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

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.

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

10 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 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 a
15 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.

30 This invention is also particularly directed to a pharmaceutical composition of 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:

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

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 alpha-adrenergic receptor blocker.

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

This invention is also directed to a method, hereinafter termed "Method A", 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 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, 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.

25 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.

Amlodipine is a racemic compound due to the symmetry at position 4 of the
10 dihydropyridine ring. The R and S enantiomers may be prepared as described by Arrowsmith et al., J. Med. Chem., 1986, 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.

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., 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 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 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 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, but are not limited to: bepridil, which may be prepared as disclosed in U.S. Patent No. 3,962, 238 or U.S. Reissue No. 30,577; clentiazem, 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. Patent No. 3,261,859; 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.

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; cilnidipine, 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; lomerizine, 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 1,265,758; 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

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; moveltopril, which may be prepared as disclosed in Belgian Patent No. 893,553; perindopril, which may be prepared as disclosed in U.S. Patent No. 4,508,729; 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; and trandolapril, 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; amosulalol, 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. 3,663,607 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

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 3,961,071; 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; 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 No. 3,501,769; nadolol, which may be prepared as disclosed in U.S. Patent No. 3,935, 267; 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. 1,077,603; 30 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

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. 3,960,891; 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; labetolol, 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. 3,511,836; 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:

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. 3,663,597; 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. 4,663,325; nafronyl, which may be prepared as disclosed in U.S. Patent No. 3,334,096; nicametate, which may be prepared as disclosed in Blicke 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; benziodarone, 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.

3,282,938; clobenfural, 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, 155, 165; cloricromen, which may be prepared as disclosed in U.S. Patent No. 4,452,811; dilazep, 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; ganglefene, 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. 168,308; 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; pentrinitrol, which may be prepared as disclosed in German Patent No. 638,422-3;
25 perhexilline, which may be prepared as disclosed above; pimefylline, 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; propatyl 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; visnadine, 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; bufeniode, 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; ciclonicate, 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; eledoisin, 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; ifenprodil, which may be prepared as disclosed above; iloprost, which may be prepared as disclosed in U.S. Patent No. 4,692,464; 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. 3,056,836; 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; moxisylyte, which may be prepared as disclosed in German Patent No. 905,738; nafronyl, which may be prepared as disclosed above; nicametate, which may be prepared as disclosed above; nicergoline, which may be prepared as disclosed above; nicofuranose, 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; pentifylline, which may be prepared as disclosed above; pentoxifylline, 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, Budaveri, Ed., New Jersey, 1996, p. 1353; suloctidil, 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.*, 1968, 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. 639,386; arbutin, which may be prepared as disclosed in *Tschitschibabin, Annalen*, 1930, 479, 303; chlorazaniil, 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, 90, 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. 902,658; bendroflumethiazide, which may be prepared as disclosed in U.S. Patent No. 3,265,573; 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 1,365,504; 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; teclothiazide, 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; ambuside, 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

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; tripamide, 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

of Atherosclerosis

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

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

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 utility of the compounds of this invention in conventional assays and the clinical trial 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 electrocardigram (ECG) such as Holter monitoring, exercise stress testing such as a treadmill and evaluation of myocardial

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 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 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 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) 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 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 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.

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
5 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
10 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.
15 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
20 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
25 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
30 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

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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

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

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;
nicardipine, generally about 32 mg to about 120 mg;
20 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;
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 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 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 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 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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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.

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

PRODUCT 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, mibefradil, 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.

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 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.

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.

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 or trandolapril.

20. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha blocker
15 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 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, mibefradil, 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 or trandolapril.

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; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

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

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

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.

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

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 antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

44. A pharmaceutical composition of claim 42 wherein said therapeutic effect is antianginal; 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;

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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92. A method of claim 87 wherein said therapeutic treatment comprises cardiac risk management.

93. A method of claim 87 wherein said therapeutic treatment comprises antiatherosclerotic treatment.

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United States Patent [19]

[11] Patent Number: 5,155,120

Lazar et al.

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[54] METHOD FOR TREATING CONGESTIVE
HEART FAILURE

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[57] ABSTRACT

Related U.S. Application Data

[63] Continuation of Ser. No. 650,838, Jan. 14, 1991, abandoned.

Method for the treatment of congestive heart failure
using amlodipine and the pharmaceutically acceptable
acid addition salts thereof.

[51] Int. Cl.⁵ A01N 43/40

[52] U.S. Cl. 514/356

[58] Field of Search 514/356

3 Claims, No Drawings

METHOD FOR TREATING CONGESTIVE HEART FAILURE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of co-pending application Ser. No. 07/650,838, filed Jan. 14, 1991, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the antihypertensive agent amlodipine and its pharmaceutically acceptable acid addition salts and their use in treating congestive heart failure.

2. Description of the Prior Art

Congestive heart failure, regardless of its etiology, is characterized by a weakness of the myocardial tissue of the left and/or right ventricles of the heart to pump and circulate blood into systemic and/or pulmonary circulations. It is accompanied by circulatory and neurohumoral changes which result in failure to deliver sufficient blood and oxygen supply to peripheral tissues and vital organs. If left untreated the health of a patient with congestive heart failure could deteriorate to the point where the disease would be fatal.

While there are several therapies available for the treatment of congestive heart failure, the most widely used is digitalis. Its use is limited because of its slow onset of action and the small difference between the maximum therapeutic and minimum toxic dose levels.

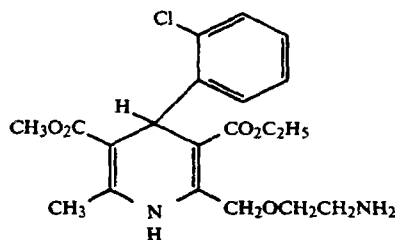
SUMMARY OF THE INVENTION

A therapy has now been found for treating congestive heart failure in a human subject having such condition which comprises orally or parenterally administering to said human subject a congestive heart failure treating amount of amlodipine and the pharmaceutically acceptable acid addition salts thereof. It is preferred that the daily dosage be given in unit dosage form of 10 mg once a day orally.

While amlodipine belongs to a family of calcium channel blockers useful as antihypertensive and in the treatment of ischemic heart disease such agents are considered ineffective in treating congestive heart disease and may be deleterious if administered to a patient in heart failure. Consequently, the discovery that amlodipine is useful in treating congestive heart failure is unexpected.

DETAILED DESCRIPTION OF THE INVENTION

As previously mentioned, the antihypertensive compound of the present method invention is known in the art. Amlodipine, 3-ethyl-5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate, and its pharmaceutically acceptable acid addition salts are claimed and their preparation described in U.S. Pat. Nos. 4,572,909 and 4,879,303. The chemical structure of amlodipine is as follows:



Although the generic name of amlodipine represents the free base, the present method invention is meant to embrace pharmaceutically acceptable acid addition salts, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, gluconate, methanesulfate, ethanesulfate, benzenesulfonate and p-toluenesulfonate salts.

In the treatment of congestive heart failure it is generally preferred to administer amlodipine or its pharmaceutically acceptable acid addition salts orally once a day. In using amlodipine or one of its pharmaceutically acceptable acid addition salts in congestive heart failure, a dosage level of 5 mg to 20 mg per day is therapeutically effective, and a preferred dose is 10 mg per day.

