

FORMULARIO ÚNICO DE OPOSICIÓN

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

**SOLICITUD
PUBLICADA**

Número del expediente: 03-113785

Solicitante: WARNER LAMBERT COMPANY LLC

Apoderado: CARLOS REINALDO OLARTE GARCIA

Título de la nueva creación o denominación del signo: COMPOSICIONES

FARMACÉUTICAS DE AMLODIFINA Y ATORVASTATINA

Gaceta: 554

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A. Dirección: CALLE 80 No. 78b-201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>890.106.527-5</u>
	Teléfono: 371 99 00 Fax: 373 08 18 E-mail:	
REPRESENTANTE O APODERADO	Nombre: LUIS FERNANDO RINCÓN Dirección: CALLE 119ª No. 53.99 Teléfono: 613 34 18 Fax: 24 47 87 E-mail: negocios@optimum-co.com	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>79.532.186</u> TP <u>113438</u>

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causa: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

Comprobante de pago No. _____

Fecha _____

ANEXOS

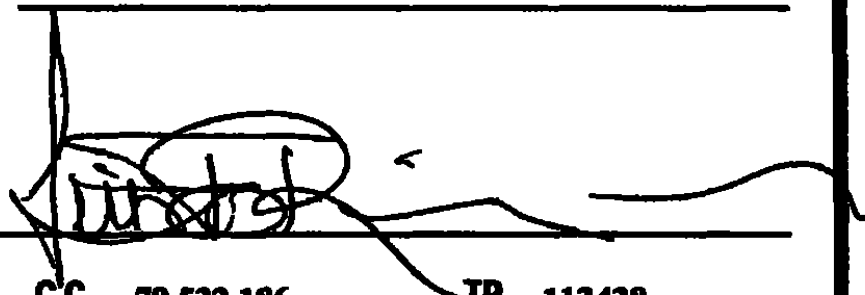
162

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: LUÍS FERNANDO RINCÓN CUELLAR

FIRMA:



C.C. 79.532.186

TP 113438

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 03-113785
Asunto : Oposición a la solicitud de patente de Invención titulada "COMPOSICIONES FARMACÉUTICAS DE AMLODIPINA Y ATORVASTATINA".
Solicitante : WARNER LAMBERT COMPANY LLC.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 554 del 29 de Julio de 2005

Yo, *Luis Fernando Rincón Cuellar*, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad *PROCAPS S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invención titulada "COMPOSICIONES FARMACÉUTICAS DE AMLODIPINA Y ATORVASTATINA", solicitada por *WARNER LAMBERT COMPANY LLC.*, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada debido a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida atentaría directamente a la comercialización que pretende mi representada, en materia de atorvastatina en particular. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

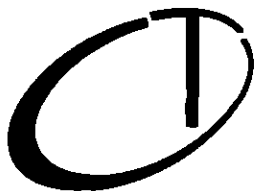
2.1. La solicitud objeto de la presente fue presentada el 31 de diciembre de 2003, reivindicando prioridad bajo las solicitudes US60/309133 del 2001-07-31 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 554 del 29 de julio de 2005, página 426, N° publicación 287, cuya publicación internacional corresponde a la WO03/011283 del 2003-02-13.

2.2. La solicitud colombiana 03-113785 objeto de la presente oposición, se refiere a una composición farmacéutica, que comprende dos componentes: (a) un componente que comprende una granulación de atorvastatina o sus sales farmacéuticamente aceptables y un vehículo que incluye un agente alcalinizante que forma un pH mayor 5; y (b) un segundo componente que comprende amlodipina o sus sales farmacéuticamente aceptables y un vehículo que excluye un

agente alcalinizante que forma un pH mayor que 5, en donde los dos componentes se combinan para formar una composición final para una forma de dosificación sólida; donde dicha composición farmacéutica en la que el componente (a) es una granulación húmeda; el componente (b) es un componente de polvo seco; y el agente alcalinizante en el componente (a) es un regulador de la biodisponibilidad y mejorador de la estabilidad; donde dicha composición farmacéutica el agente alcalinizante en el componente (a) se selecciona entre el grupo que consiste en: carbonato de calcio, fosfato de dicalcio y fosfato de tricalcio; donde la relación atorvastatina o una sal farmacéuticamente aceptable de la misma a carbonato de calcio en el componente (a) es aproximadamente 1:1 a aproximadamente 1:4 p/p; y, donde la composición farmacéutica comprende aproximadamente 0,25% a aproximadamente 10% de amlodipina o una sal farmacéuticamente aceptable de la misma y aproximadamente 2,5% a aproximadamente 20% de atorvastatina o una sal farmacéuticamente aceptable de la misma. El documento también se refiere a un proceso para la preparación de dicho compuesto y su aplicación.

2.3. En primera instancia, se debe advertir que la reivindicación 14 se refiere al uso y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)"*, los usos no están contemplados como patentables. Solo serán patentables los productos o procedimientos.

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
- D5: WO0064443, 2000-11-02
- D6: WO0073271, 2000-12-07

2.5. Básicamente, la presente solicitud se refiere a la combinación de amlodipino 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 cardiacos. 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 amlodipino, junto con la acción como bloqueador de los canales de calcio y su utilidad como antihipertensivo y la falla cardiaca congestiva. Según la acción terapéutica indicada en el documento D3, la amlodipina está indicada para el 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 tiene 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 o sus profarmacos mutuos tal como el ofamlodipino 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 o sus profarmacos mutuos tal como el ofamlodipino 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. 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 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 cardíacos. 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 cardíacos. 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. Por su parte, el documento D5 se refiere a la combinación de la amlodipina con atorvastatina o un metabolito de la atorvastatina que 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. Según se expone en este documento, la inhibición del daño oxidativo 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. Según se explica, 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 los rayos X. El documento D5, también revela que 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. De esta manera, una combinación dentro de un mismo medicamento que comprenda amlodipina y atorvastatina combinado, es conocido en la técnica también con base en documento D5.

2.12. El documento D6, revela sales mutuas de amlodipino y atorvastatina y a las composiciones farmacéuticas de los mismos para tratar la angina de pecho, la aterosclerosis y la hipertensión y la hiperlipidemia en un mamífero mediante el uso de estos profármacos y composiciones. Este documento también se refiere a los procedimientos para tratar el riesgo cardíaco en un mamífero, incluyendo humanos, que presenta síntomas de riesgo cardíaco mediante la administración de estas sales y composiciones.

2.13. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 03-113785 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los tres requisitos necesarios para su protección.

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

2.14.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 31 de julio de 2001, ya era conocido, pues como se demostró, era parte del arte anterior con base en los documentos D4, D5 y D6, un medicamento que comprenda amlodipina y atorvastatina combinado sobre el cual busca protección en el capítulo reivindicatorio.

2.14.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 31 de julio de 2001, 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.

2.14.3. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN

consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el uso, y este no es aplicable 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 usos, no cumplen con el requisito de la aplicación industrial.

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

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

2.17. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"COMPOSICIONES FARMACÉUTICAS DE AMLODIPINA Y ATORVASTATINA"**, solicitada por **WARNER LAMBERT COMPANY LLC**,

solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 554.

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
- D5: WO0064443, 2000-11-02
- D6: WO0073271, 2000-12-07

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 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
- D5: WO0064443, 2000-11-02
- D6: WO0073271, 2000-12-07

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

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a **LUIS FERNANDO RINCON CUELLAR**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 113438 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente 03 113.785, titulada **"COMPOSICIONES FARMACÉUTICAS DE AMLODIPINO Y ATORVASTATINA"**, publicada en la gaceta No. 554 del 29 de Julio de 2005, número de publicación 287, página 426 y cuyo solicitante es la sociedad **WARNER-LAMBERT COMPANY LLC**.

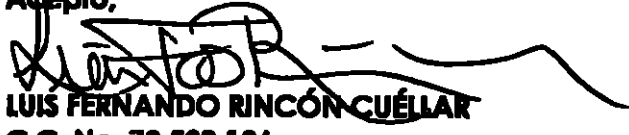
Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados.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

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

Dado y Firmado en Barranquilla (Colombia) el 1 día del mes de Septiembre de 2005.


PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. N° 16.251.923 de Palmira
Representante Legal → atrás

Acepto,


LUIS FERNANDO RINCÓN CUÉLLAR
C.C. No. 79.532.186
T.P. 113438

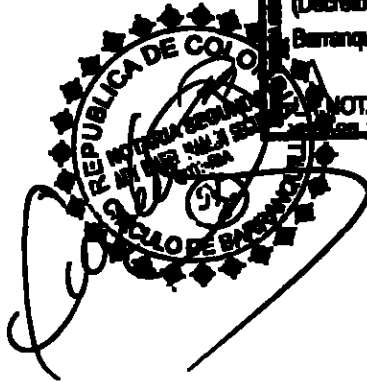
ADY BASIL NAMED SEGURA
 NOTARIA SEGURA DEL CÍRCULO DE BARRANQUILLA
 CERTIFICA

Que la(s) firma(s) que aparece(n) en el documento que
 antecede es/son la(s) de NADER TONDA
TOTELAND

Que aparece(n) registrada(s) en esta Notaría previa
 confrontación de la(s) misma(s).
 (Decreto 980/70)

Barranquilla 06 de sept de 2005

NOTARIA



**DILIGENCIA DE RECONOCIMIENTO
 Y PRESENTACION PERSONAL**

Ante el Notario Once del Círculo de Bogotá de
 Bogotá, compareció [Signature]

Quien exhibió la C.C. No. 7532123
 expedida en [Signature] T.P. 113038

y declaró que la firma y huella que aparecen en
 el presente memorial son suyas y que el conte-
 nido del mismo es cierto.

Memorial dirigido a [Signature]

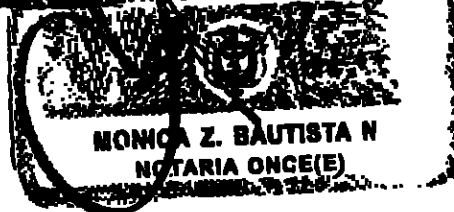
Estado de Bogotá D.C. 20 OCT 2005

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

REPUBLICA DE COLOMBIA
 NOTARIO ONCE DEL CÍRCULO DE SANTAFÉ DE BOGOTÁ
 A 11 DEL CÍRCULO DE
 SANTAFÉ DE BOGOTÁ, D.C.



18
AS

SUPERINDUSTRIA Y COMERCIO
Radiacion : 83113785 00000004 Folios: 249
Fecha (AMD): 2005-10-21 09:36:13
Tramite : 011 PCT-PATENT 279 FASE NACI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

MIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 81.203
FECHA : OCTUBRE 21 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	36871353	23/09/2005	470,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	235,000.00
		TOTAL :	235,000.00

SON: DOSCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



***** Pag.01
CAMARA DE COMERCIO
DE BARRANQUILLA
08*****
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 *****

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PROCAPS S.A. -----

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

C E R T I F I C A

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

C E R T I F I C A

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

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

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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 l s procesos de fabricacion de sustancias quimicas, farmaceuticas,alimentos y cosmeticas, asi como la comercializacion interna y externa de l s productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e)La compra,venta,exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de 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 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 correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con

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



***** Pag.03
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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 act 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, 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 ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para

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

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

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C A M A R A D E C O M E R C I O
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PROCAPS S.A. -----

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

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	Lozada Villareal Milena	C.****32,748,111=
Revisor Fiscal.		

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
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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 mercancias y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, com-

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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, ampli 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 senor 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 *****

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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 comabiaras y demas documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo act 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 representaci n 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 mercancias 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 *****

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

PROCAPS S.A. -----

C E R T I F I C A

Que su ultima Renovacion fue el: 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.

C E R T I F I C A

Que los actos de registro aqui certificados quedan en firme cinco dias
habiles, contados a partir de la fecha de su inscripcion siempre que,
dentro de dicho termino, no sean objeto de los recursos de reposición
ante esta entidad, y/o de apelacion para ante la Superintendencia de
Industria y Comercio. -----

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EL SECRETARIO
MARIBEL REYES OVIEDO

NO ES VALIDO POR ESTA CARA

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NO ES VALIDO POR ESTA CARA

D1- US4681893

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

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,983,140	9/1976	Endo et al.	549/292
4,049,495	9/1977	Endo et al.	435/125
4,137,322	1/1979	Endo et al.	548/344 X
4,198,425	4/1980	Mitsui et al.	514/460
4,255,444	3/1981	Oka et al.	549/292 X
4,262,013	4/1981	Mitsui et al.	549/292 X
4,375,475	3/1983	Willard et al.	514/460

OTHER PUBLICATIONS

Singer, et al.; *Proc. Soc. Exper. Biol. Med.*; vol. 102, pp. 370-373, (1959).

Hulcher; *Arch. Biochem. Biophys.*, vol. 146, pp. 422-427, (1971).

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 American 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

1
**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-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), 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 Mitrus 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.

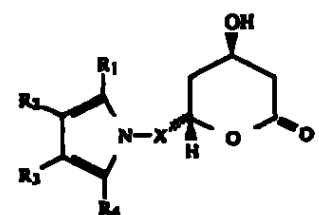
Published PCT application No. WO 84/01231 discloses certain indole analogs and derivatives of mevalonolactone having utility as hypolipoproteinemic and antiatherosclerotic agents.

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 $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{C}-\text{H}_2-$ or $-\text{CH}_2\text{CH}(\text{CH}_3)-$.

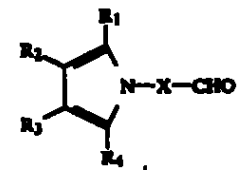
R₁ is 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

Either 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; 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 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.

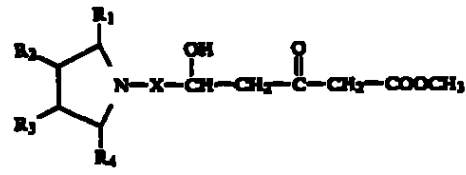
R₄ is alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl.

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

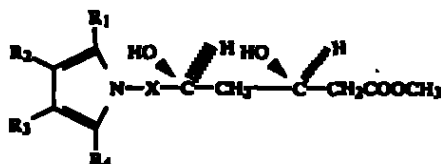
In another aspect of the present invention, there is provided a method of preparing the compounds of structural formula I above which comprises the steps of (a) first reacting a substituted [(pyrrol-1-yl)alkyl]aldehyde compound of the formula



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



- (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 alkanoxyloxy 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

are alkyl or trifluoromethyl with isopropyl being particularly preferred.

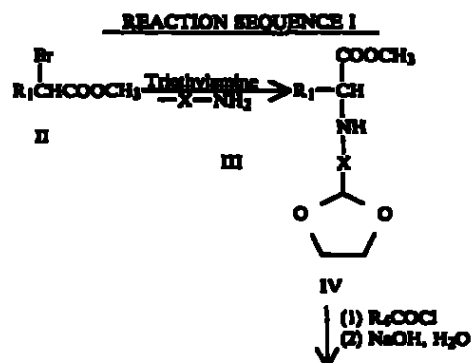
The preferred reaction sequence which is used to prepare compounds of the present invention involves the cycloaddition of a disubstituted acetylene, in which one substituent is carboxamido or N-substituted carboxamido, to an appropriately substituted N-acylaminocarboxylic acid to form a substituted pyrrole. 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.

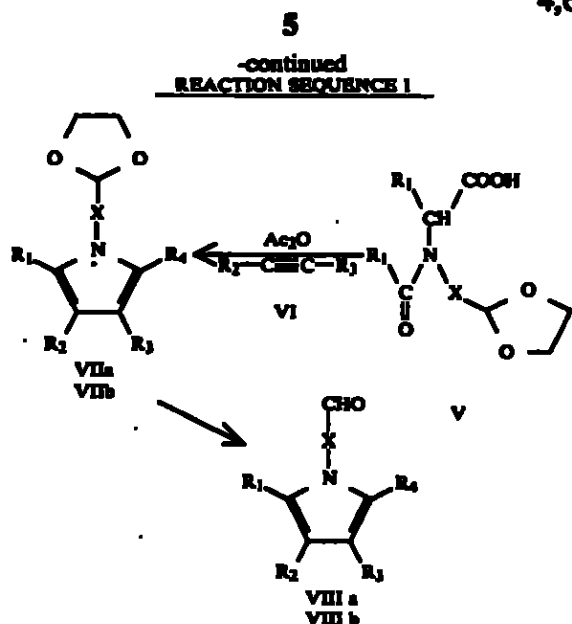
Thus, in compounds of the present invention, the substituent at either position 3 or 4 of the pyrrole nucleus is $-\text{CONR}_3\text{R}_4$ where R_3 and R_4 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, 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 alkanoxyloxy of from two to eight carbon atoms.