It is to be appreciated that still other variations may also occur in this respect, depending upon the individual response to said medicament, as well as on the particular type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger dosages may be employed without causing any harmful or deleterious side effects to occur provided that such higher dose levels are first divided into several smaller doses that are to be administered throughout the day. Amlodipine can be given alone or in combination with digitalis, thiazide diuretics, other diuretics, ACE inhibitors, etc.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and dicalcium phosphate may be employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid 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 and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft elastic 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 suspension and/or elixirs are desired for oral administration, the essential active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

Although the preferred mode of administration of amlodipine or one of its pharmaceutically acceptable acid addition salts is oral, they may be administered parenterally as well.

For purposes of parenteral administration, solutions of amlodipine in sesame or peanut oil or in aqueous-propylene glycol may be employed, as well as sterile aqueous solutions of the corresponding water-soluble acid addition salts previously enumerated. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular and subcutaneous injection purposes. In this connection, the sterile aqueous media employed are readily obtained by standard techniques well known to those skilled in the art. For instance, distilled water is ordinarily used as the liquid diluent and the final preparation is passed through a suitable bacterial filter, such as a sintered-glass filter or a diatomaceous-earth or unglazed porcelain filter. Preferred filters of this type include the Berkefeld, the Chamberland and the asbestos disc-metal Seitz filter, wherein the fluid is sucked through the filter candle into a sterile container with the aid of a suction pump. The necessary steps should be taken throughout the preparation of these injectable solutions to ensure that the final products are obtained in a sterile condition.

The following examples are provided solely for the purpose of illustration and are not to be construed as limitations of this invention, many variations of which are possible without departing from the spirit or scope thereof. The clinical studies which comprise the following example were conducted with amlodipine benzenesulfonate.

EXAMPLE

I. Purpose of Study

The purpose of the study was to evaluate the efficacy of fixed doses amlodipine tablets (10 mg/day) compared with placebo in the chronic treatment (8 wks) of patients with significantly compromised left ventricular function.

II. Trial Design

This was a randomized, parallel, double-blind, placebo-controlled study of amlodipine in outpatients with NYHA functional class IIM-III chronic heart failure. The duration of this study was 10 weeks; a 2 week single-blind placebo phase was followed by an 8 week double-blind phase during which patients received either placebo or amlodipine. The study consisted of three phases:

- (1) stabilization and screening phase.
- (2) single-blind phase.
- (3) double-blind phase.

Stabilization and Screening Phase

Prior to entry into the study, the patient had to meet the following criteria:

- (1) patient body weight had to be stable (± 4 pounds) at least two weeks;
 - (2) in patients on ACE inhibitors, therapeutic regimen had to be constant for 12 weeks;
 - (3) in patients on therapeutic regimens with digitalis and diuretics, the regimen had to be constant for at least four weeks;
 - (4) any therapy which was specifically listed in exclusion criteria had to be discontinued for at least two weeks.
- On meeting these criteria, patients underwent baseline screening which included clinical evaluation, one week of exercise test, a chest X-ray, laboratory safety tests, and determination of left ventricular ejection fraction. At several centers, patients had radionuclide angio-

graphic studies using the multiple gated equilibrium cardiac blood-pool imaging technique (at rest and optionally on exercise). The use of two dimensional and Doppler echocardiography was optional. Once the screening visit was completed, patients entered the single-blind phase of study.

Single-blind Outpatient Phase

During the single-blind outpatient phase, all patients had to complete 2 consecutive treadmill tests with total exercise time within 15% of one another. One additional exercise test was allowed if the duration of the two previous tests were not within 15%. However, in order to qualify for continuation in this study, exercise tests took place within the time period of 14-28 days (single-blind placebo phase). After the last exercise test was completed, 24-hour Holter ECG monitoring was performed on those patients who qualified for randomization.

Double-blind Outpatient Phase

After the single-blind phase, patients who qualified were randomized into the double-blind outpatient phase (8 week duration). Patients were allocated to treatments by means of computer generated randomized lists. The assignment was stratified by the presence or absence of ACE inhibitor therapy. Drug was provided for the two groups identified as "ACE Inhibitors"; and "No ACE Inhibitors," respectively.

The patients were evaluated at the end of study weeks 4, 6, 8 and 10 (2, 4, 6, and 8 weeks of double-blind treatment). At each clinic visit, a sitting blood pressure, pulse rate, and body weight was determined. A 12-lead ECG, treadmill exercise test, and a 24 hour Holter ECG monitoring was performed at the end of study weeks 6 and 10. Radionuclide angiography, two dimensional, and Doppler echocardiography (these two tests were optional and were done in selected centers), and chest X-ray were performed at the end of week 10.

Additional Optional Parameters

At the end of weeks 2 and 10 of the study, 50 ml of blood was collected for optional determination of cardio-renal hormones. Determination of gated radionuclide ventriculography at rest and during exercises was done at screening and at the end of week 10.

III. Subject Selection Criteria

A. Inclusion in Study

1. Age 21-80 years.
2. Males, or non-pregnant, non-lactating or postmenopausal females.
- 3 Outpatients.
- 4 Medical history and physical examination before inclusion in the study.
5. Written informed consent from the patient to participate in the study.
6. Diagnostic criteria, each of the following:
 - a) clinical diagnosis of congestive heart failure.
 - b) objective evidence of CHF, present for at least 6 weeks detected by: left ventricular ejection fraction of 0.40 or less at rest (as measured by radionuclide angiography or contrast ventriculography) and,
 - c) New York Heart Association functional class IIM to III.
7. Etiology of heart failure to be:
 - a) Ischemic heart disease,
 - b) Myocardial disease of known or unknown cause.

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8. All patients to be in stable clinical condition and could receive concomitant therapy with furose-mide and a digitalis preparation, ACE inhibitors and/or vasodilators such as intermittent therapy with sublingual nitroglycerine. However, ACE inhibitor dosages must have been constant for at least 12 weeks. Sublingual nitroglycerin p.r.n. was allowed for angina attack relief.
9. Patients must be capable of undertaking a treadmill exercise test using the modified Naughton protocol and have a duration of at least 2 minutes but less than 16 minutes.

IV. Clinical Observation and Laboratory Measurements

A. Efficacy

Effect of amlodipine treatment on efficacy parameters was evaluated as follows:

1. Symptom Rating: At each visit patients received a detailed cardiopulmonary assessment of symptoms (dyspnea, fatigue, orthopnea, paroxysmal nocturnal and clinical dyspnea and edema) signs including lung congestion and ankle and pedal edema graded on a 4 point scale in absolute terms.
2. Patient Self-Assessment (Quality of Life Questionnaire): At each review visit, patients completed the self-assessment analysis of symptoms questionnaire (graded on a "thermometer scale" and exercise capabilities duration of a fixed pattern of activity) recorded at screening, at the end of single-blind period, after 4 weeks of double-blind therapy and at the end of double-blind therapy.
3. Global Evaluation: The investigator determined a global graded estimate of the patient's condition at each review visit and at the end of the double-blind therapy.
4. The following parameters were measured at baseline, at the end of 2 weeks single-blind therapy, after 4 weeks of double-blind therapy, and at the end of 8 weeks of double-blind therapy.
 - a) 24-hour Holter monitoring;
 - b) Standard 12-lead ECG immediately prior to each exercise test;
 - c) Exercise tolerance (duration) as measured by treadmill exercise testing using the modified Naughton protocol. Optional measurement of oxygen consumption at peak exercise was also included.
 - d) In selected centers, resting radionuclide imaging left ventricular ejection fraction was performed at screening and at the end of the double-blind phase (10th week of study). There was an optional determination of two-dimensional echocardiography and Doppler echocardiography and measurement of cardiorenal hormones in selected centers.

V. Statistical Methodology

Baseline for total exercise time was defined as the mean recorded time (in secs) of the last 2 exercise tests during the single-blind placebo phase. The baseline LVEF was at the screening visit. Baseline for ECG, body weight and norepinephrine was at week 2.

The statistical analyses for efficacy parameters were carried out on two subsets of patients corresponding to two definitions of study "end";

- 1) Final-baseline Analysis: All patients who completed the study are included in this subset. For the total

exercise time, patients also have to satisfy the "reproducible" criterion for their exercise test. That is, the two consecutive treadmill tests have to be within 120 to 900 seconds and within 15% of one another.

- 2) Intent to Treat Analysis: All patients who had efficacy measurements collected during the double-blind treatment period were included for this analysis.

The comparison between treatment groups for the above mentioned parameters were based on the difference in the log (base e) scale; i.e., the log change is defined as:

$$c = \ln(\text{Final Test}) - \ln(\text{Baseline Test})$$

- 15 which can also be expressed as

$$c = \ln(\text{Final}/\text{Baseline}).$$

That is, c is the log-ratio of the parameter between the final and baseline visits.

The mean percentage change between the final and baseline visit can be obtained through anti-log transformation as:

$$\% \text{ change} = [\exp(c) - 1] * 100$$

where

$$c = \text{mean} [\log(\text{Final}) - \log(\text{Baseline})]$$

The statistical assessments of between treatment group difference in changes from baseline to final visit for the total exercise time, LVEF, norepinephrine, body weight and ECG parameters were performed by a three-way analysis of variance (ANOVA):

$$\text{Change}_{ijkl} = M + T_i + C_j + B_k + B^*T_{ik} + E_{ijk}$$

where:

Change_{ijkl} is the change for the i th patient with the i th treatment and the k th background ACE inhibitor at center j

M is the overall mean

T_i is the i th treatment group, $i=1$ (amlodipine), 2(placebo)

C_j is the fixed center effect, $j=1$ to 14

B_k is the background ACE inhibitor therapy, $k=(\text{ACE}, 2(\text{No ACE}))$

B^*T_{ik} is the treatment and background ACE inhibitor therapy interaction term

E_{ijk} represents the random error and E is normally distributed $N(0,d)$.

The statistical assessments of between treatment group difference in changes from baseline to final visit for each background therapy groups were performed by a two-way analysis of variance (ANOVA):

$$\text{Change}_{ijk} = M + T_i + C_j + E_{ijk}$$

where:

Change_{ijk} is the change for the k th patient with i th treatment at center j

M is the overall mean

T_i is the i th treatment group, $i=1$ (amlodipine), 2(placebo)

C_j is the fixed center effect, $j=1$ to 14

E_{ijk} represents the random error and E is normally distributed $N(0,d)$.

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Treatment effects were based on the ANOVA model using Type III Sum of Squares to derive F-statistics and Least Squares Estimates (LSE). A 95% confidence interval was derived from the LSE which had a t-distribution with degrees of freedom equal to those of the error Sums of Squares of the ANOVA model. Two-tailed tests were performed on all parameters.

To compare the average effect between amlodipine and the effect of placebo, a Least Square Estimate (LSE) based on the above three-way ANOVA model was used. The LSE for this difference was obtained by the ESTIMATE option in SAS GLM procedure.

The SAS procedure FREQ with the RANK option was used to perform a Cochran-Mantel-Hanszel test for the investigator's global evaluation, and endpoint to baseline change in NYHA class, dyspnea, nocturnal dyspnea, orthopnea, fatigue and edema.

VI. Baseline Patient Characteristics

A total of 19 female and 99 male patients participated in this study. Both treatment groups were balanced with respect to age, body weight, race, and NYHA class (i.e., Class II and III). Duration of CHF in the amlodipine group was 34 months, and 26 months in the placebo group.

About half of the patients in each group had a history of old myocardial infarction and/or angina pectoris, and symptoms of chronic ischemic heart disease. A significant number also had conduction disorders of the heart and diabetes mellitus. As a whole, the two groups of patients were comparable in terms of the profile and severity of baseline disease.

The majority of patients were on cardiac glycosides (amlodipine 48, placebo 51) and loop diuretics (amlodipine 44, placebo 50). There was no clinically important changes in the use of or dosages of these drugs during the study. Out of 118 patients, 79 (38 amlodipine, 41 placebo) patients were also taking converting enzyme inhibitors. The two treatment groups were also well balanced within the subsets of patients receiving or not receiving ACE inhibitors.

VII. Drug Administration

Medication was dispensed in identically matching amlodipine and placebo tablets with individually coded bottles prepared for each patient.

The patients received amlodipine or placebo in a single tablet q.d. Double-blind medication was taken in the morning for a period of 8 weeks. Clinical deterioration, with objective evidence of fluid retention, was indicated by an increase in furosemide dosage or other diuretics as needed.

Patients were instructed to take 1 tablet each morning on the morning of a study visit; patients came to the study undosed. After all study parameters were completed, the study medication was dispensed from a new bottle.

Duration (range) of treatment for amlodipine was 60-71 days and 50.9 (5-74) days for placebo.

VIII. Results

A. Efficacy

Performance: Exercise performance was the primary end points to be analyzed in this study. To randomization, potential subjects were required to participate in two exercise tests and the total time had to be within 15% of one another. All

exercise tests were to be conducted at same time of the day, 0.5-4 hours after dosing and at least 2 hours after a light meal. Termination of the exercise was based only on dyspnea and/or fatigue (not chest pain or ST segment depression). Exercise time was assessed three times prior to randomization and after 4 and 8 weeks of double-blind treatment.

After 8 weeks of therapy, there was a greater increase in exercise time in the amlodipine group than in the placebo group. This increase was statistically significant in both evaluable patient analysis ($p=0.02$) and intent to treat analysis ($p=0.019$). In the amlodipine intent-to-treat group, the increase in exercise time was 74 seconds (14.5%) as compared to 17 seconds (3.0%) in the placebo group.

In the above analysis of exercise time, a comparison was based on the mean exercise time of two baseline exercise tests. To minimize a "learning" effect of exercise, the data was also analyzed using only the last baseline exercise test. After 8 weeks of therapy, there was a greater ($p=0.0354$) increase in exercise time in the amlodipine intent-to-treat group as compared to the placebo group.

In the case of clinical deterioration the protocol allowed an adjustment of diuretic dosing. Thus, it can be speculated that an improvement in exercise time after amlodipine was related to the increase in diuretic therapy. This possibility was examined but failed to establish the relationship between the increase in diuretic therapy and the improvement in exercise time.

Investigator's Rating: At the end of the study, the investigator's global assessment showed that more patients improved ($p<0.027$) on amlodipine (31/56, 55%) than on placebo (17/58, 29%).

The percent of improvement in the ACE inhibitor group was 57% (17/37) in amlodipine; 33% (13/39) in placebo. The percent of patients improving was smaller for the group with no ACE inhibitors: 53% (10/19) in amlodipine and 21% (4/19) in placebo.