Preferred groups for R_3 and R_4 are hydrogen, phenyl, or substituted phenyl. In a particularly preferred group of compounds within the present invention, R_3 is hydrogen and R_4 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 mesonic 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



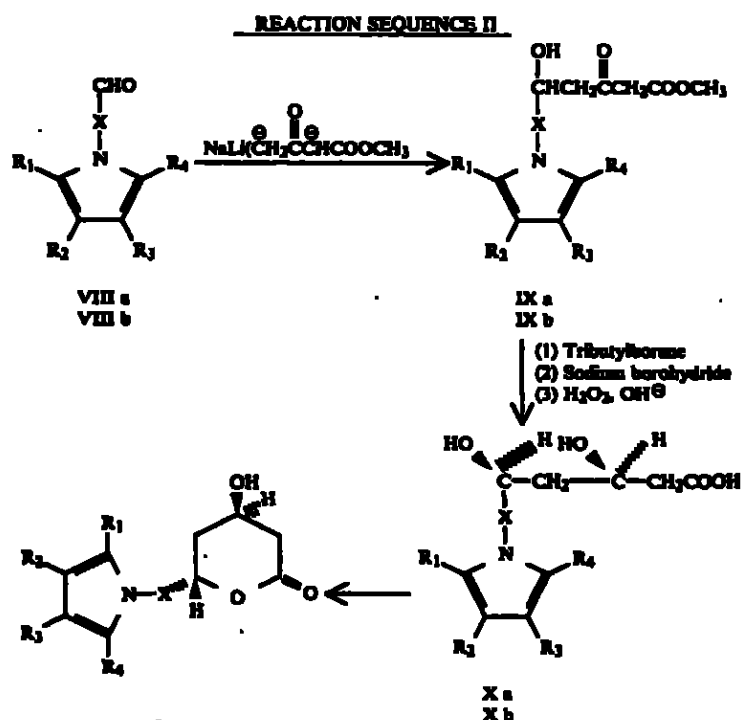


known in the art, and subsequently further purified, if desired, by recrystallization. On the other hand, in the case where R₄ is 1-methylethyl, the cyclo-addition reaction yields predominantly one product which can be purified by recrystallization alone.

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,



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 R₄ 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-one, 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 nonapopifiable

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.

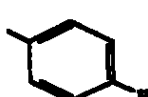
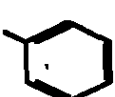
For preparing suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted, and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

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
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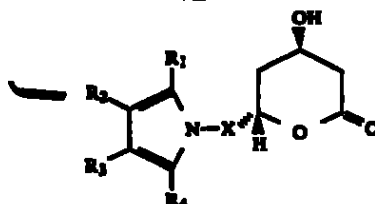


TABLE I-continued

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
Compacts (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-fluorobenzenecetic 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-fluorobenzenecetic 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-fluorobenzenecetic 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]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzenecetic acid, ethyl ester.

Thirty grams (100 mmol) of α -[2-(1,3-dioxolan-2-yl)ethyl]amino]-4-fluorobenzenecetic 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 isobutyryl 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-fluorobenzenecetic acid, ethyl ester.

The 90 MHz proton magnetic resonance spectrum of a deuteriochloroform 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-fluorobenzenecetic 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 300 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-fluorobenzenecetic acid which was used without further purification.

The 90 MHz proton magnetic resonance spectrum of a deuteriochloroform 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, 6.32%.

The infrared spectrum of a KBr pellet of the compound showed principal peaks at 2215, 1630, 1595, 1549, 1490, 1443, 1330, 736, 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-fluorobenzenecetic 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)-8-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)-8-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 , β -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)-8-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 , β -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 , β -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-dioxolan-2-yl)ethyl]amino]-4-fluorobenzenecetic acid.

α -[2-(1,3-Dioxolan-2-yl)ethyl]amino]-4-fluorobenzenecetic 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-dioxolan-2-yl)ethyl]amino]-4-fluorobenzenecetic 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-Dioxolan-2-yl)ethyl]amino]-4-fluorobenzenecetic 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

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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 homogeneous 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%.

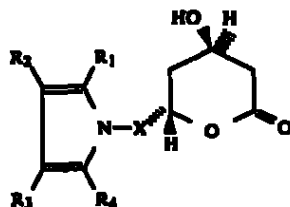
The trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide was found, upon recrystallization from toluene to contain 0.25 mols of toluene as solvent of crystallization, mp 106°-111° C.

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

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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

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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.

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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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PCT

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(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).			
(72) Inventor; and (73) Invention/Applicant (for US only): SCOTT, Robert, Andrew, Donald [ZA/US]; 302 Riverside Avenue, Riverside, CT 06878 (US).			
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(54) Title: COMBINATION THERAPY COMPRISING ATORVASTATIN AND AN ANTIHYPERTENSIVE AGENT			
(57) Abstract This invention relates to pharmaceutical combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents whereby these synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms of cardiac risk, including humans.			

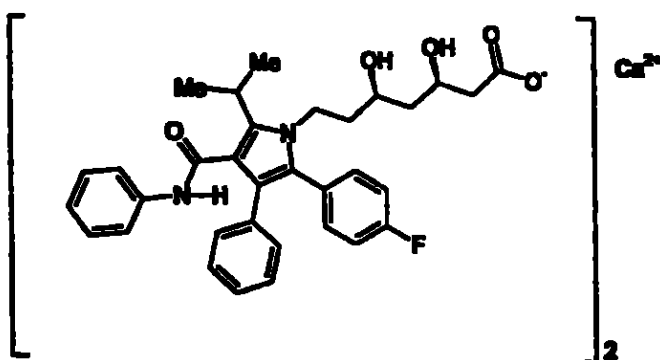
COMBINATION THERAPY COMPRISING ATORVASTATIN AND AN ANTIHYPERTENSIVE AGENT

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.

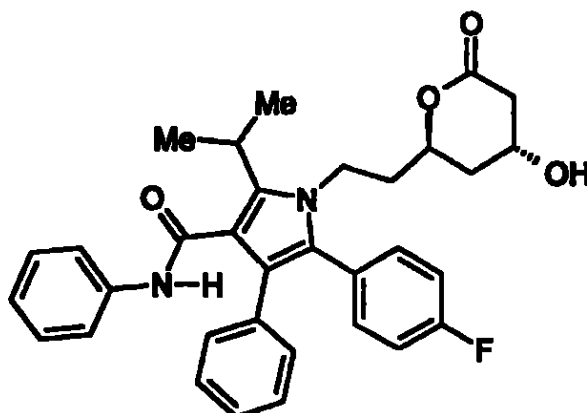
BACKGROUND OF THE INVENTION

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-

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

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

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
10 who undergo PTCA or other surgical procedures designed to treat angina pectoris frequently experience complications such as restenosis. This restenosis may be manifested either as a short term proliferative response to angioplasty-induced trauma or as long term progression of the atherosclerotic process in both graft vessels and angioplastied segments.

15 The symptomatic management of angina pectoris involves the use of a number of drugs, frequently as a combination of two or more of the following classes: beta blockers, nitrates and calcium channel blockers. Most, if not all, of these patients require therapy with a lipid lowering agent as well. The National Cholesterol Education Program (NCEP) recognizes patients with existing coronary artery disease
20 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
25 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
30 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

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.

Kramach 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, 1108-13; and Waters, D. et al., A controlled clinical trial to assess the effect of a calcium channel

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- blocker on the progression of coronary atherosclerosis, *Circulation*, 1990, 82, 1940-53.) U.S. 4,681,693 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, nifedipine, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine.

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

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

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

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

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

20 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, lercidipine, lacidipine, nicardipine, nifedipine, nimodipine, nilecidipine, nitrendipine or felodipine.

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

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

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

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

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

This invention is also more particularly directed to a pharmaceutical
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 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.
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This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition DB", of Composition DA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.
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This invention is also particularly directed to a pharmaceutical composition of Composition D wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

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.

20 This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition EA", of Composition E 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.

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

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

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

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

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

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

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

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

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

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

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

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

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.

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 Arrowmith 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

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. 3,982, 238 or U.S. Release No. 30,577; clemizem, which may be prepared as disclosed in U.S. Patent No. 4,567,175; diltiazem, which may be prepared as disclosed in U.S. Patent No. 3,582, 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; milbetradil, 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; semotladil, which may be prepared as disclosed in U.S. Patent No. 4,788,635; 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. 3,281,859; aranipine, which may be prepared as disclosed in U.S. Patent No. 4,572,909; bamidipine, 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. 4,284,611; isradipine, which may be prepared as disclosed in U.S. Patent No.
10 4,488,972; lacidipine, which may be prepared as disclosed in U.S. Patent No. 4,801,599; lorcanidipine, 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; idoflazine, which may be prepared as disclosed in U.S. Patent No. 3,287,104; lomerizine, which may be prepared as disclosed in U.S. Patent No. 4,883,325; bencyclane, which may be prepared as disclosed in Hungarian Patent No. 151,885; etafenone, which may be prepared as disclosed in German Patent No.
25 1,285,758; and perhexiline, which may be prepared as disclosed in British Patent No. 1,025,578. The disclosures of all such U.S. Patents are incorporated herein by reference.

Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) which are within the scope of this invention include, but are not limited to: alacepril, which may be
30 prepared as disclosed in U.S. Patent No. 4,248,883; benazepril, which may be prepared as disclosed in U.S. Patent No. 4,410,520; captopril, which may be prepared as disclosed in U.S. Patent Nos. 4,048,889 and 4,105,778; 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
5 as disclosed in U.S. Patent No. 4,555,502; moxetopril, which may be prepared as disclosed in Belgian Patent No. 893,553; perindopril, which may be prepared as disclosed in U.S. Patent No. 4,508,729; 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.
10 Patent No. 4,470,972; temocapril, which may be prepared as disclosed in U.S. Patent No. 4,699,905; andtrandolapril, which may be prepared as disclosed in U.S. Patent No. 4,933,381. The disclosures of all such U.S. patents are incorporated herein by reference.

Angiotensin-II receptor antagonists (A-II antagonists) which are within the
15 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
20 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; amosulolol, 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. 3,883,607 or 3,838,671; befunolol, which may be prepared as disclosed in U.S. Patent No. 3,853,923; betaxolol, which may be prepared as disclosed in U.S. Patent No. 4,252,984; bevantolol, which may be prepared as disclosed in U.S. Patent No. 3,857,981; bisoprolol, which may be prepared as disclosed in U.S. Patent No. 4,171,370; bopindolol, which may be
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prepared as disclosed in U.S. Patent No. 4,340,541; bucumolol, which may be prepared as disclosed in U.S. Patent No. 3,663,570; bufetolol, which may be prepared as disclosed in U.S. Patent No. 3,723,476; bufuralol, which may be prepared as disclosed in U.S. Patent No. 3,829,836; bunitolol, 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; butofololol, 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; 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. 4,603,067; 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; cioranolol, which may be prepared as disclosed in German Patent No. 2,213,044; 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. 4,483,176; mepindolol, which may be prepared as disclosed in Seeman et al., Helv. Chim. Acta, 1971, 54, 241; 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. 3,501,789; nadolol, which may be prepared as disclosed in U.S. Patent No. 3,835, 267; nadoxolol, which may be prepared as disclosed in U.S. Patent No. 3,819,702; nabivalol, which may be prepared as disclosed in U.S. Patent No. 4,654,382; 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; perbutolol, which may be prepared as disclosed in U.S. Patent No. 3,551,483; pindolol, which may be prepared as disclosed in Swiss Patent Nos. 469,002 and 472,404; practolol, which may be prepared as disclosed in U.S. Patent

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No. 3,408,387; pronethalol, which may be prepared as disclosed in British Patent No. 909,357; propranolol, which may be prepared as disclosed in U.S. Patent Nos. 3,337,628 and 3,520,919; sotalol, which may be prepared as disclosed in Uloth et al., Journal of Medicinal Chemistry, 1988, 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. 4,129,585; 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; depiprazole, 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; fenspride, which may be prepared as disclosed in U.S. Patent No. 3,399,192; indoramin, which may be prepared as disclosed in U.S. Patent No. 3,527,761; labetalol, which may be prepared as disclosed above; naftopidil, which may be prepared as disclosed in U.S. Patent No. 3,997,666; nicergoline, which may be prepared as disclosed in U.S. Patent No. 3,228,943; prazosin, which may be prepared as disclosed in U.S. Patent No. 3,511,836; 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; eburnamonine, 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. 3,773,839; 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; naftronyl, which may be prepared as disclosed in U.S. Patent No. 3,334,096; nicametate, which may be prepared as disclosed in Blücke 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; pentifyline, 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. 3,010,985; bendazol, which may be prepared as disclosed in J. Chem. Soc. 1968, 2426; benturodil hemisuccinate, which may be prepared as disclosed in U.S. Patent No. 3,355,463; benzlodarone, which may be prepared as disclosed in U.S. Patent No. 3,012,042; chloracizine, which may be prepared as disclosed in British Patent No. 740,932; chromonar, which may be prepared as disclosed in U.S. Patent No.

3,282,938; clobenfurol, which may be prepared as disclosed in British Patent No. 1,160,925; clonitrate, which may be prepared from propanediol according to methods well known to those skilled in the art, e.g., see *Annalen*, 1870, 165, 165; cloricromen, which may be prepared as disclosed in U.S. Patent No. 4,452,811; dilaazep, which
5 may be prepared as disclosed in U.S. Patent No. 3,532,685; dipyridamole, which may be prepared as disclosed in British Patent No. 807,826; droprenilamine, which may be prepared as disclosed in German Patent No. 2,521,113; efloxate, which may be prepared as disclosed in British Patent Nos. 803,372 and 824,547; erythryl 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. 1,285,758; 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; ganglofene, which may be prepared as disclosed in U.S.S.R. Patent No. 115,905; hexastrol, 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; khalin, 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. 838,422-3;
25 perhexiline, which may be prepared as disclosed above; pinefyline, 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; troinitrate phosphate, which may be prepared by nitration of triethanolamine followed by precipitation with phosphoric

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; benzocaine, 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, 78, 252; brovincamine, which may be prepared as disclosed in U.S. Patent No. 4,146,643; bufenolol, which may be prepared as disclosed in U.S. Patent No. 3,542,870; butilmedil, 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; ciclonicats, 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; cycloandelate, which may be prepared as disclosed above; diisopropylamine dichloroacetate, which may be prepared as disclosed above; elodisin, 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; hepronicats, which may be prepared as disclosed in U.S. Patent No. 3,384,642; ilenprodil, which may be prepared as disclosed above; iloprost, which may be prepared as disclosed in U.S. Patent No. 4,692,484; inositol niacinate, which may be prepared as disclosed in Badgett et al., *Journal of the American Chemical Society*, 1947, 69, 2907; isosuprine, 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.*, 1981, 6, 210; kallikrein, which may be prepared as disclosed in German Patent No. 1,102,973; moxidlyte, which may be prepared as disclosed in German Patent No. 905,738; nafonyl, 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

No. 368,523; 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; pirobedil, which may be prepared as disclosed in U.S. Patent No. 3,269,067; 5 prostaglandin E₁, which may be prepared by any of the methods referenced in the Merck Index, Twelfth Edition, Budavari, Ed., New Jersey, 1996, p. 1353; sulotidil, which may be prepared as disclosed in German Patent No. 2,334,404; tolazoline, which may be prepared as disclosed in U.S. Patent No. 2,161,938; and xanthinol nicotinate, which may be prepared as disclosed in German Patent No. 1,102,750 or 10 Korbonits et al., Acta. Pharm. Hung., 1968, 38, 66. 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. 639,366; arbutin, which may be prepared as disclosed in Techischibabin, Annalen, 1830, 472, 303; chlorazanzil, 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 disclosed in U.S. Patent No. 4,018,690; perhexiline, which may be prepared as 25 disclosed above; ticrynafen, which may be prepared as disclosed in U.S. Patent No. 3,758,606; triamterene which may be prepared as disclosed in U.S. Patent No. 3,061,230; 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: atthiazide, 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

(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. 3,670,720; 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; tecilothiazide, 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. 3,168,329; 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; chloramphenamide, 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; ethoxotamide, 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. 3,358,892; methazolamide, which may be prepared as disclosed in U.S. Patent No. 2,783,241; pretanide, 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; triamide, 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. 3,587,777. The disclosures of all such U.S. patents are incorporated herein by reference.