Left Ventricular Ejection Fraction (LVEF): Treatment with amlodipine did not affect LVEF in the trial as a whole. However, LVEF tended to increase with amlodipine in patients treated with converting enzyme inhibitors, but not in the smaller group of patients who did not receive ACE inhibitors.

Plasma Norepinephrine: Plasma norepinephrine decreased in patients treated with amlodipine (358 to 263 pg/ml), but increased on placebo (365 to 439 pg/ml, amlodipine vs placebo, $p=0.018$). Similar quantitative changes were observed in the group receiving ACE inhibitors as well as in group not receiving ACE inhibitors.

Body Weight: At the end of the study, there were no significant differences in body weight between the amlodipine and placebo groups and amlodipine and placebo groups when analyzed by the presence of edema.

Peripheral Edema: Two percent (2%) of patients in the amlodipine group and 3% in the placebo group showed an improvement in peripheral edema. Seventy-four percent (74%) of patients in the amlodipine group and 84% of patients in the placebo group showed no change in peripheral edema. Twenty-four percent (24%) of the amlodipine treated patients and 13% of the placebo patients showed a deterioration of edema. These differences were not statistically significant.

Patients Clinical Symptoms: The table below summarizes the changes in NYHA class, dyspnea, nocturnal

dyspnea, and fatigue during therapy. In all of these indices, an improvement was detected with amlodipine treatment as compared to placebo. An improvement in nocturnal dyspnea and fatigue observed after amlodipine therapy approached a statistical significance ($p=0.06$).

Conclusions

In this double-blind study, the clinical safety and efficacy of amlodipine was evaluated in 118 patients with heart failure. All patients had NYHA class II or III symptoms, left ventricular ejection fraction less than

Parameters	Group	Number of Patients Who			Total No. Pts.	P Value Baseline vs. 8 weeks
		Improved	Had No Change	Worsened		
NYHA Class	Amlodipine	12	33	3	48	0.229
	Placebo	10	31	8	49	
Dyspnea	Amlodipine	15	28	9	52	0.318
	Placebo	13	29	15	57	
Nocturnal Dyspnea	Amlodipine	6	43	4	53	0.06
	Placebo	3	45	9	57	
Orthopnea	Amlodipine	6	43	4	53	0.205
	Placebo	10	45	1	56	
Fatigue	Amlodipine	23	23	7	53	0.06
	Placebo	15	29	12	56	

Patients Quality of Life Questionnaire: Patient self assessment was made on study weeks 2, 6 and 10 which consisted of 15 questions. These questions were converted into seven (7) CHF-QOL scales including dyspnea, fatigue, affect, locus of control, sleep, life satisfaction, and total evaluation of quality of life. The results indicate that treatment effects were in favor of amlodipine for those symptoms—specific scales most related to disease activity. Patients receiving amlodipine reported an improvement in dyspnea and fatigue. This improvement was statistically significant ($p<0.01$). All changes in quality of life assessment were in favor of amlodipine, and the total score p-value was equal to 0.06. The table below summarizes the key efficacy and safety parameters which showed an improvement or favorable trend in amlodipine treated (intent-to-treat analysis) patients as compared to the placebo group.

	Amlodipine	Placebo
Mean Increase in Exercise Time in sec: (N = 50 amlodipine, 54 placebo) Investigators Global Assessment:	73.7 (14.5%)	17.3 (3.0%)
Worsening	10	10
No Change	15	31
Improvement	31	17
Increase in LV Ejection Fraction (%): (N = 47 for amlodipine and placebo)	2.8 (11.5%)	1.8 (6.9%)

40%, and the majority were treated with digoxin and diuretics. The analysis of data revealed that after 8 weeks of double-blind therapy, exercise time was significantly increased in the amlodipine treated group as compared to the placebo group. In addition, more patients treated with amlodipine experienced an improvement in CHF (NYHA class & related symptoms). Although amlodipine did not affect left ventricular ejection fraction, this particular variable tended to increase with amlodipine in patients treated with converting enzyme inhibitors. In patients treated with amlodipine, plasma norepinephrine significantly decreased, and significantly increased in the placebo group. Furthermore, as detected by a quality of life questionnaire, patients treated with amlodipine had a statistically significant improvement in both dyspnea and fatigue.

This study showed that in patients with class II-III CHF, amlodipine therapy increased exercise time, improved symptoms, and had no effect on ejection fraction in patients treated with or without ACE inhibitors.

We claim:

1. A method of treating congestive heart failure in a human subject having such condition which comprises orally administering to said human subject a congestive heart failure treating amount of amlodipine as a pharmaceutically acceptable acid addition salt thereof.

2. The method of claim 1, wherein the daily dosage is in unit dosage form of 10 mg.

3. The method of claim 2, wherein the daily dosage is given once a day.

* * * * *

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: THERAPEUTIC COMBINATIONS COMPRISING AMLODIPIN AND ATORVASTATIN			
(57) Abstract This invention relates to pharmaceutical combinations of amlodipine or a pharmaceutically acceptable acid addition salt thereof and atorvastatin or a pharmaceutically acceptable salt thereof, 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 amlodipine and atorvastatin whereby those 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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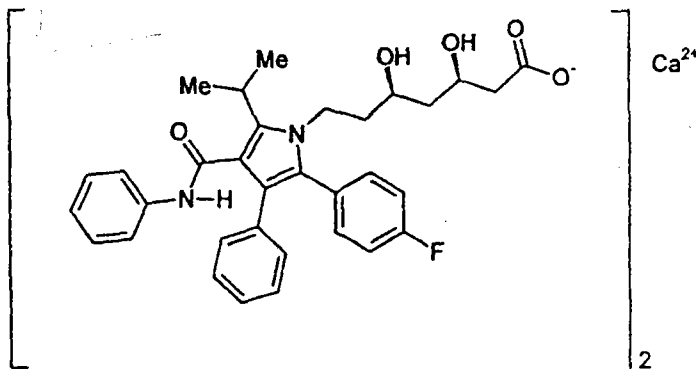
THERAPEUTIC COMBINATIONS COMPRISING AMLODIPIN AND ATORVASTATIN

This invention relates to pharmaceutical combinations of amlodipine and pharmaceutically acceptable acid addition salts thereof and atorvastatin and pharmaceutically acceptable salts thereof, kits containing such combinations and
5 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 amlodipine and atorvastatin whereby those additive and synergistic combinations are useful in treating subjects
10 suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms or signs of cardiac risk, including humans.

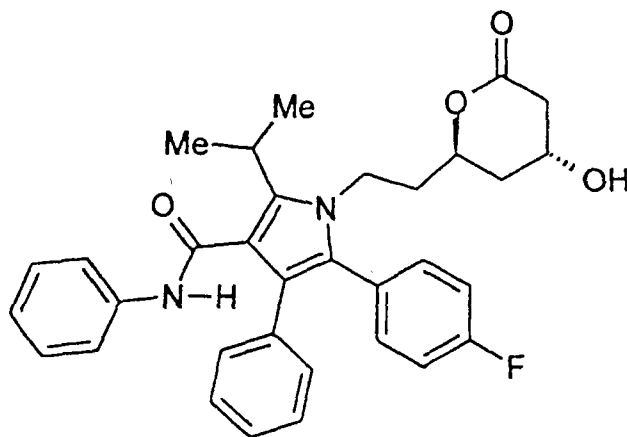
BACKGROUND OF THE INVENTION

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.
15 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
20 incorporated herein by reference, is currently sold as Lipitor® and has the formula

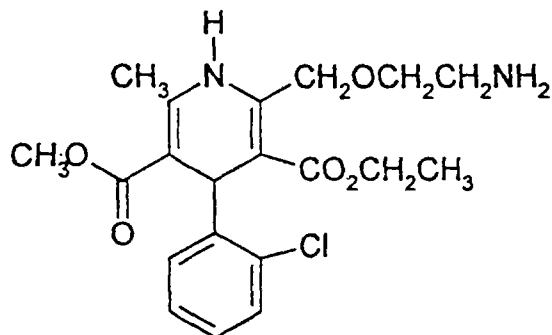


Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA. As such,
25 atorvastatin calcium is a potent lipid lowering compound. The free carboxylic acid form of atorvastatin exists predominantly as the lactone of the formula

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

Amlodipine and related dihydropyridine compounds are disclosed in U.S. Patent No. 4,572,909, which is incorporated herein by reference, as potent anti-ischemic and antihypertensive agents. U.S. Patent No. 4,879,303, which is incorporated herein by reference, discloses amlodipine benzenesulfonate salt (also termed amlodipine besylate). Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers. As such, amlodipine, amlodipine besylate and other pharmaceutically acceptable acid addition salts of amlodipine have utility as antihypertensive agents and as antiischemic agents. Amlodipine and its pharmaceutically acceptable acid addition salts are also disclosed in U.S. Patent No. 5,155,120 as having utility in the treatment of congestive heart failure. Amlodipine besylate is currently sold as Norvasc®. Amlodipine has the formula



Atherosclerosis is a condition characterized by irregularly distributed lipid deposits in the intima of arteries, including coronary, carotid and peripheral arteries.

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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
5 secondary risk factors such as, *inter alia*, smoking, obesity and lack of exercise, and 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
10 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
15 Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S), Lancet, 1994, 344, 1383-89; 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).

20 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.

Currently the treatment of symptomatic angina pectoris varies significantly from country to country. In the U.S., patients who present with symptomatic, stable
25 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
30 vessels and angioplastied segments.

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

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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.

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

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
15 generally better than patient compliance with hyperlipidemia. It would therefore be 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
20 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
25 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).
30 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

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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
5 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.

Kramsch et al., *Journal of Human Hypertension* (1995) (Suppl. 1), 53-59 disclose the use of calcium channel blockers, including amlodipine, to treat
10 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 o coronary artery disease by nifedipine, *Lancet*, 1990, 335, 1109-13; and
15 Waters, D. et al., A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis, *Circulation*, 1990, 82, 1940-53.) U.S. 4,681,893 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
20 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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SUMMARY OF THE INVENTION

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

- 5 a. an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof;
- b. an amount of atorvastatin or a pharmaceutically acceptable salt thereof; and
- c. a pharmaceutically acceptable carrier or diluent.

10 This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition AA", of Composition A comprising amlodipine besylate.

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

15 This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition B", for use with a second pharmaceutical composition for achieving an antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater than the sum of the antihypertensive and hypolipidemic effects achieved by
20 administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a
25 pharmaceutically acceptable carrier or diluent.

 This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition BA", of Composition B wherein said second pharmaceutical composition comprises amlodipine besylate.

30 This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition BB", of Composition BA comprising the hemicalcium salt of atorvastatin.

 This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition C", for use with a second pharmaceutical

composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater than the sum of the antihypertensive and hypolipidemic effects achieved by administering said first and second pharmaceutical compositions separately and
5 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 amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

10 This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition CA", of Composition C comprising amlodipine besylate.

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

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition D", for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater
20 than the antihypertensive and hypolipidemic effects 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 amlodipine or
25 a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition DA", of Composition D comprising amlodipine besylate.

30 This invention is more particularly directed to a first 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 directed to a first pharmaceutical composition, hereinafter termed "Composition E", for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater
5 than the antihypertensive and hypolipidemic effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an
10 amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition EA", of Composition E wherein said second pharmaceutical composition comprises amlodipine besylate.

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

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition F", for use with a second pharmaceutical
20 composition for achieving an antianginal effect in a mammal suffering from angina pectoris, which effect is greater than the sum of the antiangina effects 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
25 diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition FA", of Composition F comprising amlodipine
30 besylate.

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

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This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition G", for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering from angina pectoris, which effect is greater than the sum of the antiangina effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition GA", of Composition G wherein said second pharmaceutical composition comprises amlodipine besylate.

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

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition H", for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering from angina pectoris, which effect is greater than the antianginal effects 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 amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition HA", of Composition H comprising amlodipine besylate.

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

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition J", for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering from angina pectoris, which effect is greater than the antianginal effects achieved by administering
5 said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a
10 pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition JA", of Composition J wherein said second pharmaceutical composition comprises amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition JB", of Composition JA comprising the
15 hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition K", for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is
20 greater than the sum of the antiatherosclerotic effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an
25 amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition KA", of Composition K wherein said second pharmaceutical composition comprises amlodipine besylate.

30 This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition KB", of Composition KA comprising the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a composition, hereinafter termed "Composition KC", of Composition KB wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

5 This invention is still more particularly directed to a composition of Composition KC wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

This invention is also particularly directed to a composition of Composition KB wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

10 This invention is also particularly directed to a composition of Composition KB wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

This invention is more particularly directed to a composition, hereinafter termed "Composition KD", of Composition KB wherein said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques.

15 This invention is still more particularly directed to a composition of Composition KD wherein said regression of atherosclerotic plaques occurs in coronary arteries.

This invention is also particularly directed to a composition of Composition KD wherein said regression of atherosclerotic plaques occurs in carotid arteries.

20 This invention is also particularly directed to a composition of Composition KD wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition L", for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the sum of the antiatherosclerotic effects 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 diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

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This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition LA", of Composition L comprising amlodipine besylate.

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

This invention is still more particularly directed to a composition, hereinafter termed "LC", of Composition LB wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

10 This invention is still more particularly directed to a composition of Composition LC wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

This invention is also particularly directed to a composition of Composition LC wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

15 This invention is also particularly directed to a composition of Composition LC wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

This invention is more particularly directed to a composition, hereinafter termed "Composition LD", of Composition LB wherein said antiatherosclerotic effect
20 is manifested by a regression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition LD wherein said regression of atherosclerotic plaques occurs in coronary arteries.

25 This invention is also particularly directed to a composition of Composition LD wherein said regression of atherosclerotic plaques occurs in carotid arteries.

This invention is also particularly directed to a composition of Composition LD wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

30 This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition M", for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the antiatherosclerotic effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical

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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 amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition MA", of Composition M comprising amlodipine besylate.

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

This invention is still more particularly directed to a composition, hereinafter termed "Composition MC", of Composition MB wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition MC wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

This invention is also particularly directed to a composition of Composition MC wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

This invention is also particularly directed to a composition of Composition MC wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

This invention is more particularly directed to a composition, hereinafter termed "Composition MD", of Composition MB wherein said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition MD wherein said regression of atherosclerotic plaques occurs in coronary arteries.

This invention is also particularly directed to a composition of Composition MD wherein said regression of atherosclerotic plaques occurs in carotid arteries.