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

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

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

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

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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 diseases. 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.
- 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 760 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.
- 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 40% determined by catheterization or radionuclide ventriculography or ECHO cardiogram at the time of the qualifying angiogram or within the previous three months of the acceptance of the qualifying angiogram

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

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

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

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

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

The primary endpoint of the study is the change in the average mean
5 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
10 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
15 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
20 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
25 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
30 treatment of angina pectoris in mammals (e.g., humans) is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

**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.

10 **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 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.

15 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 nitroglycerine, isosorbide-5-
20 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
25 two attacks of angina per week while on stable doses of long acting nitrate are generally permitted to skip the wash out phase. After subjects are stabilized on nitrates, the subjects enter the randomization phase provided the subjects continue to have either one or two angina attacks per week. In the randomization phase, the
30 subjects are randomly placed into one of the four arms of the study set forth below. After completing the wash out phase, subjects in compliance with the entry criteria undergo twenty four hour ambulatory electrocardiogram (ECG) such as Holter monitoring, exercise stress testing such as a treadmill and evaluation of myocardial

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

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

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

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

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

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

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

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

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

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

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
- 15 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 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
- 25 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. 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

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

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

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

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

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

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

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

15 diltiazem, generally about 120 mg to about 480 mg;
verapamil, generally about 20 mg to about 48 mg;
felodipine, generally about 2.5 mg to about 40 mg;
laserdipine, 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;
25 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
amloride, 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 tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are
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desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

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

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

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

Pharmaceutical compositions according to the invention may contain 0.1%-
25 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.

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

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addition salt thereof and atorvastatin or a pharmaceutically acceptable salt thereof. The kit includes container means for containing the separate compositions such as a divided bottle or a divided foil packet. however, the separate compositions may also be contained within a single, undivided container. Typically the kit includes directions
5 for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

10 It should be understood that the invention is not limited to the particular embodiments described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

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, milbepradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine or a pharmaceutically acceptable salt of said calcium channel blocker.
5. A pharmaceutical composition of claim 4 wherein said calcium channel blocker is felodipine, nifedipine or a pharmaceutically acceptable salt thereof.
- 25 6. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan or a pharmaceutically acceptable salt of said A-II antagonist.
7. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is a diuretic, said diuretic being amiloride, bendroflumethiazide
- 30 or a pharmaceutically acceptable salt thereof.
8. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol or a pharmaceutically acceptable salt thereof.

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 ortrandolapril.

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

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

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

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

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 receptor blocker being carvedilol.

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

30. A pharmaceutical composition of claim 23 wherein said 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 effective for cardiac risk management.

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

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

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

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

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

39. A pharmaceutical composition of claim 37 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is
25 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
30 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 pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

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

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

- 5 48. A method of claim 47 comprising the hemicalcium salt of atorvastatin.
49. A method of claim 47 wherein said therapeutic treatment comprises antihypertensive and antihyperlipidemic treatment.
50. A method of claim 47 wherein said therapeutic treatment comprises antilanginal 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.

D3-US5155120



US005155120A

United States Patent [19]

[11] **Patent Number:** 5,155,120

Lazar et al.

[45] **Date of Patent:** Oct. 13, 1992

[54] **METHOD FOR TREATING CONGESTIVE HEART FAILURE**

[75] **Inventors:** Jeffrey D. Lazar; Joseph F. Soukhrade; Svetoslav K. Vanev, all of Groton, Conn.

[73] **Assignee:** Pfizer Inc, New York, N.Y.

[21] **Appl. No.:** 767,173

[22] **Filed:** Sep. 27, 1991

Related U.S. Application Data

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

[51] **Int. Cl.⁵** A01N 43/40

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

[58] **Field of Search** 514/356

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Primary Examiner—Frederick E. Waddell

Assistant Examiner—Gregory Hook

Attorney, Agent, or Firm—Peter C. Richardson; J.

Trevor Lumb; James M. McManus

[57] **ABSTRACT**

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

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.

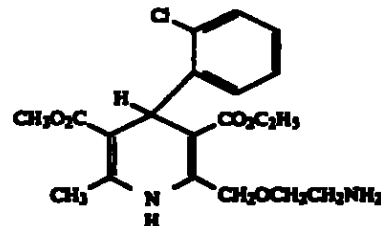
SUMMARY OF THE INVENTION

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 benzene-sulfonate.

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) for at least two weeks;
- 2) in patients on ACE inhibitors, therapeutic regimen had to be constant for 12 weeks;
- 3) therapeutic regimens with digitalis and diuretics had to be constant for at least four weeks;
- 4) therapy which was specifically listed in exclusion criteria had to be discontinued for at least two weeks.

Upon meeting these criteria, patients underwent baseline screening which included clinical evaluation, one treadmill exercise test, a chest X-ray, laboratory safety tests, and determination of left ventricular ejection fraction. In 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 cardiovascular hormones. Determination of gated radionuclide ventriculography at rest and during exercise 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.

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 param-
eters was evaluated as follows:

1. Symptom Rating: At each visit patients received a
detailed cardiopulmonary assessment of symptoms
(dyspnea, fatigue, orthopnea, paroxysmal noctur-
nal 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 Question-
naire): 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 base-
line, 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 op-
tional determination of two-dimensional
echocardiography and Doppler echocardiogra-
phy 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 com-
pleted the study are included in this subset. For the total

exercise time, patients also have to satisfy the "repro-
ducible" 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 differ-
ence 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

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

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 transfor-
mation as:

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

where

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

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):

$$\text{Change}_{ij} = M + T_i + C_j + B_k + B^*T_k + E_{ijk}$$

where:

Change_{ij} 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=(ACE, 2(No ACE))

*B***T_k* 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):

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

where:

Change_{jk} 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*).

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-Haenszel 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 treated by an increase in furosemide dosage or other diuretics as needed.

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

The duration (range) of treatment for amlodipine was 50.2 (10-71) days and 50.9 (5-74) days for placebo.

VIII. Results

A. Efficacy

Exercise Performance: Exercise performance was one of the primary end points to be analyzed in this study. Prior to randomization, potential subjects were required to participate in two exercise tests and the total exercise 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	Amlodipine	6	43	4	53	0.06
Dyspnea	Placebo	3	45	9	57	
Orthopnea	Amlodipine	6	43	4	53	0.203
	Placebo	10	45	1	56	
Fatigue	Amlodipine	23	23	7	53	0.06
	Placebo	13	29	12	54	

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 min: (N = 50 amlodipine, 54 placebo) Investigators Global Assessment:	72.7 (14.3%)	17.3 (3.0%)
Worsening	10	10
No Change	13	31
Improvement	31	17
Increase in L.V 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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(21) International Application Number: PCT/IB98/01225 (22) International Filing Date: 11 August 1998 (11.08.98) (30) Priority Data: 60/037,275 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) Inventors; and (75) Inventors/Applicants (for US only): BUCH, Jan [DK/US]; Unit 6, 48 Spring Street, Greenwich, CT 06830 (US). SCOTT, Robert, Andrew, Donald [ZA/US]; 302 Riverside Avenue, Riverside, CT 06878 (US). (74) Agents: SPIEGEL, Allen, J. et al.; c/o Simpson, Allison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IR, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.
(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 these synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms of cardiac risk, including humans.			

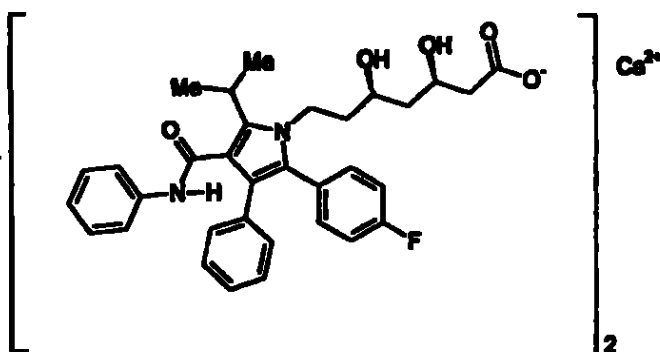
THERAPEUTIC COMBINATIONS COMPRISING AMLODIPIN AND ATORVASTATIN

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 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 suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms or signs of cardiac risk, including humans.

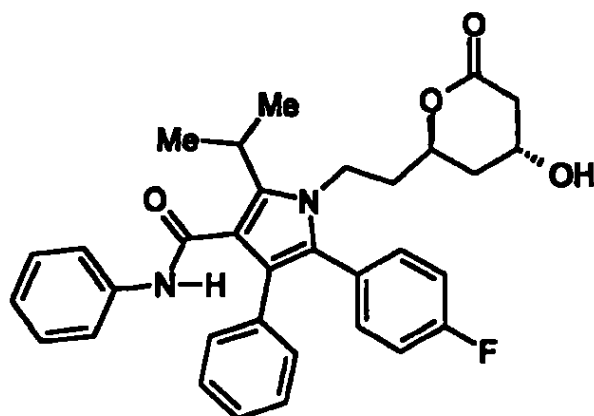
BACKGROUND OF THE INVENTION

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

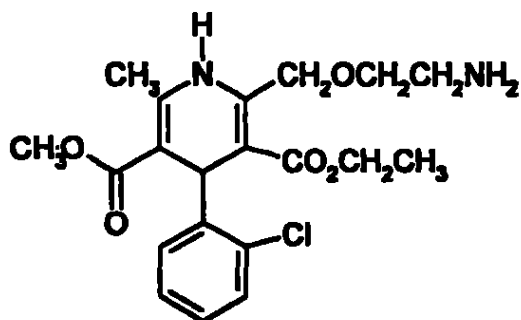


Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA. As such, atorvastatin calcium is a potent lipid lowering compound. The free carboxylic acid form of atorvastatin exists predominantly as the lactone of the formula



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

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.

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

5 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.

10 Kramach et al., Journal of Human Hypertension (1995) (Suppl. 1), 53-59 disclose 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 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:

- 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.

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.

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 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 BA", of Composition B wherein said second pharmaceutical composition comprises amlodipine besylate.

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

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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 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.

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 second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

15 This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition D", 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 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 a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

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

25 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.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition E", 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 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 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.

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 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 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 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.

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
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 JA", of Composition J wherein said second pharmaceutical composition comprises amlodipine besylate.

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

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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 is manifested by a regression of atherosclerotic plaques.

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

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

25 This invention is also particularly directed to a composition of Composition LD 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 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.

10 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.

15 This invention is more particularly directed to a first pharmaceutical 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.

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

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
15 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 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.

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
10 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.

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
25 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.

This invention is also directed to a method, hereinafter termed "Method A", for
15 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
20 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.

This invention is particularly directed to a method, hereinafter Method B, of
25 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.

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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.

15 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.

20 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.

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

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

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).
15 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 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.

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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. 4,681,692, 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-benzyphenethylamine), 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 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 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 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.

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

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.

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

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

25 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 the treatment of symptomatic angina.

30 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 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
5 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-
10 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
15 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.
20 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
25 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
30 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

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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 are evaluated to complete the study.

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

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

20 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.

25 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 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**

5 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
10 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.

15 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
20 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,
25 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.

30 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

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, Easton, 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

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.

15

PRODUCT 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 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 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 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 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 10. A first pharmaceutical composition 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 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.

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

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

25 13. A first pharmaceutical composition 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 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.

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

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

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

28. 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.

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
25 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.
56. A composition of claim 53 wherein said progression of atherosclerotic
10 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.
61. A first pharmaceutical composition for use with a second
20 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
25 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.
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.

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

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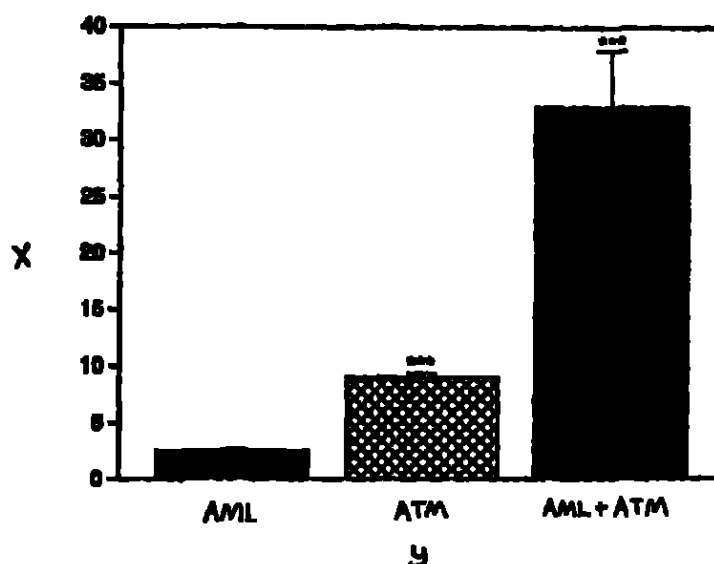
92. A method of claim 87 wherein said therapeutic treatment comprises cardiac risk management.

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

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(71)(72) Applicant and Inventor: MASON, R., Preston [US/US]; Post Office Box 585, Sewickley, PA 15143 (US).			
(74) Agents: COHEN, Jerry et al.; Perkins, Smith & Cohen, LLP, One Beacon Street, Boston, MA 02108 (US).		Published With international search report.	

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(57) Abstract

The combination of amlodipine with either atorvastatin or atorvastatin metabolite shows a synergistic antioxidant effect on lipid peroxidation in human low-density lipoproteins and membrane vesicles enriched with polyunsaturated fatty acids. Inhibition of oxy-radical damage by this drug combination was observed at therapeutic levels in a manner that could not be reproduced by the combination of amlodipine with other statins or the natural antioxidant, vitamin E. The basis for this potent activity is attributed to the chemical structures of these compounds and their molecular interactions with phospholipid molecules, as determined by x-ray diffraction analyses. This combination therapy can be used to treat cardiovascular disorders, especially coronary artery disease, by increasing the resistance of low-density lipoproteins and vascular cell membranes against oxidative modification.

SYNERGISTIC EFFECTS OF AMLODIPINE AND ATORVASTATIN

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Cross Reference to Related Applications

This application claims priority from the following four United States provisional patent applications: U.S. Application No. 60/130,665, filed on April 23, 1999; U.S. Application No. 60/145,305, filed on July 23, 1999; U.S. Application
10 No. 60/151,121, filed on August 27, 1999; and U.S. Applications No. 60/166,592, filed on November 19, 1999.

Field of Invention

The present invention relates to pharmaceutical compositions and
15 combinations to treat arterial and related heart disease and related ailments.

Background of the Invention

Coronary artery disease (CAD) is the leading cause of mortality in the developed world, and is associated with substantial morbidity as well. Typically,
20 the patient with CAD has several concomitant conditions, including hypertension, diabetes, and dyslipidemia, increasing overall risk for poor outcomes and complicating treatment.