This invention is also particularly directed to a composition of Composition MD wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

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This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition N", for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the antiatherosclerotic effects achieved by administering said first or
5 second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or
10 diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition NA", of Composition N wherein said second pharmaceutical composition comprises amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical
15 composition, hereinafter termed "Composition NB", of Composition NA comprising the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a composition, hereinafter termed "Composition NC", of Composition NB wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

20 This invention is still more particularly directed to a composition of Composition NC wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

This invention is also particularly directed to a composition of Composition NC wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

25 This invention is also particularly directed to a composition of Composition NC wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

This invention is more particularly directed to a composition, hereinafter termed "Composition ND", of Composition NB wherein said antiatherosclerotic effect
30 is manifested by a regression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition ND wherein said regression of atherosclerotic plaques occurs in coronary arteries.

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This invention is also particularly directed to a composition of Composition ND wherein said regression of atherosclerotic plaques occurs in carotid arteries.

This invention is also particularly directed to a composition of Composition ND wherein said regression of atherosclerotic plaques occurs in the peripheral arterial
5 system.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition P", for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the sum of the cardiac risk management
10 effects 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 diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and
15 a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition PA", of Composition P comprising amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical
20 composition of Composition PA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition Q", for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse
25 cardiac event, which effect is greater than the sum of the cardiac risk management effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition
30 comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition QA", of Composition Q wherein said second pharmaceutical composition comprises amlodipine besylate.

5 This invention is more particularly directed to a first pharmaceutical composition of Composition QA comprising the hemicalcium salt of atorvastatin.

10 This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition R", for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the cardiac risk management effects 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 amlodipine or a pharmaceutically acceptable acid addition salt thereof and
15 a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition RA", of Composition R comprising amlodipine besylate.

20 This invention is more particularly directed to a first pharmaceutical composition of Composition RA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

25 This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition S", for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the cardiac risk management effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition
30 comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition SA", of Composition S wherein said second pharmaceutical composition comprises amlodipine besylate.

5 This invention is more particularly directed to a first pharmaceutical composition of Composition S comprising the hemicalcium salt of atorvastatin.

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

- 10 a. an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;
- b. an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and
- 15 c. container means for containing said first and second dosage forms.

This invention is particularly directed to a kit, hereinafter termed "Kit AA", of Kit A comprising amlodipine besylate.

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

20 This invention is still more particularly directed to a kit, hereinafter termed "Kit AC", of Kit AB wherein said therapeutic effect is treatment of hypertension and hyperlipidemia.

This invention is still more particularly directed to a kit, hereinafter termed "Kit AD", of Kit AB wherein said therapeutic effect is treatment of angina pectoris.

25 This invention is also particularly directed to a kit, hereinafter termed "Kit AE", of Kit AB wherein said therapeutic effect is management of cardiac risk.

This invention is also particularly directed to a kit, hereinafter termed "Kit AF", of Kit AB wherein said therapeutic effect is treatment of atherosclerosis.

30 This invention is still more particularly directed to a kit, hereinafter termed "Kit AG", of Kit AF wherein said treatment of atherosclerosis slows the progression of atherosclerotic plaques.

This invention is further directed to a kit, hereinafter termed "Kit AH", of Kit AG wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

This invention is still further directed to a kit, hereinafter termed "Kit AJ", of Kit AG wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

This invention is still further directed to a kit, hereinafter termed "Kit AK", of Kit AG wherein said progression of atherosclerotic plaques is slowed in the peripheral
5 arterial system.

This invention is still further directed to a kit, hereinafter termed "Kit AL", of Kit AF wherein said treatment of atherosclerosis causes the regression of atherosclerotic plaques.

This invention is still further directed to a kit of Kit AL wherein said regression
10 of atherosclerotic plaques occurs in coronary arteries.

This invention is still further directed to a kit of Kit AL wherein said regression of atherosclerotic plaques occurs in carotid arteries.

This invention is still further directed to a kit of Kit AL wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

15 This invention is also directed to a method, hereinafter termed "Method A", 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 amlodipine or a pharmaceutically acceptable acid addition salt thereof; and

20 (b) an amount of a second compound, said second compound being atorvastatin 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.

25 This invention is particularly directed to a method, hereinafter Method B, of Method A comprising amlodipine besylate.

This invention is more particularly directed to a method, hereinafter termed "Method C", of Method B comprising the hemicalcium salt of atorvastatin.

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

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

This invention is further directed to a method, hereinafter termed "Method G", of Method C wherein said first compound and said second compound are administered sequentially in either order.

10 This invention is still further directed to a method of Method A wherein said therapeutic treatment comprises antihypertensive treatment and antihyperlipidemic treatment.

This invention is still further directed to a method of Method F wherein said therapeutic treatment comprises antihypertensive treatment and antihyperlipidemic treatment.

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This invention is still further directed to a method of Method G wherein said therapeutic treatment comprises antihypertensive treatment and antihyperlipidemic treatment.

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

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This invention is further directed to a method of Method F wherein said therapeutic treatment comprises antianginal treatment.

This invention is further directed to a method of Method G wherein said therapeutic treatment comprises antianginal treatment.

25 This invention is further directed to a method of Method A wherein said therapeutic treatment comprises cardiac risk management.

This invention is further directed to a method of Method F wherein said therapeutic treatment comprises cardiac risk management.

This invention is further directed to a method of Method G wherein said therapeutic treatment comprises cardiac risk management.

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This invention is further directed to a method of Method A wherein said therapeutic treatment comprises antiatherosclerotic treatment.

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This invention is further directed to a method of Method F wherein said therapeutic treatment comprises antiatherosclerotic treatment.

This invention is further directed to a method of Method G wherein said therapeutic treatment comprises antiatherosclerotic treatment.

- 5 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., 1986, 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
- 10 Number PCT/EP94/02697). The R(+) isomer has little or no calcium channel 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
- 15 or the racemic mixture of the R(+) isomer and the S(-) isomer for use in the 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
- 20 Framingham Risk Equation as set forth above. The term "cardiac risk management" means that the risk of future adverse cardiac events is substantially reduced.

DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutical compositions of this invention comprise amlodipine or a pharmaceutically acceptable acid addition salt thereof and/or atorvastatin or a pharmaceutically acceptable salt thereof.

5 Amlodipine may readily be prepared as described in U.S. Patent No. 4,572,909 which is incorporated herein by reference. Amlodipine besylate, which is currently sold as Norvasc®, may be prepared as described in U.S. Patent No. 4,879,303, which is incorporated herein by reference. Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers.

10 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, besylate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

15 Other acid addition salts of amlodipine may be prepared by reacting the free base form of amlodipine with the appropriate acid. When the salt is of a monobasic acid (e.g., 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
20 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 or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base of amlodipine and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be
25 otherwise isolated by concentration and/or addition of a non-solvent.

Atorvastatin may readily be prepared as described in U.S. Patent No. 4,681,892, 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.

30 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, 5 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, 10 acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

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, 15 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 (e.g., sodium or 20 potassium ethylhexanoate, magnesium oleate) and employing a solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates. The salts may also be isolated by concentrating the reaction solution and/or by adding 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 25 monobasic acid (e.g., 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 30 phosphate 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

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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.

In addition, amlodipine, pharmaceutically acceptable acid addition salts thereof, atorvastatin and pharmaceutically acceptable salts thereof may occur as
5 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
10 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.