Among antihypertensive therapies, the lipophilic dihydropyridine-type calcium channel blocker (CCB) amlodipine besylate (AML) is a very well-tolerated agent with an established record of safety and effectiveness for the treatment of hypertension and angina. A potential therapeutic role for AML in the treatment of patients with CAD was recently shown in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc® (AML) Trial (PREVENT). This three-year trial evaluated the effects of AML compared to placebo on the development and progression of atherosclerotic lesions in coronary and carotid arteries among patients with documented CAD (Byington RP, Miller ME, Herrington D, et al. Rationale, design, and baseline characteristics of the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). *Am. J. Cardiol.* 1997; 80:1087-1090). The results of PREVENT showed impressive clinical benefits with AML therapy, including an overall 30% reduction in major documented events or procedures (Byington RP, Chen J, Furberg CD, Pitt B. Effect of amlodipine on cardiovascular events and procedures. *J. Am. Coll. Cardiol.* 1999; 33:314A). AML therapy was also associated with a significant slowing in the progression of carotid atherosclerosis, as measured by B-mode ultrasonographic assessments (Byington R, Riley W, Booth D, et al. Effect of amlodipine on progression of carotid atherosclerosis in patients with documented heart disease. *Am. J. Hypertens.* 1999; 12:42A-43A). The clinical benefit seen with AML in CAD has not been previously reported with other CCBs, including dihydropyridine-type agents that have been used to examine this question (Waters D, Lesperance J,

- Francetich M, et al. A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis. *Circulation* 1990; 82:1940-1953; Lichtlen PR, Hugenholtz PG, Rafflenbeul W, et al. Retardation of coronary artery disease in humans by the calcium-channel blocker nifedipine: Results of the INTACT study (International Nifedipine Trial on Antiatherosclerotic Therapy). *Cardiovasc. Drugs Ther.* 1990; 4:S1047-S1068; Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial. *JAMA* 1996; 276:785-791). This observation has led to interest in potential antiatherogenic properties of AML, including antioxidant effects that are independent of calcium channel modulation (Mason RP, Leeds PR, Jacob RF, et al. Inhibition of excessive neuronal apoptosis by the calcium antagonist amlodipine and antioxidants in cerebellar granule cells. *J. Neurochem.* 1999; 72:1448-1456; Tulenko TN, Laury-Kleintop L, Walter MF, Mason RP. Cholesterol, calcium and atherosclerosis: Is there a role for calcium channel blockers in atheroprotection? *Int. J. Cardiol.* 1997; 62 (2 Suppl):55S-66S; Krams DM, Sharma RC. Limits of lipid-lowering therapy: The benefits of amlodipine as an anti-atherosclerotic agent. *J. Hum. Hypertens.* 1995; 9 (Suppl 1):S3-S9).
- 20 Hypolipidemic therapy has also been demonstrated to be very useful in reducing morbidity and mortality associated with CAD. Among HMG-CoA reductase inhibitors, atorvastatin calcium (AT) has been shown to be very effective

- as hypolipdemic therapy (Nawrocki JW, Weiss SR, Davidson MH, et al. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor. *Arterioscler. Thromb. Vasc. Biol.* 1995; 15:678-682; Bakker-Arkema RG, Davidson MH, Goldstein RJ, et al.
- 5 Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA* 1996; 275:128-133). In a recent clinical study involving patients with stable and advanced CAD, aggressive lipid-lowering therapy with atorvastatin significantly delayed the time to a first ischemic event and reduced, by 36%, the overall incidence of cardiovascular events, as compared to
- 10 angioplasty with usual medical care (Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy combined with angioplasty in stable coronary artery disease. *N. Engl. J. Med.* 1999; 341:70-76). In addition, the hydroxylated metabolites of AT have been shown to exhibit antioxidant effects in lipoprotein preparations (Aviram M, Rosenblat M, Bisgaier CL, Newton RS. Atorvastatin and
- 15 gemfibrozil metabolites, but not the parent drugs, are potent antioxidants against lipoprotein oxidation. *Atherosclerosis* 1998; 138:271-280).

However, no pharmaceutical composition currently exists that treats both hypertension and hyperlipidemia. Such a pharmaceutical composition would have

20 several benefits. For example, the multiple risk factors for arterial and related heart disease that are often present in an individual patient could be targeted simultaneously. Additionally, the ease of taking one combined dosage could

significantly enhance patient compliance with therapeutic regimens.

Therefore, it is an object of this invention to provide a combination therapy that will treat the multiple pathological processes involved in arterial and related heart disease. These include, but are not limited to, hypertension and hyperlipidemia. It is also an object of this invention to develop useful and convenient dosage levels and forms of such a combination therapeutic. Preferably, this pharmaceutical composition would have synergistic effects on these hallmarks of arterial and related heart disease, such that the individual effects of the components of this composition would be enhanced by their combination.

Thus, this invention encompasses a therapeutic goal for the treatment of CAD that entails the development of drugs that can simultaneously target multiple underlying disease processes that contribute to atherosclerosis, thereby altering the course of the disease. Therefore, using this invention, CAD therapy may have increased positive outcomes if the use of an antihypertensive agent and HMG-CoA reductase inhibitor was combined in a single delivery system.

Summary of the Invention

Unexpectedly, when AML and AT were combined, they had a synergistic effect in preventing lipid peroxidation in human low-density lipoproteins (LDL) and lipid membranes; this effect occurred in addition to their well-established

therapeutic effects on both dyslipidemia and hypertension. The activity of the combination is considered synergistic as the measured effect significantly exceeded any additive effects of the two drugs. Therefore, these agents have heretofore unrecognized synergistic antioxidant effects, a property that would enable these agents to increase the resistance of LDL and vascular cell membranes to oxidative modification during atherogenesis. Indeed, oxidative modification of lipids is a well-established cause of injury to the endothelium and underlying smooth muscle (Roas R. Atherosclerosis – An inflammatory disease. *N. Engl. J. Med.* 1999; 340:115-126; Diaz MN, Frei B, Vita JA, Keaney JF. Antioxidants and atherosclerotic heart disease. *N. Engl. J. Med.* 1997; 337:408-416). Lipophilic agents that protect against lipid peroxidation have been shown to reduce lesion development in various models of atherosclerosis as well as clinical studies (Diaz MN, Frei B, Vita JA, Keaney JF. Antioxidants and atherosclerotic heart disease. *N. Engl. J. Med.* 1997; 337:408-416). Moreover, the benefit associated with hypolipidemic therapy is attributed to both its effect on plasma very low-density lipoproteins (VLDL), LDL, and high-density lipoproteins (HDL) levels and, as a consequence, to a reduction in the potential formation of atherogenic oxidized lipoproteins.

Scientific analyses that support the combined use of AML (Norvasc®) and AT (Lipitor®) in a single delivery system for the treatment of cardiovascular disease are described in this invention. Specifically, the synergistic antioxidant activities of

the calcium channel blocker, AML, and the HMG-CoA reductase inhibitor, AT, including its active hydroxylated metabolite (ATM), were evaluated in human LDL and lipid membranes enriched with polyunsaturated fatty acids (PUFA), the key target for oxy-radical damage in atherosclerosis. The synergistic effects of these agents were demonstrated in membranes prepared in the presence of cholesterol. The combination of AML with ATM effected a dramatic and sustained reduction in lipid oxy-radical damage at concentrations as low as 10.0 nM. The dose-dependent antioxidant activity associated with the combination of these drugs at therapeutic levels was highly synergistic and could not be effectively reproduced by the endogenous agent, vitamin E. Synergistic inhibition of lipid peroxidation was also observed with the combination of AML and AT. Antioxidant activity was not observed, however, when AML was combined with other HMG-CoA reductase inhibitors, including lovastatin and mevastatin. As determined by x-ray diffraction and chemical analyses, the distinct activity described for this drug combination can be attributed to strong physico-chemical interactions with the membrane bilayer that are independent of the well-characterized effects of these drugs on calcium transport and cholesterol metabolism. This synergistic antioxidant benefit constitutes a new pharmacologic mechanism of action for these compounds and a compelling rationale for the combined use of the active ingredients in Norvasc® and Lipitor® in the treatment of cardiovascular disease by reducing the levels of LDL in plasma and improving protection of LDL and cellular membranes against oxidation. This new property complements the established effects of these drugs on hypertension and

dyslipidemia.

Other objects, features, and advantages of the present invention will be apparent from the following Detailed Description of the Preferred Embodiments
5 taken in conjunction with the accompanying drawings in which:

Brief Description of the Drawings

Figure 1 shows the synergistic effects of AML and ATM on lipid peroxidation at a low, therapeutic concentration of drug (100.0 nM) in membranes
10 containing physiologic levels of cholesterol. x is percent inhibition of lipid peroxidation and y is treatment with amlodipine (AML), atorvastatin metabolite (ATM), and the combination of both (AML + ATM) at a level of 100 nM. Values are mean $\pm$ standard deviation for n = 6. ... indicates p<0.001 versus control and other treatments.

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Figure 2 shows the dose-dependent antioxidant effect of the combination of AML and ATM over a broad range of concentrations (0.01 through 10.0 μ M). x is percent inhibition of lipid peroxidation and y is treatment with the combination of AML and ATM at the micromolar concentrations indicated. Values are mean $\pm$
20 standard deviation for n = 6. ... indicates p<0.001 versus control and other treatments.

Figure 3 shows the superior antioxidant activity of the AML/ATM combination over vitamin E as a function of time at an identical concentration (10.0 μ M). x is percent inhibition of lipid peroxidation and y is treatment with the combination of amlodipine and atorvastatin metabolite (AML + ATM), darkened panel, or vitamin E (E), cross-hatched panel, both at 10 μ M. Values are mean $\pm$ standard deviation for n = 6 to 12. ... indicates p<0.001 versus control and other treatments.

Figure 4 shows the comparative antioxidant activity of AML/ATM versus AML/AT at two different concentrations. x is percent inhibition of lipid peroxidation and y is treatment with the combination of amlodipine and atorvastatin metabolite (AML + ATM), darkened panel, or amlodipine and atorvastatin (AML + AT), cross-hatched panel, at the micromolar concentrations indicated. Values are mean $\pm$ standard deviation for n = 5 to 6. ... indicates p<0.001 versus control and other treatments.

Figure 5 shows the sites of proton abstraction (S1, S2, and S3) for ATM that contribute to antioxidant activity in the 5A panel along with resonance stabilization calculations (Panels 5B through 5D).

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Figure 6 shows the comparative effects of AML antioxidant activity when combined with different HMG-CoA reductase inhibitors at the same concentration.

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x is percent inhibition of lipid peroxidation and y is treatment with the combination of amlodipine and atorvastatin metabolite (AML + ATM), darkened panel; amlodipine and atorvastatin (AML + AT), darkened panel; amlodipine and mevastatin (AML + M), cross-hatched panel; or amlodipine and lovastatin (AML + L), no lipid peroxidation inhibition; all at 1.0 μ M. Values are mean $\pm$ standard deviation for n = 6 to 12. ... indicates $p < 0.001$ versus control and other treatments.

Figure 7 shows the synergistic antioxidant effects of AML and ATM in human LDL samples, as compared to Trolox C (soluble vitamin E). In panel A, x is thiobarbituric reactive substances (TBARS) formation measured at an absorbance of 532 nm and y is time in hours. The control is indicated by filled circles with solid lines, Trolox C (soluble vitamin E) is indicated by filled, inverted triangles with small dashed lines, AML alone is indicated by open diamonds with long dashed lines, ATM alone is indicated by open circles with alternating long and short dashed lines, and AML and ATM is indicated by filled squares with dotted lines. In panel B, x is thiobarbituric reactive substances (TBARS) formation measured at an absorbance of 532 nm and y is treatment with the combination of amlodipine (AML), darkened panel; atorvastatin metabolite (ATM), cross-hatched panel; or amlodipine and atorvastatin metabolite (AML + ATM), darkened panel, at a concentration of 3.0 μ M. Values are mean $\pm$ standard deviation. ... indicates $p < 0.001$ versus control and other treatments.

Figure 8 shows the computed enthalpies for ATM, AML and their respective radical species.

Figure 9 shows x-ray diffraction determination of the separate versus
5 combined lipid membrane interactions of AML and ATM. x is relative electron density and y is angstroms from the middle of the lipid bilayer. In all three panels the control is the solid line. In panel A, AML is the dotted line; in panel B, ATM is the dotted line; in panel C, the combination of AML and ATM is the dotted line. The darkened areas in each panel are the difference in electron densities between the
10 control and treatment electron density profiles.

Figure 10 shows the separate versus combined effects of AML and ATM on membrane bilayer dimensions as determined by x-ray diffraction analysis. x is the change in membrane width in angstroms and y is the treatment with AML, darkened
15 panel; ATM, cross-hatched panel; AT, darkened panel; and the combination of AML and ATM, hatched panel. Values are mean $\pm$ standard deviation. ... indicates $p < 0.001$ versus control and other treatments.

Detailed Description of Embodiments

20 *Synergistic Antioxidant Effects of Amlodipine with the Atorvastatin/Atorvastatin Metabolite in Lipid Membranes:* The separate and combined dose-dependent antioxidant activities of AML, AT and ATM were tested

in membrane vesicles reconstituted from phospholipids enriched with cholesterol and the PUFA, dilinoleoyl phosphatidylcholine, at a 0.5:1 mole ratio. Membrane vesicles were used in these experiments for the following reasons: 1) this system is well-defined and highly reproducible; 2) linoleic acid represents the primary target for oxidative damage and is common in vascular cell membranes and lipoprotein particles; 3) this membrane system does not contain calcium channels or the HMG CoA reductase enzyme and; 4) lipid peroxidation in this system can be initiated spontaneously at 37°C in the absence of exogenous chemical initiators, such as high levels of iron and ascorbate. In these experiments, oxidation occurred in a gradual, time-dependent manner that was measured spectrophotometrically over a 72 h period.

In Figure 1, the synergistic antioxidant activity of AML and ATM was demonstrated in membrane vesicles composed of cholesterol and phospholipid at levels that reproduce physiologic-like conditions (Tulenko TN, Chen M, Mason PE, Mason RP. Physical effects of cholesterol on arterial smooth muscle membranes: Evidence of immiscible cholesterol domains and alterations in bilayer width during atherogenesis. *J. Lipid Res.* 1998; 39:947-956). At 100.0 nM, only the ATM separately produced any significant inhibition (9% of control) of lipid peroxidation in this membrane preparation enriched with cholesterol. When the agents were combined, however, the extent of inhibition increased to 33%, an effect significantly ($p < 0.01$) greater than that measured for the agents separately. The

antioxidant activity of the combination was very apparent: the drugs inhibited lipid peroxide formation ($>5 \times 10^2 \mu\text{M}$) at a concentration of 100.0 nM (the control level of lipid peroxide formation was 1.6 mM). This drug combination produced an effect that was highly dose-dependent over a broad range of concentrations (Figure 2). Significant inhibition ($p<0.05$) was observed as low as 10.0 nM with an IC_{50} of 500.0 nM. Greater than 90% inhibition ($>1 \text{ mM}$ lipid peroxide formation) was observed at a concentration of 10.0 μM for the combination (Figure 2). The fact that inhibition was observed at sub-micromolar levels indicates that the benefit observed with the combination of AML and ATM is of therapeutic relevance.

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The antioxidant effect of the combination persisted over time in a manner that could not be reproduced by vitamin E, even at an elevated concentration (10.0 μM) (Figure 3). This observation is consistent with the concept that vitamin E or α -tocopherol is gradually consumed during the lipid peroxidation process. By contrast, the activity of the AML/ATM combination was not affected by the length of the incubation period in which the total lipid peroxide level increased to 2.2 mM at the 72 h time point.

The combination of AML with ATM was significantly more effective in inhibiting lipid peroxide formation than the combination of AML and AT (Figure 4). At levels of 100.0 nM and 1.0 μM , the effect of the combination of AML with ATM was 45% and 86% greater, respectively, than that observed for the

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combination of AML and AT. The increased polarity of ATM, mediated by its additional hydroxy group, may facilitate stronger interactions with the formally charged AML, leading to distinct interactions with phospholipid molecules, as evidenced by x-ray diffraction analysis. The additional hydroxy group associated with the ATM also provides an additional abstractable proton that can be donated to free radical molecules (Figure 5). Following the loss of the proton, the remaining unpaired free electron can be effectively stabilized in resonance structures of the metabolite, as shown in Figure 5. The distinct antioxidant activity of the combination of AML with ATM is indicated by the observation that a similar effect could not be reproduced when AML was combined with each of two other statins (mevastatin and lovastatin), as demonstrated in Figure 6.

The results of *in vivo* investigations have indicated an important role for lipophilic antioxidants in reducing cardiovascular morbidity and mortality, especially CAD. LDL particles that have greater resistance to oxidative damage exhibit reduced cytotoxicity, interfere less with endothelium-derived nitric oxide production, and do not contribute to foam cell formation (Diaz MN, Frei B, Vita JA, Keaney JF. Antioxidants and atherosclerotic heart disease. *N. Engl. J. Med.* 1997; 337:408-416). Supplementation with an antioxidant has been shown to increase LDL resistance to oxidative modification and reduce endothelial cell cytotoxicity (Belcher JD, Balla J, Balla G, et al. Vitamin E, LDL, and endothelium. Brief oral vitamin supplementation prevents oxidized LDL-mediated vascular injury in vitro.