15 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:

20 Effect of Amlodipine and Atorvastatin. Alone
and in Combination, on the Treatment
of Atherosclerosis

This study is a prospective randomized evaluation of the effect of a combination of amlodipine and atorvastatin on the progression/regression of coronary
25 and carotid artery disease. The study is used to show that a combination of amlodipine and atorvastatin 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.

30 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

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preferred to study about 1200 subjects in this study. Subjects are admitted into the study after satisfying certain entry criteria set forth below.

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 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 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 ejection fraction of greater than 30% 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 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 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 amlodipine besylate (10 mgs) and placebo or atorvastatin calcium (80 mgs) and placebo or amlodipine besylate(10 mgs) and atorvastatin calcium(80 mgs). All doses set forth in this protocol are per day doses. The amount of amlodipine besylate may be varied as required. Generally, a subject will start out taking 10 mg and the amount will be titrated down to as little as 5 mg as determined by the clinical physician. The amount of atorvastatin calcium will similarly

be titrated down from 80 mg if it is determined by the physician to be in the best interests of the subject. 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 atorvastatin calcium may be used in this invention. Calculation of the dosage amount for these other forms of atorvastatin calcium and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

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 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 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 amlodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof reduces the progression of atherosclerotic 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 pharmaceutically acceptable salts thereof and amlodipine or pharmaceutically acceptable acid addition salts thereof will

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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.

- 5 The secondary objective of this study is to show that the combination of amlodipine or a pharmaceutically acceptable acid addition salt thereof and atorvastatin or a pharmaceutically 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
- 10 (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
- 15 or will decrease. These results represent slowed progression of atherosclerosis, halted progression of atherosclerosis and regression of atherosclerosis, respectively.

- 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
- 20 protocol described below:

Effect of Amlodipine and Atorvastatin, Alone
and in Combination, on the
Treatment of Angina

- This study is a double blind, parallel arm, randomized study to show the
- 25 effectiveness of amlodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof 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
- 30 evidences of cardiac ischemia: (1) stress test segment elevation of about one 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 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 and stabilized on a long acting nitrate such as, for example, nitroglycerin, 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 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 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 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 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 calcium (about 2.5 mg to about 160 mg); (3) amlodipine besylate (about 2.5 mg to about 20 mg); or (4) a combination of the above doses of amlodipine besylate and atorvastatin calcium together. The subjects are then monitored for two to twenty four weeks. 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 atorvastatin calcium may be used in this invention. Calculation of the dosage amount for these other forms of atorvastatin calcium and amlodipine besylate is easily accomplished by
5 performing a simple ratio relative to the molecular weights of the species involved.

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) evaluation of myocardial perfusion using PET scanning. Patients keep a diary of
10 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 nitroglycerine provides a reasonably accurate record of the number of anginal
15 attacks.

To demonstrate the effectiveness of the drug combination of this invention, and to determine the dosage amounts 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 detected by
20 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 photoemission tomography (PET).

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
25 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 Amlodipine and Atorvastatin, Alone and in
Combination, on the Treatment of Subjects Having
30 Both Hypertension and Hyperlipidemia

This study is a double blind, parallel arm, randomized study to show the effectiveness of amlodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof 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
5 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
10 (CHD) and has less than two positive risk factors, then the subject is considered to have hyperlipidemia 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 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
15 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
20 HDL of greater than 60 is considered a negative risk factor and will offset one of the above mentioned positive risk factors.

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
25 minutes apart.

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
30 forth the amount of saturated and unsaturated fat which can be consumed as a 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 week wash out and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure and (2) fasting lipid screen. The fasting lipid
5 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.

After the baseline investigations are performed subjects are started on one of the following: (1) a fixed dose of amlodipine besylate, generally about 2.5 to 10 mg;
10 (2) a fixed dose of atorvastatin calcium, generally about 10 to 80mg; or (3) a combination of the above doses of amlodipine besylate and atorvastatin calcium together. Subjects remain on these doses for a minimum of six weeks, and generally for no more than eight weeks. 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
15 other salt forms of atorvastatin calcium may be used in this invention. Calculation of the dosage amount for these other forms of atorvastatin calcium and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. The subjects return to the testing center at the conclusion of the six to eight weeks so that the baseline evaluations can be repeated.
20 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
25 indicate the utility of the drug combination.

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:

Effects of Amlodipine and Atorvastatin, 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 amlodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof given in combination are effective in reducing the overall calculated risk of 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 amlodipine and atorvastatin 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 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 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 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.

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 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. 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 amlodipine (about 2.5 to 10 mg); (2) a fixed dose of atorvastatin (about 10 to 80mg); or (3) the combination of the above doses of amlodipine and atorvastatin. 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 atorvastatin calcium may be used in this invention. Calculation of the dosage amount for these other forms of atorvastatin calcium and amlodipine besylate is easily accomplished by 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.

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 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.

The following dosage amounts and other dosage amounts set forth elsewhere in the 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

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, amlodipine besylate is generally administered in a dosage of about 2.5 mg to about 20 mg. Preferably, amlodipine besylate is administered in a dosage of about 5 mg to about 10 mg. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate may be used in this invention. Calculation of the dosage amount for these other forms of or the free base form or other salt forms of amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

In general, in accordance with this invention, atorvastatin is administered in a dosage of about 2.5 mg to about 160 mg. Preferably, atorvastatin is administered in a dosage of about 10 mg to about 80 mg. It will be recognized by a skilled person that the free base form or other salt forms of atorvastatin calcium may be used in this invention. Calculation of the dosage amount for these other forms of or the free base form or other salt forms of atorvastatin calcium is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of 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 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 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 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 using methods well known to those skilled in the art. The method of preferred administration will be determined by the attendant physician or other person
- 10 skilled in the art after an evaluation of the subject's condition and requirements. The generally preferred formulation of amlodipine is Norvasc®. The generally preferred formulation of atorvastatin is Lipitor®.

- 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
- 15 of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient 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
- 20 standard techniques well-known to those skilled in the art.

Methods of preparing various pharmaceutical compositions with a certain 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).

- 25 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 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.

- 30 Since the present invention relates to the treatment of diseases and conditions with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical

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compositions in kit form. The kit includes two separate pharmaceutical compositions: amlodipine or a pharmaceutically acceptable acid 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 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.

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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535PRODUCT CLAIMS

1. A pharmaceutical composition comprising:
 - a. an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof;
 - b. an amount of atorvastatin or a pharmaceutically acceptable salt thereof; and
 - c. a pharmaceutically acceptable carrier or diluent.
2. A pharmaceutical composition of claim 1 comprising amlodipine besylate.
3. A pharmaceutical composition of claim 2 comprising the hemicalcium salt of atorvastatin.
4. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater than the sum of the antihypertensive and hypolipidemic effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.
5. A first pharmaceutical composition of claim 4 wherein said second pharmaceutical composition comprises amlodipine besylate.
6. A first pharmaceutical composition of claim 5 comprising the hemicalcium salt of atorvastatin.
7. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater than the sum of the antihypertensive and hypolipidemic effects 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 diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

5 8. A first pharmaceutical composition of claim 7 comprising amlodipine besylate.