Arterioscler. Thromb. 1993; 13:1779-1789). Probucol, a lipophilic antioxidant, attenuated the formation of atherosclerotic plaques in cholesterol-fed primates, an effect that correlated with increased resistance of LDL to oxidative damage (Sasahara M, Raines EW, Chait A, et al. Inhibition of hypercholesterolemia-induced

5 atherosclerosis in the nonhuman primate by probucol. I. Is the extent of atherosclerosis related to resistance of LDL to oxidation? *J. Clin. Invest.* 1994; 94:155-164). This antioxidant inhibited the formation of lesions in Watanabe hereditary hyperlipidemic (WHHL) rabbits, a well-characterized animal model of atherosclerosis, independent of cholesterol-lowering effects (Carew TE, Schwenke

10 DC, Steinberg D. Antiatherogenic effect of probucol unrelated to its hypocholesterolemic effect: Evidence that antioxidants in vivo can selectively inhibit low density lipoprotein degradation in macrophage-rich fatty streaks and slow the progression of atherosclerosis in the Watanabe heritable hyperlipidemic rabbit. *Proc. Natl. Acad. Sci. USA* 1987; 84:7725-7729). Beyond these animal

15 studies, a placebo-controlled clinical study demonstrated that probucol reduced restenosis by 47% in patients with CAD following coronary-artery balloon angioplasty, presumably due to its antioxidant effects (Tardif JC, Cote G, Lesperance J, et al. Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group. *N. Engl. J. Med.*

20 1997; 337:365-372). In a separate study, it was demonstrated that probucol, unlike antioxidant vitamins, had a beneficial effect on vascular remodeling in patients that had underwent angioplasty, as determined by intravascular ultrasound techniques

(Cote G, Tardif J-C, Lesperance J, et al. Effects of probucol on vascular remodeling after coronary angioplasty. *Circulation* 1999; 99:30-35).

Thus, a review of the available data provides a mechanistic rationale for the
5 use of lipophilic antioxidants to interfere with inflammatory processes associated
with CAD. By increasing the resistance of LDL and vascular cell membranes to
oxidative damage, agents with antioxidant activity may effectively interfere with
pathologic alterations in the vessel wall during atherogenesis. These processes
include, but are not limited to, foam cell formation, endothelial dysfunction and
10 toxicity, leukocyte and platelet adhesion, and arterial vasospasm, secondary to a loss
of normal nitric oxide production. These cellular observations support
epidemiologic analyses that indicate an inverse association between the serum
levels of certain antioxidants and adverse outcomes associated with coronary
disease (Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett
15 WC. Vitamin E consumption and the risk of coronary disease in women. *N. Engl. J.
Med.* 1993; 328:1450-1456; Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E,
Colditz GA, Willett WC. Vitamin E consumption and the risk of coronary heart
disease in men. *N. Engl. J. Med.* 1993; 328:1450-1456; Enstrom JE, Kanim LE,
Klein MA. Vitamin C intake and mortality among a sample of the United States
20 population. *Epidemiology* 1992; 3:194-202; Riemersma RA, Wood DA, Macintyre
CC, Elton R, Gey KF, Oliver MF. Low plasma vitamins E and C. Increased risk of
angina in Scottish men. *Ann. N. Y. Acad. Sci.* 1989; 570:291-295; Ramirez J,

Flowers NC. Leukocyte ascorbic acid and its relationship to coronary artery disease in man. *Am. J. Clin. Nutr.* 1980; 33:2079-2087; Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N. Engl. J. Med.* 1996; 334:1145-1149; Losonczy KG, Harris TB, Havlik RJ. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: The Established Populations for Epidemiologic Studies of the Elderly. *Am. J. Clin. Nutr.* 1996; 64:190-196). Several of these epidemiologic studies showed benefit with vitamin E, an antioxidant with limited capacity to interfere with oxidative modification. The results of this study would predict that the combination of AML and ATM would be significantly more effective than vitamin E in reducing vascular injury associated with CAD.

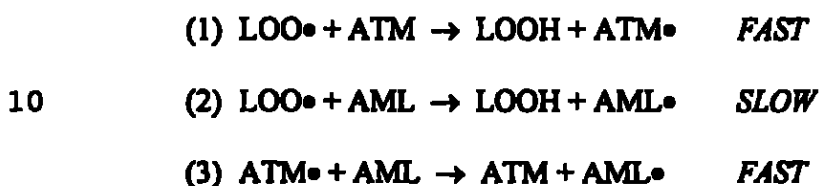
Synergistic Antioxidant Effects of Amlodipine with the Hydroxy Atorvastatin

Metabolite in Human LDL: The separate and combined antioxidant effects of AML and ATM were also evaluated in human LDL preparations. The ability of these agents to inhibit LDL peroxidation was assessed *in vitro* following addition of copper (10.0 μ M) by measuring the levels of thiobarbituric reactive substances (TBARS), a marker of lipid peroxidation. Figure 7 shows that the rate of LDL oxidation was characterized by sigmoidal curve kinetics with an initial lag phase followed by a sharp propagation and final plateau phase (Esterbauer H, Gebicki J, Puhl H, Jurgens G. The role of lipid peroxidation and antioxidants in oxidative

modification of LDL. *Free Radic. Biol. Med.* 1992; 13:341-390). After a 4 h incubation period, the differential effects of these compounds could be clearly observed at a concentration of 3.0 μ M. As compared to control lipid peroxidation (100% TBARS formation), TBARS formation for AML and ATM were 93.3 $\pm$ 6% and 65.6 $\pm$ 7%, respectively. When combined, however, TBARS formation was only 29.3 $\pm$ 6%, levels that were significantly ($p < 0.01$) lower than that observed for either drug alone. The synergistic antioxidant effect of the combination persisted at the 6 h time point. These findings provide further evidence for synergistic activity consistent with that observed in membrane vesicles, as the drug combination produced a level of inhibition that substantially exceeded their expected additive effect. The antioxidant activity of vitamin E was similar to that observed for ATM alone in these experiments.

Chemical Mechanisms for the Synergistic Activity of Amlodipine and Atorvastatin Metabolite: The synergistic antioxidant activity observed for this drug combination in LDL and reconstituted lipid membranes suggests that these compounds interact directly with each other to scavenge lipid radicals. Based on thermodynamic considerations (Figure 8), it is proposed that ATM reacts more quickly with lipid radicals (equation 1) than does AML, as described in equation 2. If these are the only two pathways available for these drugs when added together to the system, then their combined effect would only be additive. However, the combination of both compounds provides the possibility for a third pathway

(equation 3), an alternative that is supported by the results of the peroxidation experiments in both LDL and lipid membranes. The combination of pathways 1 and 3 would produce a synergistic effect as it occurs more rapidly than pathway 2. Indeed, semi-empirical calculations suggest that reaction 3 is a favorable, exothermic process ($\Delta H_f = -40.7$ kJ/mol). Thus, the presence of the fast inhibitor (ATM) enables the slower inhibitor (AML) to remove free radicals more rapidly than if reacting with the lipid radicals on its own. The three pathways describing these interactions are as follows, in which $\text{LOO}\cdot$ represents a lipid radical:



As a result of this synergy between AML and ATM, the recycled metabolite is now available for additional scavenging of lipid radicals. Overall, differences in the rates of inhibition between AML and ATM are based, in part, on the calculated enthalpies for these compounds and their respective radicals (Figure 8). The smaller (i.e., more negative) the ΔH_f value, the more favorable is hydrogen abstraction associated with radical formation. Once formed, the unpaired radical associated with radical species can be stabilized in resonance structures.

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Molecular Membrane Interactions of Amlodipine and Atorvastatin/Atorvastatin Metabolite: Small-angle x-ray diffraction approaches

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were used to examine the molecular membrane interactions of the AML and ATM combination. This highly quantitative technique provides direct information on the structure of the membrane lipid bilayer in the absence and presence of the drugs. It has been previously reported that AML has high affinity for membrane lipids ($K_p > 10^3$) under atherosclerotic conditions, as compared to other CCBs (Mason RP, Moisey DM, Shajenko L. Cholesterol alters the binding of Ca^{2+} channel blockers to the membrane lipid bilayer. *Mol. Pharmacol.* 1992; 41:315-321). The distinct lipophilicity of AML is attributed to its amphiphilic chemical structure that directs the molecule to an advantageous location in the membrane where it can then interfere with the propagation of free radicals by both biophysical and biochemical mechanisms, as previously described in detail by my laboratory (Mason RP, Leeds PR, Jacob RF, et al. Inhibition of excessive neuronal apoptosis by the calcium antagonist amlodipine and antioxidants in cerebellar granule cells. *J. Neurochem.* 1999; 72:1448-1456; Mason RP, Moisey DM, Shajenko L. Cholesterol alters the binding of Ca^{2+} channel blockers to the membrane lipid bilayer. *Mol. Pharmacol.* 1992; 41:315-321; Mason RP, Campbell SF, Wang SD, Herbette LG. Comparison of location and binding for the positively charged 1,4-dihydropyridine calcium channel antagonist amlodipine with uncharged drugs of this class in cardiac membranes. *Mol. Pharmacol.* 1989; 36:634-640; Mason RP, Walter MF, Trumbore MW, Olmstead Jr. EG, Mason PE. Membrane antioxidant effects of the charged dihydropyridine calcium antagonist amlodipine. *J. Mol. Cell. Cardiol.* 1999; 31:275-281) In membranes that are not enriched with cholesterol, amlodipine

inhibited lipid peroxidation in a manner that could not be reproduced by other CCBs or the angiotensin converting enzyme (ACE)-inhibitor, captopril (Mason RP, Walter MF, Trumbore MW, Olmstead Jr. EG, Mason PE. Membrane antioxidant effects of the charged dihydropyridine calcium antagonist amlodipine. *J. Mol. Cell. Cardiol.*

- 5 1999; 31:275-281). In the same way, the chemical structure of the atorvastatin metabolite has amphiphilic properties that would enable the drug to interact strongly with the membrane lipid bilayer, as recently reported by my laboratory (Mason RP. Inhibition of oxidative damage to low density lipoproteins and isolated membranes by atorvastatin and its active metabolite. *J. Am. Coll. Cardiol.* 2000; 35:317A).

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- For these studies, the combination of AML and ATM were added to membrane vesicles reconstituted from cholesterol and phospholipid at a 0.5:1 mole ratio (Figure 9). X-ray diffraction analysis of the membrane samples produced strong and reproducible diffraction patterns for representative control and drug-
- 15 containing samples. In the absence of drug, the overall membrane bilayer width, including surface hydration, was 55.5 Å with an intrabilayer headgroup separation of 44 Å. The addition of the two drugs together at a ratio of drug to phospholipid of 1:15 produced distinct changes in the structure and organization of the phospholipid bilayer, as compared to the drugs added separately (Figure 9). In the presence of the
- 20 drug combination, the overall membrane bilayer width, including surface hydration, was reduced to 53.5 Å with an intrabilayer headgroup separation of 41 Å. Separately, the membrane bilayer widths of membranes containing AML and ATM

alone were 54.8 Å and 58.0 Å, respectively (Figure 10). These structural findings provide direct evidence that the combination of these agents differentially modulate the structure of lipid molecules, as compared to their separate effects.

5 Direct subtraction of the membrane electron density profiles (Å versus electrons/Å³) demonstrated large differences in lipid structure that could be attributed to the presence of the drugs (Figure 9). Specifically, the addition of the drug combination produced a broad increase in electron density associated with the upper hydrocarbon core/hydrated headgroup region of the membrane bilayer, ± 11-
10 21 Å from the center of the bilayer. This large increase in electron density distributed over 10 Å is attributed to the equilibrium location of the drugs in the membrane. Concomitant with this change was an observed disordering effect associated with the central hydrocarbon core region of the membrane, ± 0-11 Å. This decrease in electron density is due to an increase in molecular volume resulting
15 from the insertion of the drug molecules into a region of high molecular density near the membrane hydrocarbon core/water interface. Thus, it can be concluded from these data that the insertion of the drug combination into the membrane bilayer alters the intermolecular packing constraints of the phospholipid molecules in a manner similar to that observed with either reducing cholesterol content or
20 increasing sample temperature (Tulenko TN, Chen M, Mason PE, Mason RP. Physical effects of cholesterol on arterial smooth muscle membranes: Evidence of immiscible cholesterol domains and alterations in bilayer width during

atherogenesis. *J. Lipid. Res.* 1998; 39:947-956; Chang HM, Reitstetter R, Mason RP, Gruener R. Attenuation of channel kinetics and conductance by cholesterol: An interpretation using structural stress as a unifying concept. *J. Membr. Biol.* 1995; 143:51-63). Such changes in biophysical properties have been shown to interfere
5 with the propagation of free radicals through the lipid bilayer matrix (McLean LR, Hagaman KA. Effect of lipid physical state on the rate of peroxidation of liposomes. *Free Radic. Biol. Med.* 1992; 12:113-119).

Separately, AML and ATM effected distinct changes in membrane structure,
10 as compared to the drug combination, due to specific interactions with constituent phospholipid molecules (Figures 9 and 10). While the drug combination effected a 2 Å or 4% decrease ($p<0.01$) in overall membrane width, the ATM separately produced a 5% increase ($p<0.01$) in width (2.5 Å) while AML alone did not significantly alter membrane dimensions, including the intrabilayer headgroup
15 separation. As compared to AML alone, ATM produced a larger reduction in hydrocarbon core electron density. This effect on membrane structure may contribute to its greater antioxidant potency, as compared to AML. The combination of AML and ATM effected a new site of interaction with the membrane lipid bilayer, in addition to their separate locations in the membrane
20 (Figure 9).

Therefore, this invention is drawn to a pharmaceutical composition

comprising amlodipine and an atorvastatin compound. These individual pharmaceutical agents can be formulated in combination, or separately, in salts, forms, and dosages that produce maximal therapeutic responses. This combination therapy is designed to treat the various pathophysiological manifestations of arterial and related heart disease, including, but not limited to, hypertension, hyperlipidemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris. Specifically, this combination therapy will be designed to lower blood pressure and systemic lipid concentrations as well as the related pathophysiological results of the lack of their regulation, including, but not limited to, arterial weakening and plaque deposition. The effects of these individual agents on these various processes and events related to arterial and related heart disease, when used in combination can be additive and/or synergistic.

It will now be apparent to those skilled in the art that other embodiments, improvements, details, and uses can be made that are consistent with the letter and spirit of the foregoing disclosure and within the scope of this patent and the appended claims.

Experimental Methods

Dilinoleoyl phosphatidylcholine (DLPC), 1-palmitoyl-2-oleoyl phosphatidylcholine (POPC) and unesterified cholesterol were obtained from

- Avanti Polar Lipids Inc. (Alabaster, AL) and stored at -80°C. Aliquots of LDL (L-2139) from human plasma were obtained from Sigma Chemical Co. (St. Louis, MO). Sephadex G-25 M (PD-10) columns were purchased from Pharmacia Biotech Inc. (Piscataway, NJ). Amlodipine besylate was obtained from Pfizer Central Research (Groton, CT) while atorvastatin calcium and its hydroxy metabolite were provided by Parke Davis (Ann Arbor, MI). Vitamin E, Trolox (a vitamin E analog), lovastatin, and mevastatin were purchased from Sigma Chemical Co. (St. Louis, MO).
- 10 ***Membrane Lipid Peroxidation Analysis:*** The separate and combined dose-dependent antioxidant activities of these agents were examined in membranes enriched with PUFA prepared at a 0.5 cholesterol to phospholipid mole ratio (Mason RP, Walter MF, Trumbore MW, Olmstead Jr. EG, Mason PE. Membrane antioxidant effects of the charged dihydropyridine calcium antagonist amlodipine. *J. Mol. Cell. Cardiol.* 1999; 31:275-281). The lipid (dilinoleoyl phosphatidylcholine and cholesterol) used for these samples was dissolved in HPLC-grade chloroform (25.0 mg/ml). An aliquot of the lipids (1.0 mg) was added to individual glass 13 x 100-mm test tubes and chloroform was removed by shell-drying under a steady stream of N₂ gas. The lipids were dried down in the absence or presence of drug(s)
- 15 dissolved in ethanol. Residual solvent was removed under vacuum while the samples were shielded from light. Membrane vesicles were produced by rapidly mixing the dried lipids at room temperature following addition of 1.0 ml HEPES
- 20

buffered saline (0.5 mM HEPES and 154.0 mM NaCl, pH, 7.2). The final phospholipid concentration was 1.0 mg/ml buffer and the final concentration of drug ranged from 10.0 nM through 10.0 μ M.

5 Membrane lipid peroxidation was carried out at 37°C in a shaking water bath without the addition of exogenous stimulants, as previously described in detail (Mason RP, Walter MF, Trumbore MW, Olmstead Jr. EG, Mason PE. Membrane antioxidant effects of the charged dihydropyridine calcium antagonist amlodipine. *J. Mol. Cell. Cardiol.* 1999; 31:275-281). At various time intervals (24, 48, 65, 72h),
10 an aliquot of lipid sample (10 to 100 μ l) was removed before 25 μ l of 5.0 mM ethylenediaminetetracetic acid (EDTA) and 20 μ l of 35.0 mM butylated hydroxytoluene (BHT) was immediately added to the sample to stop the peroxidation reaction.

15 The extent of membrane lipid peroxidation was measured by the CHOD-Iodide assay as previously described in detail (El-Saadani M, Esterbauer H, el-Sayed M, Goher M, Nassar AY, Jurgens G. A spectrophotometric assay for lipid peroxides in serum lipoproteins using a commercially available reagent. *J. Lipid Res.* 1989; 30:627-630). The quantity of I_3^- was measured from the following
20 reaction in which L represents a phospholipid molecule:



An aliquot of the membrane sample was removed at various time points and then added to 1.0 ml of CHOD color reagent (E.M. Science, Gibbstown, NJ) that includes 20.0 μM BHT, 24.0 μM EDTA, and 0.2% Triton-X. The sample was then covered with foil and allowed to incubate for 2 h in the absence of light before

5 measuring the absorbance of the sample at 365 nm ($\epsilon = 2.4 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$). The background sample was run along the test samples in triplicate and contains 76.7 μl of 0.652 mM HEPES, 20 μl of 5.0 mM EDTA and 3.3 μl of DDI water. The extent of lipid peroxidation was measured in triplicate for each drug concentration and compared to control samples that did not contain drug. The statistical significance

10 of these experiments was assessed by the non-paired *t*-test. Significance was accepted at $p < 0.05$.

LDL Oxidation Determination: In addition to lipid membranes, the antioxidant activity of AML and ATM was evaluated in human LDL. The EDTA

15 content of the LDL samples obtained from human plasma was removed by gel filtration with PD-10 Sephadex G25-M filtration columns; PBS (nitrogen purged) was used as the eluent. The LDL samples (50 μg of protein/mL) were then preincubated with or without drug (3.0 μM) for 30 min at 37°C. Oxidation of LDL was then induced by the addition of 10.0 μM CuSO_4 . The time course of LDL

20 oxidation, measured by TBARS formation, was followed for 6 h at 37°C (Mak IT, Kramer JH, Weglicki WB. Potentiation of free radical-induced lipid peroxidative injury to sarcolemmal membranes by lipid amphiphiles. *J. Biol. Chem.* 1986;

- 261:1153-1157). LDL oxidation, as determined by the TBARS methods, followed sigmoidal curve kinetics with an initial lag phase followed by a sharp propagation and final plateau phase (Esterbauer H, Gebicki J, Puhl H, Jurgens G. The role of lipid peroxidation and antioxidants in oxidative modification of LDL. *Free Radic. Biol. Med.* 1992; 13:341-390). The protein content of the LDL was determined using the Coomassie Protein Plus assay kit from Pierce Chemical (Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal. Biochem.* 1976; 72:248-254).
- 10 **Small angle X-ray diffraction analysis:** Small-angle X-ray diffraction analyses were used to directly examine the molecular membrane interactions of AML, AT, and ATM. The lipids (1-palmitoyl-2-oleoyl phosphatidylcholine and cholesterol) used for these samples were dissolved in HPLC-grade chloroform (10.0 mg/ml). Membrane vesicles were produced from these lipids by the same method
- 15 as described for the peroxidation experiments. The final phospholipid concentration was 5.0 mg/ml buffer and the mole ratio of drug to phospholipid was 1:15. Membrane samples were oriented for diffraction analysis by subjecting them to centrifugation as previously described (Chester DW, Herbette LG, Mason RP, Joslyn AF, Triggle DJ, Koppel DE. Diffusion of dihydropyridine calcium channel
- 20 antagonists in cardiac sarcolemmal lipid multibilayers. *Biophys. J.* 1987; 52:1021-1030). Briefly, vesicles were placed in sedimentation cells that contained an aluminum foil substrate. The vesicles were sedimented in an SW-28 rotor

(Beckman Instruments, Fullerton, CA) at 35,000 x g for 1.5 h at 5°C. Following centrifugation, the supernatant was removed from the pellets and the samples were then mounted on to curved glass supports. Samples were placed in sealed canisters to control relative humidity and temperature during the diffraction experiments, as
5 previously described in detail (Chester DW, Herbette LG, Mason RP, Joslyn AF, Triggie DJ, Koppel DE. Diffusion of dihydropyridine calcium channel antagonists in cardiac sarcolemmal lipid multibilayers. *Biophys. J.* 1987; 52:1021-1030).

X-ray diffraction experiments were conducted by aligning the samples at
10 grazing incidence with respect to a collimated, nickel-filtered monochromatic X-ray source ($\text{CuK}_\alpha = 1.54 \text{ \AA}$) produced by a high-brilliance rotating anode microfocus generator (Rigaku Rotaflex RU-200, Danvers, MA). The fixed geometry beam line consisted of a single, nickel-coated Franks mirror to define a line source where $\text{K}_{\alpha 1}$ and $\text{K}_{\alpha 2}$ are unresolved. The diffraction data were collected on a one-dimensional,
15 position-sensitive electronic detector (Innovative Technologies, Newburyport, MA) placed at a distance of 150 mm from the sample. Each meridional diffraction peak was Lorentz- and background-corrected, as previously described (Mason RP, Gonye GE, Chester DW, Herbette LG. Partitioning and location of Bay K 8644, 1,4-dihydropyridine calcium channel agonist, in model and biological membranes.
20 *Biophys. J.* 1989; 55:769-778). The phases for the four-order data were determined by swelling analysis (Moody MF. X-ray diffraction pattern of nerve myelin: A method for determining the phases. *Science* 1963; 142:1173-117). Fourier

transformations of the data were generated from the diffraction data with Origin software (Microcal Software, Northampton, MA).

What is claimed is:

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1. A pharmaceutical composition comprising:
 - (a) a therapeutically effective amount of amlodipine;
 - (b) a therapeutically effective amount of an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite; and
 - 5 (c) pharmaceutically acceptable formulation agents.
2. The pharmaceutical composition of claim 1 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.
- 10 3. The pharmaceutical composition of claim 2 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.
4. The pharmaceutical composition of claim 1 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.
- 15 5. The pharmaceutical composition of claim 4 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.
6. The pharmaceutical composition of claim 1 wherein said pharmaceutical
- 20 composition reduces the risk of arterial and related heart disease.

7. The pharmaceutical composition of claim 6 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

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8. The pharmaceutical composition of claim 1 wherein said pharmaceutical composition lowers blood pressure.

9. The pharmaceutical composition of claim 8 wherein said pharmaceutical composition lowers blood pressure to a level consistent with a reduced risk of arterial and related heart disease.

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10. The pharmaceutical composition of claim 8 wherein said pharmaceutical composition lowers blood pressure to a level statistically equivalent to normal.

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11. The pharmaceutical composition of claim 1 wherein said pharmaceutical composition lowers systemic lipid concentrations.

12. The pharmaceutical composition of claim 11 wherein said pharmaceutical composition lowers systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

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13. The pharmaceutical composition of claim 11 wherein said pharmaceutical composition lowers systemic lipid concentrations to a level statistically equivalent to normal.
- 5 14. The pharmaceutical composition of claim 1 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations.
- 15 15. The pharmaceutical composition of claim 14 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level
10 consistent with a reduced risk of arterial and related heart disease.
- 15 16. The pharmaceutical composition of claim 14 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.
17. The pharmaceutical composition of claim 1 wherein said pharmaceutical composition concomitantly lowers blood pressure and systemic lipid concentrations.
- 20 18. The pharmaceutical composition of claim 17 wherein said pharmaceutical composition concomitantly lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

19. The pharmaceutical composition of claim 17 wherein said pharmaceutical composition concomitantly lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.
- 5 20. The pharmaceutical composition of claim 1 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations.
21. The pharmaceutical composition of claim 20 wherein said pharmaceutical
10 composition synergistically lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.
22. The pharmaceutical composition of claim 20 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations
15 to a level statistically equivalent to normal.
23. The pharmaceutical composition of any of claims 17, 18, and 19 wherein the concomitant lowering of blood pressure and systemic lipid concentrations results at least partially from reduced lipid oxidation.
- 20 24. The pharmaceutical composition of any of claims 20, 21, and 22 wherein the synergistic lowering of blood pressure and systemic lipid concentrations results at

least partially from reduced lipid oxidation.

25. A pharmaceutical composition comprising:

- (a) a therapeutically effective amount of amlodipine;
- 5 (b) a therapeutically effective amount of an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite; and
- (c) pharmaceutically acceptable formulation agents wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations.

- 10 26. The pharmaceutical composition of claim 25 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

27. The pharmaceutical composition of claim 26 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

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28. The pharmaceutical composition of claim 25 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

- 20 29. The pharmaceutical composition of claim 28 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

30. The pharmaceutical composition of claim 24 wherein said pharmaceutical composition reduces the risk of arterial and related heart disease.

31. The pharmaceutical composition of claim 30 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

32. The pharmaceutical composition of claim 25 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

33. The pharmaceutical composition of claim 25 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.

34. The pharmaceutical composition of any of claims 25 through 33 wherein the lowering of blood pressure and systemic lipid concentrations results at least partially from reduced lipid oxidation.

35. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of amlodipine;

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- (b) a therapeutically effective amount of an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite; and
- (c) pharmaceutically acceptable formulation agents wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations at least
- 5 partially as a result of reduced lipid oxidation.

36. The pharmaceutical composition of claim 35 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

- 10 37. The pharmaceutical composition of claim 36 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

38. The pharmaceutical composition of claim 35 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

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39. The pharmaceutical composition of claim 38 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

40. The pharmaceutical composition of claim 35 wherein said pharmaceutical
- 20 composition reduces the risk of arterial and related heart disease.

41. The pharmaceutical composition of claim 40 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

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42. The pharmaceutical composition of claim 35 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

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43. The pharmaceutical composition of claim 35 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.

44. A pharmaceutical composition comprising:

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- (a) a therapeutically effective amount of amlodipine;
 - (b) a therapeutically effective amount of an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite; and
 - (c) pharmaceutically acceptable formulation agents wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid
- 20 concentrations.

45. The pharmaceutical composition of claim 44 wherein amlodipine comprises a

therapeutically effective derivative of amlodipine.

46. The pharmaceutical composition of claim 45 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

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47. The pharmaceutical composition of claim 44 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

48. The pharmaceutical composition of claim 47 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

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49. The pharmaceutical composition of claim 44 wherein said pharmaceutical composition reduces the risk of arterial and related heart disease.

15 50. The pharmaceutical composition of claim 49 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

20 51. The pharmaceutical composition of claim 44 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

52. The pharmaceutical composition of claim 44 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.

- 5 53. The pharmaceutical composition of any of claims 44 through 52 wherein the synergistic lowering of blood pressure and systemic lipid concentrations results at least partially from reduced lipid oxidation.

54. A pharmaceutical composition comprising:

- 10 (a) a therapeutically effective amount of amlodipine;
(b) a therapeutically effective amount of an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite; and
(c) pharmaceutically acceptable formulation agents wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations
15 at least partially as a result of reduced lipid oxidation.

55. The pharmaceutical composition of claim 54 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

- 20 56. The pharmaceutical composition of claim 55 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

57. The pharmaceutical composition of claim 54 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

58. The pharmaceutical composition of claim 57 wherein the therapeutically
5 effective derivative of the atorvastatin compound is a hemicalcium salt.

59. The pharmaceutical composition of claim 54 wherein said pharmaceutical composition reduces the risk of arterial and related heart disease.

10 60. The pharmaceutical composition of claim 59 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

15 61. The pharmaceutical composition of claim 54 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

20 62. The pharmaceutical composition of claim 54 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.

63. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of a combination of amlodipine and an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite; and

5 (c) pharmaceutically acceptable formulation agents.

64. The pharmaceutical composition of claim 63 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

10 65. The pharmaceutical composition of claim 64 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

66. The pharmaceutical composition of claim 63 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

15

67. The pharmaceutical composition of claim 66 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

68. The pharmaceutical composition of claim 63 wherein said pharmaceutical
20 composition reduces the risk of arterial and related heart disease.

69. The pharmaceutical composition of claim 68 wherein said arterial and related

heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

- 5 70. The pharmaceutical composition of claim 63 wherein said pharmaceutical composition lowers blood pressure.

71. The pharmaceutical composition of claim 70 wherein said pharmaceutical composition lowers blood pressure to a level consistent with a reduced risk of
10 arterial and related heart disease.

72. The pharmaceutical composition of claim 70 wherein said pharmaceutical composition lowers blood pressure to a level statistically equivalent to normal.

- 15 73. The pharmaceutical composition of claim 63 wherein said pharmaceutical composition lowers systemic lipid concentrations.

74. The pharmaceutical composition of claim 73 wherein said pharmaceutical composition lowers systemic lipid concentrations to a level consistent with a
20 reduced risk of arterial and related heart disease.

75. The pharmaceutical composition of claim 73 wherein said pharmaceutical

composition lowers systemic lipid concentrations to a level statistically equivalent to normal.

76. The pharmaceutical composition of claim 63 wherein said pharmaceutical
5 composition lowers blood pressure and systemic lipid concentrations.

77. The pharmaceutical composition of claim 76 wherein said pharmaceutical
composition lowers blood pressure and systemic lipid concentrations to a level
consistent with a reduced risk of arterial and related heart disease.

10

78. The pharmaceutical composition of claim 76 wherein said pharmaceutical
composition lowers blood pressure and systemic lipid concentrations to a level
statistically equivalent to normal.

15 79. The pharmaceutical composition of claim 63 wherein said pharmaceutical
composition concomitantly lowers blood pressure and systemic lipid concentrations.

80. The pharmaceutical composition of claim 79 wherein said pharmaceutical
composition concomitantly lowers blood pressure and systemic lipid concentrations
20 to a level consistent with a reduced risk of arterial and related heart disease.

81. The pharmaceutical composition of claim 79 wherein said pharmaceutical composition concomitantly lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.
- 5 82. The pharmaceutical composition of claim 63 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations.
83. The pharmaceutical composition of claim 82 wherein said pharmaceutical
10 composition synergistically lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.
84. The pharmaceutical composition of claim 82 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations
15 to a level statistically equivalent to normal.
85. The pharmaceutical composition of any of claims 79, 80, and 81 wherein the concomitant lowering of blood pressure and systemic lipid concentrations results at least partially from reduced lipid oxidation.
- 20 86. The pharmaceutical composition of any of claims 82, 83, and 84 wherein the synergistic lowering of blood pressure and systemic lipid concentrations results at

least partially from reduced lipid oxidation.

87. A pharmaceutical composition comprising:

- 5 (a) a therapeutically effective amount of a combination of amlodipine and an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite; and
- (b) pharmaceutically acceptable formulation agents wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations.

- 10 88. The pharmaceutical composition of claim 87 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

89. The pharmaceutical composition of claim 88 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

15

90. The pharmaceutical composition of claim 87 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

91. The pharmaceutical composition of claim 90 wherein the therapeutically
- 20 effective derivative of the atorvastatin compound is a hemicalcium salt.

92. The pharmaceutical composition of claim 87 wherein said pharmaceutical

composition reduces the risk of arterial and related heart disease.

93. The pharmaceutical composition of claim 92 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipdemia,
5 atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

94. The pharmaceutical composition of claim 87 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level
10 consistent with a reduced risk of arterial and related heart disease.

95. The pharmaceutical composition of claim 94 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.
15

96. The pharmaceutical composition of any of claims 87 through 95 wherein the lowering of blood pressure and systemic lipid concentrations results at least partially from reduced lipid oxidation.

20 97. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of a combination of amlodipine and an atorvastatin compound selected from the group consisting of atorvastatin and

hydroxylated atorvastatin metabolite; and

(b) pharmaceutically acceptable formulation agents wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations at least partially as a result of reduced lipid oxidation.

5

98. The pharmaceutical composition of claim 97 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

99. The pharmaceutical composition of claim 98 wherein the therapeutically
10 effective derivative of amlodipine comprises amlodipine besylate.

100. The pharmaceutical composition of claim 97 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

15

101. The pharmaceutical composition of claim 100 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

102. The pharmaceutical composition of claim 97 wherein said pharmaceutical
20 composition reduces the risk of arterial and related heart disease.

103. The pharmaceutical composition of claim 102 wherein said arterial and related

heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

- 5 104. The pharmaceutical composition of claim 97 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

105. The pharmaceutical composition of claim 97 wherein said pharmaceutical
10 composition lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.

106. A pharmaceutical composition comprising:

- (a) a therapeutically effective amount of a combination of amlodipine and an
15 atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite; and
(b) pharmaceutically acceptable formulation agents wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations.