 9. A first pharmaceutical composition of claim 8 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

 10. A first pharmaceutical composition for use with a second
10 pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater than the antihypertensive and hypolipidemic effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of
15 atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

 11. A first pharmaceutical composition of claim 10 comprising amlodipine
20 besylate.

 12. A first pharmaceutical composition of claim 11 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

 13. A first pharmaceutical composition for use with a second
25 pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater than the antihypertensive and hypolipidemic effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of
30 amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

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14. A first pharmaceutical composition of claim 13 wherein said second pharmaceutical composition comprises amlodipine besylate.

15. A first pharmaceutical composition of claim 14 comprising the hemicalcium salt of atorvastatin.

5 16. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antiangina effect in a mammal suffering from anginal pectoris, which effect is greater than the sum of the antiangina effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of
10 atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

15 17. A first pharmaceutical composition of claim 16 comprising amlodipine besylate.

18. A first pharmaceutical composition of claim 17 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

19. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering
20 from angina pectoris, which effect is greater than the sum of the antiangina effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition
25 comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

20. A first pharmaceutical composition of claim 19 wherein said second pharmaceutical composition comprises amlodipine besylate.

21. A first pharmaceutical composition of claim 20 comprising the
30 hemicalcium salt of atorvastatin.

22. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering

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from angina pectoris, which effect is greater than the antianginal effects 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 amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

23. A first pharmaceutical composition of claim 22 comprising amlodipine besylate.

24. A first pharmaceutical composition of claim 23 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

25. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering from angina pectoris, which effect is greater than the antianginal effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

26. A first pharmaceutical composition of claim 25 wherein said second pharmaceutical composition comprises amlodipine besylate.

27. A first pharmaceutical composition of claim 26 comprising the hemicalcium salt of atorvastatin.

28. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the sum of the antiatherosclerotic effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an

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amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

29. A first pharmaceutical composition of claim 28 wherein said second pharmaceutical composition comprises amlodipine besylate.

5 30. A first pharmaceutical composition of claim 29 comprising the hemicalcium salt of atorvastatin.

31. A composition of claim 30 wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

10 32. A composition of claim 31 wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

33. A composition of claim 31 wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

34. A composition of claim 31 wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

15 35. A composition of claim 30 wherein said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques.

36. A composition of claim 35 wherein said regression of atherosclerotic plaques occurs in coronary arteries.

20 37. A composition of claim 35 wherein said regression of atherosclerotic plaques occurs in carotid arteries.

38. A composition of claim 35 wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

25 39. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the sum of the antiatherosclerotic effects 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 diluent, said first pharmaceutical composition comprising an amount of amlodipine or
30 a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

40. A first pharmaceutical composition of claim 39 comprising amlodipine besylate.

41. A first pharmaceutical composition of claim 40 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

5 42. A composition of claim 41 wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

43. A composition of claim 42 wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

10 44. A composition of claim 42 wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

45. A composition of claim 42 wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

46. A composition of claim 41 wherein said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques.

15 47. A composition of claim 46 wherein said regression of atherosclerotic plaques occurs in coronary arteries.

48. A composition of claim 46 wherein said regression of atherosclerotic plaques occurs in carotid arteries.

20 49. A composition of claim 46 wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

25 50. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the antiatherosclerotic effects 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 amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

30 51. A first pharmaceutical composition of claim 50 comprising amlodipine besylate.

52. A first pharmaceutical composition of claim 51 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

53. A composition of claim 52 wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

5 54. A composition of claim 53 wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

55. A composition of claim 53 wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

10 56. A composition of claim 53 wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

57. A composition of claim 52 wherein said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques.

58. A composition of claim 57 wherein said regression of atherosclerotic plaques occurs in coronary arteries.

15 59. A composition of claim 57 wherein said regression of atherosclerotic plaques occurs in carotid arteries.

60. A composition of claim 57 wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

20 61. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the antiatherosclerotic effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

25 62. A first pharmaceutical composition of claim 61 wherein said second pharmaceutical composition comprises amlodipine besylate.

30 63. A first pharmaceutical composition of claim 62 comprising the hemicalcium salt of atorvastatin.

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64. A composition of claim 63 wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

65. A composition of claim 64 wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

5 66. A composition of claim 64 wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

67. A composition of claim 64 wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

10 68. A composition of claim 63 wherein said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques.

69. A composition of claim 68 wherein said regression of atherosclerotic plaques occurs in coronary arteries.

70. A composition of claim 68 wherein said regression of atherosclerotic plaques occurs in carotid arteries.

15 71. A composition of claim 68 wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

20 72. A first pharmaceutical composition for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the sum of the cardiac risk management effects 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 diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

25 73. A first pharmaceutical composition of claim 72 comprising amlodipine besylate.

30 74. A first pharmaceutical composition of claim 73 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

75. A first pharmaceutical composition for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of

suffering an adverse cardiac event, which effect is greater than the sum of the cardiac risk management effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

76. A first pharmaceutical composition of claim 75 wherein said second pharmaceutical composition comprises amlodipine besylate.

77. A first pharmaceutical composition of claim 76 comprising the hemicalcium salt of atorvastatin.

78. A first pharmaceutical composition for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the cardiac risk management effects 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 amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

79. A first pharmaceutical composition of claim 78 comprising amlodipine besylate.

80. A first pharmaceutical composition of claim 79 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

81. A first pharmaceutical composition for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the cardiac risk management effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical

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composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

82. A first pharmaceutical composition of claim 81 wherein said second pharmaceutical composition comprises amlodipine besylate.

5 83. A first pharmaceutical composition of claim 82 comprising the hemicalcium salt of atorvastatin.

84. A kit for achieving a therapeutic effect in a mammal comprising:

a. a therapeutically effective amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;

b. a therapeutically effective amount of atorvastatin 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.

85. A kit of claim 84 comprising amlodipine besylate.

86. A kit of claim 85 comprising the hemicalcium salt of atorvastatin.

87. 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 amlodipine or a pharmaceutically acceptable acid addition salt thereof; and

(b) an amount of a second compound, said second compound being atorvastatin 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.

88. A method of claim 87 comprising amlodipine besylate.

89. A method of claim 88 comprising the hemicalcium salt of atorvastatin.

90. A method of claim 87 wherein said therapeutic treatment comprises antihypertensive treatment and antihyperlipidemic treatment.

91. A method of claim 87 wherein said therapeutic treatment comprises antianginal treatment.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-29421

EDICTO No. 14596

**LA SECRETARÍA GENERAL AD-HOC
HACE SABER:**

Que esta Superintendencia profirió **Resolución No. 22343 de 28-AGO-2006**. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud

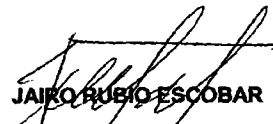
correspondiente a "EFECTOS SINERGETICOS DE LA AMLODIPINA Y ATORVASTATINA O METABOLITO DE LA ATORVASTATINA COMO BASE PARA UNA TERAPIA COMBINADA".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a los doctores Carlos Reinaldo Olarte Garcia, en su calidad de apoderado del Dr. R. Preston Mason, y José Luis Reyes Villamizar, en su calidad de apoderado de las sociedades opositoras Tecnoquímicas S.A. y Laboratorio Franco Colombiano Lafranco S.A., entregándoles copia de la misma, advirtiéndoles que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, del cual podrán hacer uso al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los **28 AGO. 2006**

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIRO RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **27-SEP-2006** Este edicto se desfija hoy **10-OCT-2006** a las cinco (5:00 p.m.)
Secretaría General Ad-Hoc
EDICTO No. 14596