20

107. The pharmaceutical composition of claim 106 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

108. The pharmaceutical composition of claim 107 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

109. The pharmaceutical composition of claim 106 wherein the atorvastatin
5 compound comprises a therapeutically effective derivative of the atorvastatin compound.

110. The pharmaceutical composition of claim 109 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

10

111. The pharmaceutical composition of claim 106 wherein said pharmaceutical composition reduces the risk of arterial and related heart disease.

112. The pharmaceutical composition of claim 111 wherein said arterial and related
15 heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

113. The pharmaceutical composition of claim 106 wherein said pharmaceutical
20 composition synergistically lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

114. The pharmaceutical composition of claim 113 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.

- 5 115. The pharmaceutical composition of any of claims 106 through 114 wherein the synergistic lowering of blood pressure and systemic lipid concentrations results at least partially from reduced lipid oxidation.

116. A pharmaceutical composition comprising:

- 10 (a) a therapeutically effective amount of a combination of amlodipine and an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite; and
- (b) pharmaceutically acceptable formulation agents wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations
- 15 at least partially as a result of reduced lipid oxidation.

117. The pharmaceutical composition of claim 116 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

- 20 118. The pharmaceutical composition of claim 117 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

119. The pharmaceutical composition of claim 116 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

- 5 120. The pharmaceutical composition of claim 119 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

121. The pharmaceutical composition of claim 116 wherein said pharmaceutical composition reduces the risk of arterial and related heart disease.

10

122. The pharmaceutical composition of claim 121 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

15

123. The pharmaceutical composition of claim 116 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

- 20 124. The pharmaceutical composition of claim 116 wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.

125. A method of treating arterial and related heart disease comprising administering a therapeutically effective amount of a combination of amlodipine and an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite.

5

126. The method of claim 125 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

127. The method of claim 126 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

128. The method of claim 127 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

129. The method of claim 128 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

130. The method of claim 125 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

131. The method of claim 125 wherein amlodipine and the atorvastatin compound are administered in the same therapeutic.

132. The method of claim 125 wherein amlodipine and the atorvastatin compound
5 are administered as separate therapeutics.

133. The method of claim 125 wherein amlodipine and the atorvastatin compound are administered at the same time.

10 134. The method of claim 125 wherein amlodipine and the atorvastatin compound are administered at different times.

135. A method of lowering blood pressure and systemic lipid concentrations comprising administering a therapeutically effective amount of a combination of
15 amlodipine and an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite.

136. The method of claim 135 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

20

137. The method of claim 136 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

138. The method of claim 135 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

5 139. The method of claim 138 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

140. The method of claim 135 wherein amlodipine and the atorvastatin compound are administered in the same therapeutic.

10

141. The method of claim 135 wherein amlodipine and the atorvastatin compound are administered as separate therapeutics.

142. The method of claim 135 wherein amlodipine and the atorvastatin compound
15 are administered at the same time.

143. The method of claim 135 wherein amlodipine and the atorvastatin compound are administered at different times.

20 144. The method of claim 135 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

145. The method of claim 144 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipidemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

5

146. The method of claim 135 wherein said pharmaceutical composition lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.

10 147. The method of any of claims 135 through 146 wherein the lowering of blood pressure and systemic lipid concentrations results at least partially from reduced lipid oxidation.

148. A method of synergistically lowering blood pressure and systemic lipid
15 concentrations comprising administering a therapeutically effective amount of a combination of amlodipine and an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite.

149. The method of claim 148 wherein amlodipine comprises a therapeutically
20 effective derivative of amlodipine.

150. The method of claim 149 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

151. The method of claim 148 wherein the atorvastatin compound comprises a
5 therapeutically effective derivative of the atorvastatin compound.

152. The method of claim 151 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

10 153. The method of claim 148 wherein amlodipine and the atorvastatin compound are administered in the same therapeutic.

154. The method of claim 148 wherein amlodipine and the atorvastatin compound are administered as separate therapeutics.

15

155. The method of claim 148 wherein amlodipine and the atorvastatin compound are administered at the same time.

156. The method of claim 148 wherein amlodipine and the atorvastatin compound
20 are administered at different times.

157. The method of claim 148 wherein said pharmaceutical composition

synergistically lowers blood pressure and systemic lipid concentrations to a level consistent with a reduced risk of arterial and related heart disease.

158. The method of claim 157 wherein said arterial and related heart disease is
5 selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

159. The method of claim 148 wherein said pharmaceutical composition
10 synergistically lowers blood pressure and systemic lipid concentrations to a level statistically equivalent to normal.

160. The method of any of claims 148 through 159 wherein the synergistic lowering
of blood pressure and systemic lipid concentrations results at least partially from
15 reduced lipid oxidation.

161. A method of inhibiting lipid oxidation comprising administering a
therapeutically effective amount of a combination of amlodipine and an atorvastatin
compound selected from the group consisting of atorvastatin and hydroxylated
20 atorvastatin metabolite.

162. The method of claim 161 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

163. The method of claim 162 wherein the therapeutically effective derivative of
5 amlodipine comprises amlodipine besylate.

164. The method of claim 161 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

10 165. The method of claim 164 wherein the therapeutically effective derivative of the atorvastatin compound is a hemicalcium salt.

166. The method of claim 161 wherein amlodipine and the atorvastatin compound
are administered in the same therapeutic.
15

167. The method of claim 161 wherein amlodipine and the atorvastatin compound
are administered as separate therapeutics.

168. The method of claim 161 wherein amlodipine and the atorvastatin compound
20 are administered at the same time.

169. The method of claim 161 wherein amlodipine and the atorvastatin compound are administered at different times.

170. The method of claim 161 wherein said pharmaceutical composition inhibits
5 lipid oxidation to an extent consistent with a reduced risk of arterial and related heart disease.

171. The method of claim 170 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipidemia, atherosclerosis,
10 arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

172. A method of synergistically inhibiting lipid oxidation comprising administering a therapeutically effective amount of a combination of amlodipine
15 and an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite.

173. The method of claim 172 wherein amlodipine comprises a therapeutically effective derivative of amlodipine.

20

174. The method of claim 173 wherein the therapeutically effective derivative of amlodipine comprises amlodipine besylate.

61

175. The method of claim 172 wherein the atorvastatin compound comprises a therapeutically effective derivative of the atorvastatin compound.

176. The method of claim 175 wherein the therapeutically effective derivative of the
5 atorvastatin compound is a hemicalcium salt.

177. The method of claim 172 wherein amlodipine and the atorvastatin compound are administered in the same therapeutic.

10 178. The method of claim 172 wherein amlodipine and the atorvastatin compound are administered as separate therapeutics.

179. The method of claim 172 wherein amlodipine and the atorvastatin compound are administered at the same time.

15

180. The method of claim 172 wherein amlodipine and the atorvastatin compound are administered at different times.

181. The method of claim 172 wherein said pharmaceutical composition
20 synergistically inhibits lipid oxidation to an extent consistent with a reduced risk of arterial and related heart disease.

182. The method of claim 181 wherein said arterial and related heart disease is selected from the group consisting of hypertension, hyperlipdemia, atherosclerosis, arteriosclerosis, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and angina pectoris.

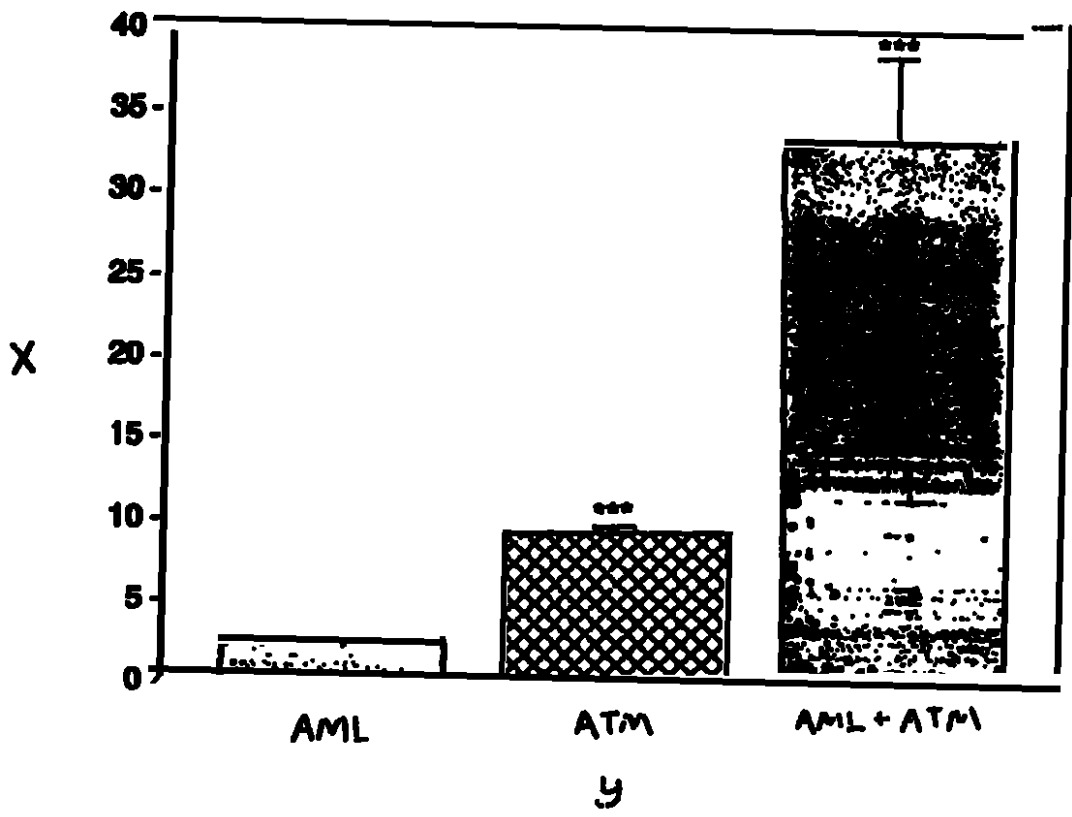


Figure 1

NO DATA

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PCP/MS/MS

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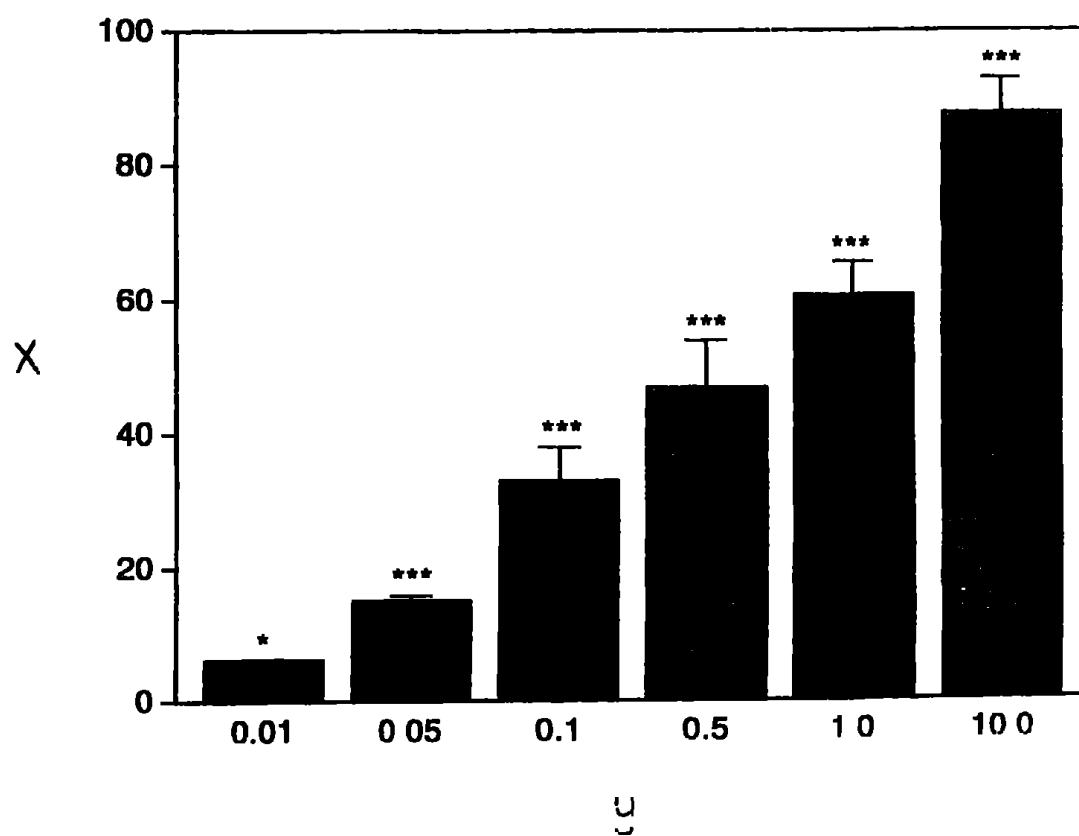


Figure 2

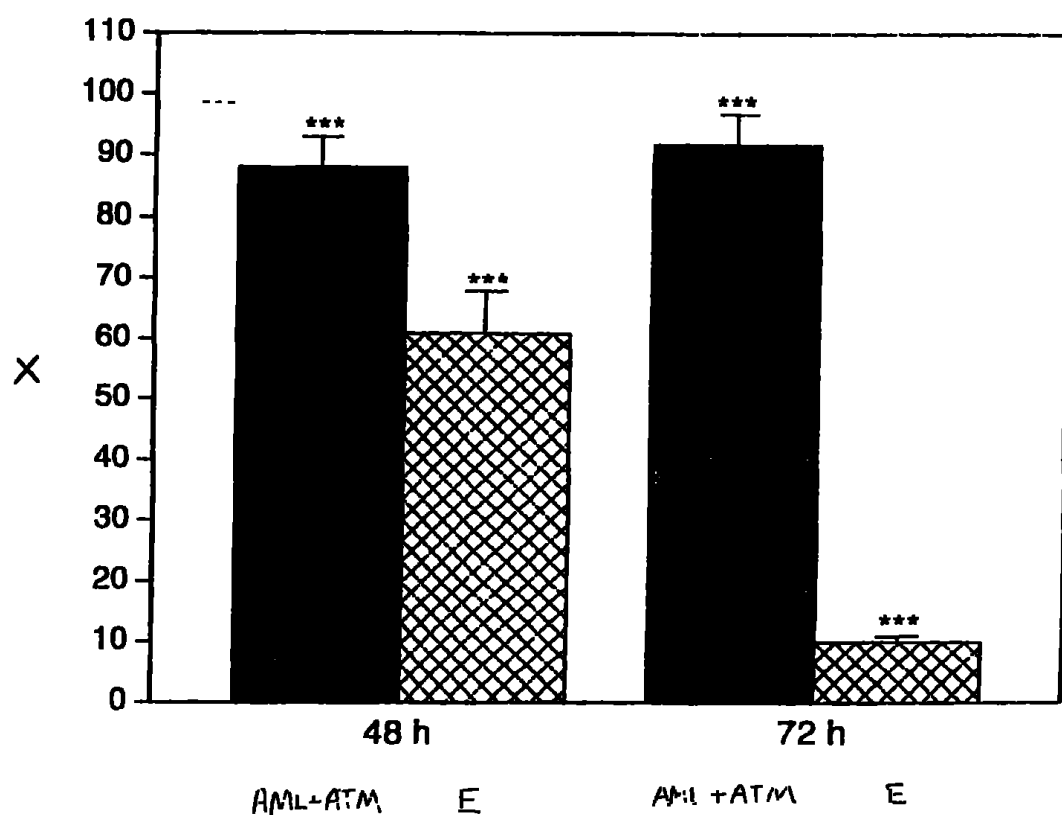
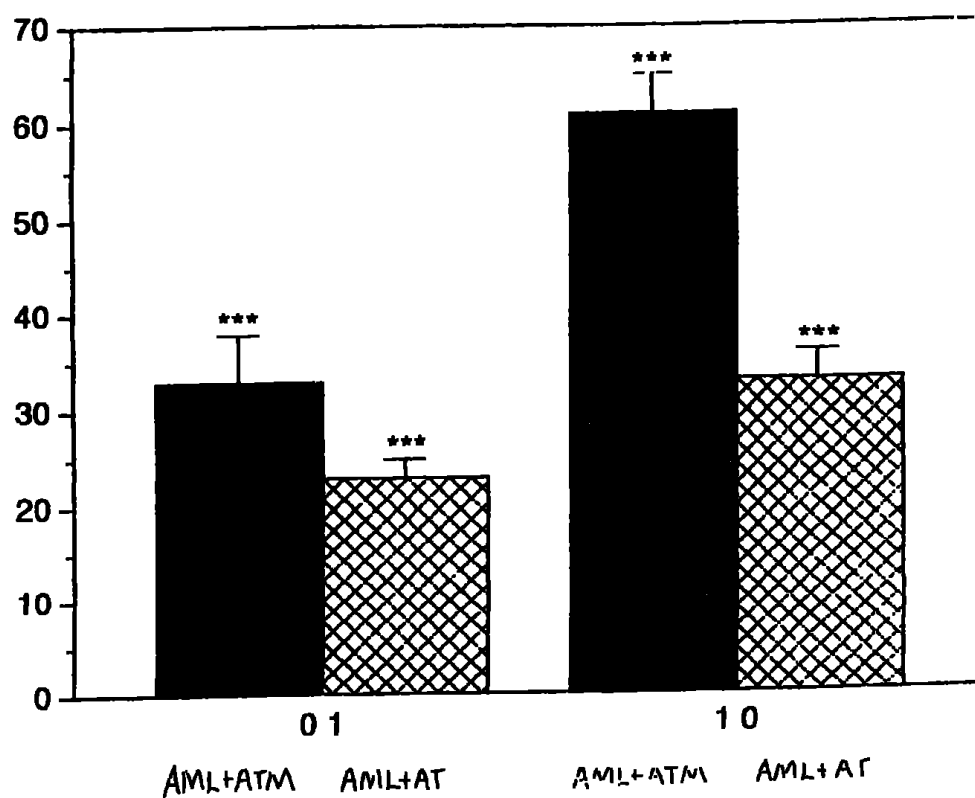


Figure 3



y
Figure 4

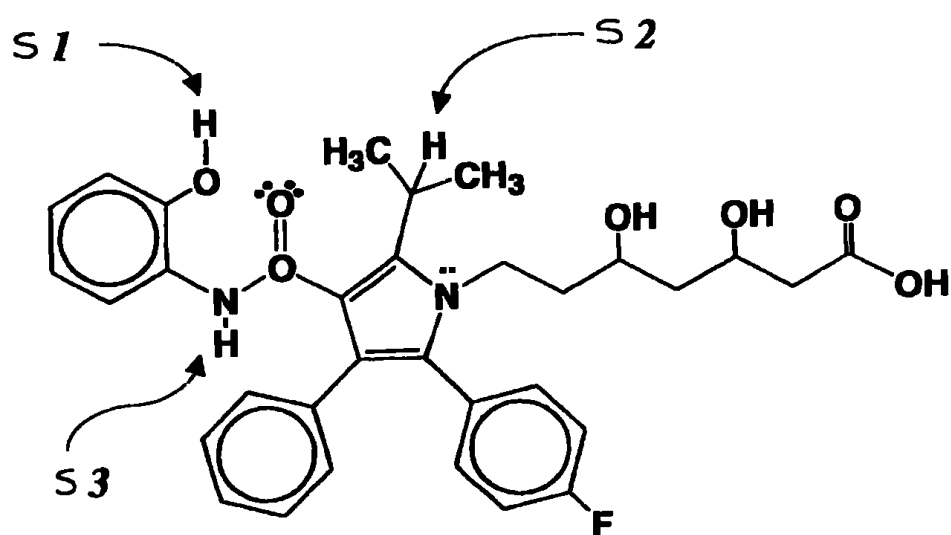


Figure 5A

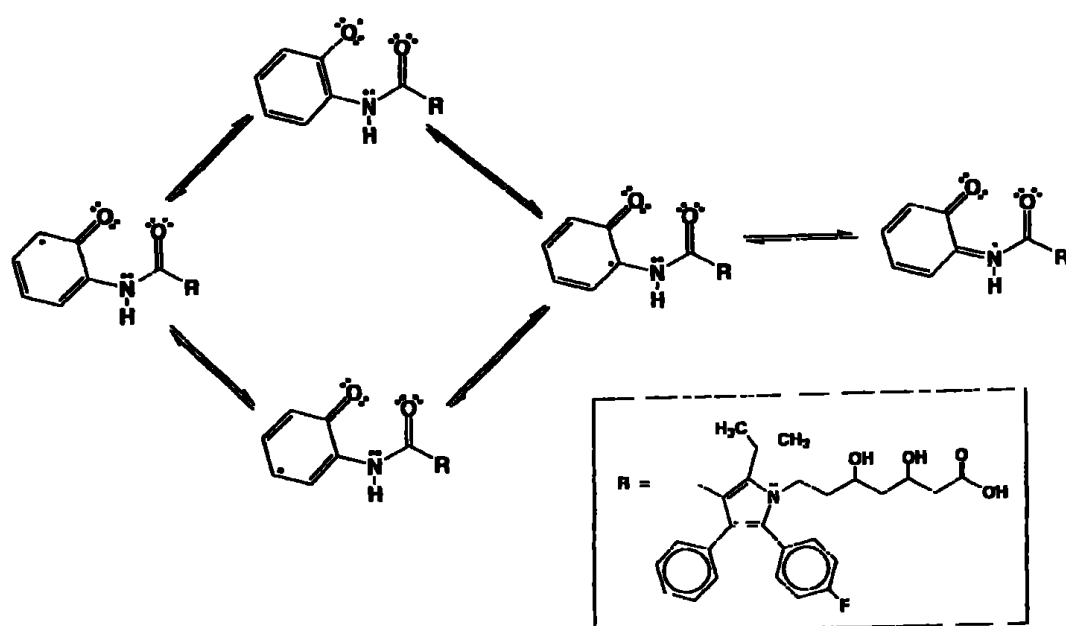


Figure 5B

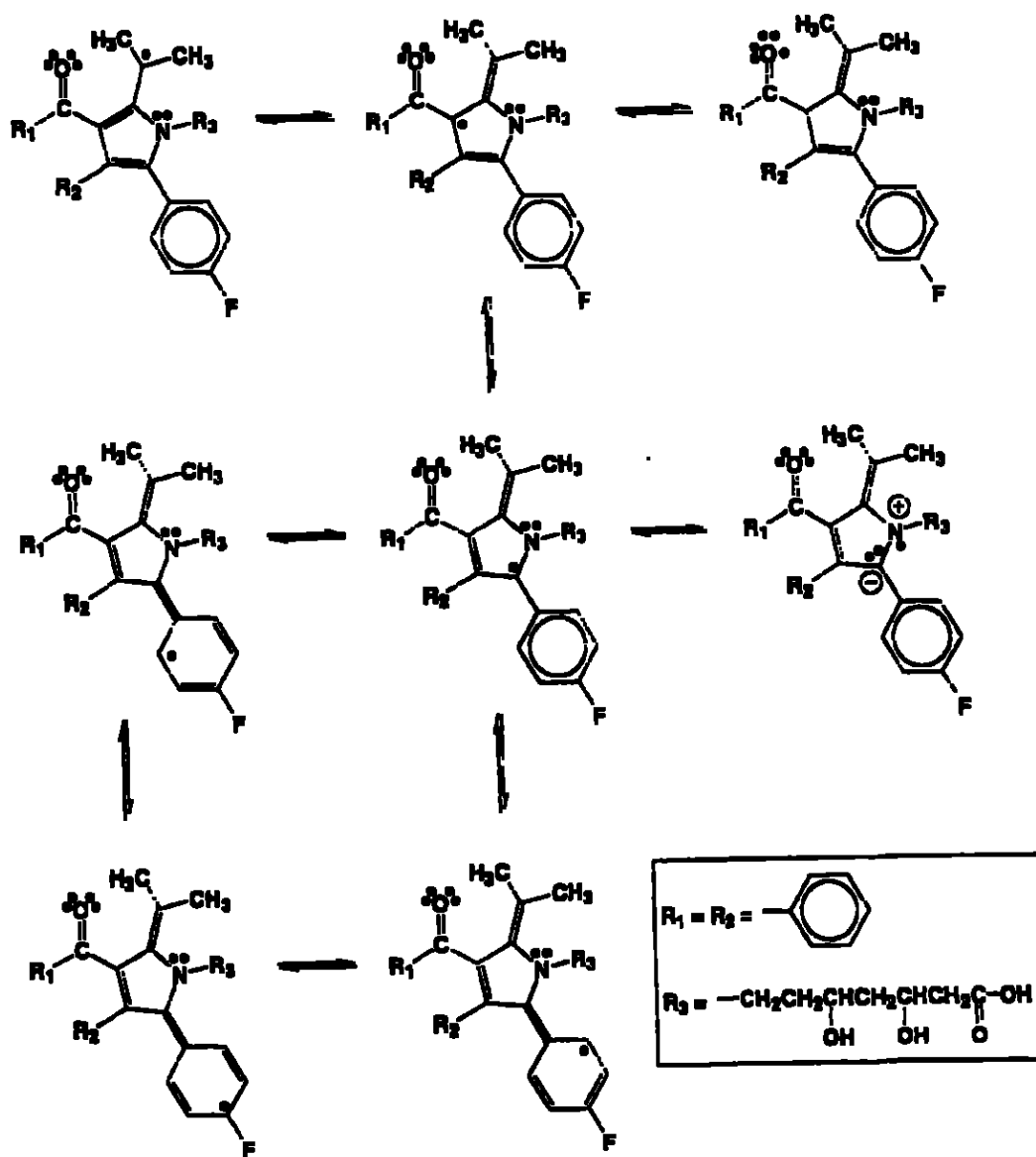


Figure 5C

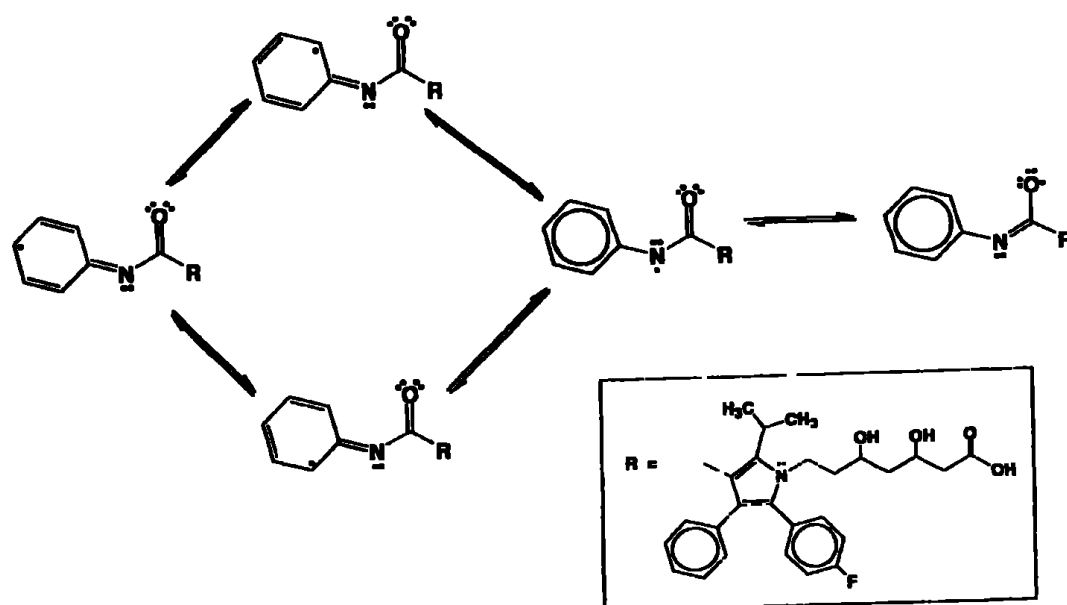
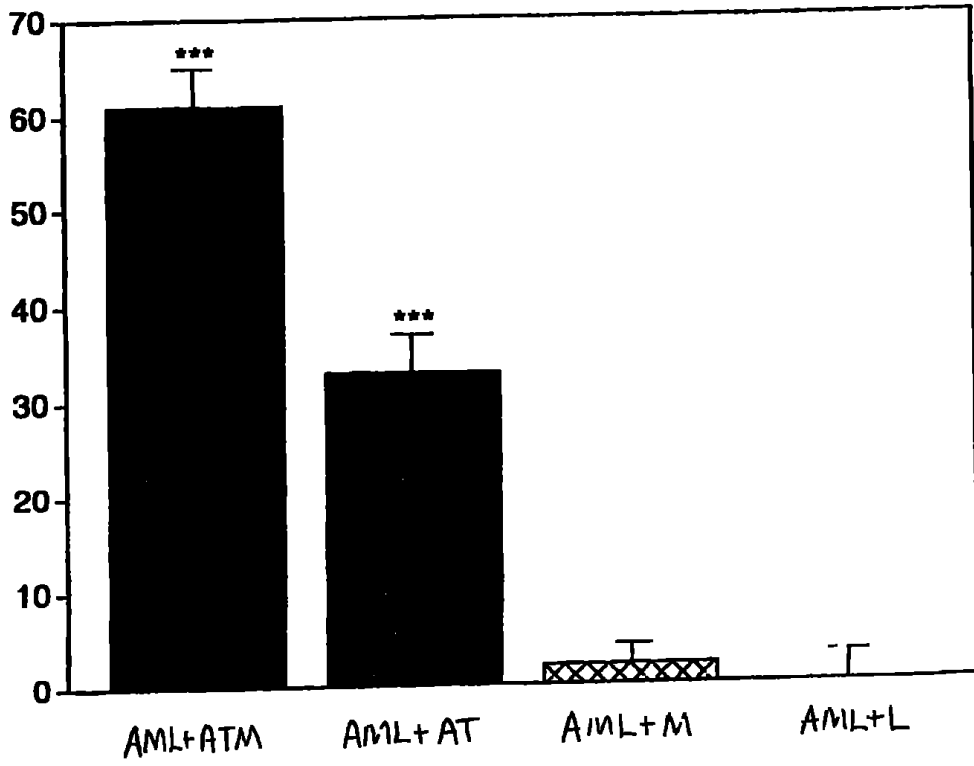


Figure 5D

X



y
Figure 6

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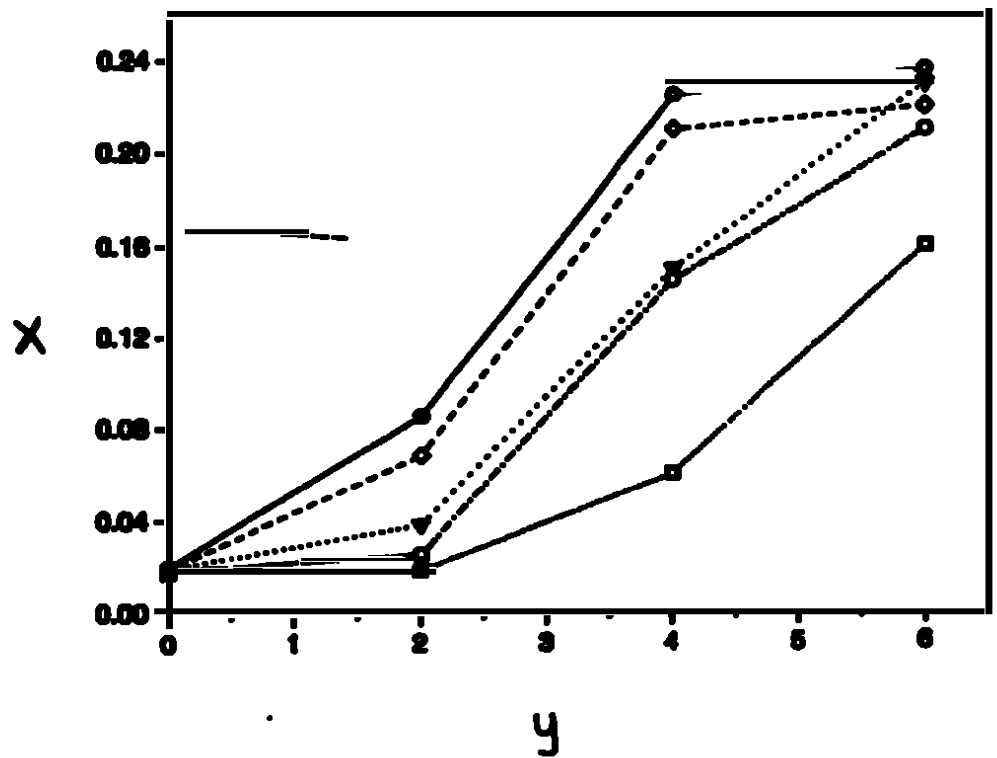


Figure 7A

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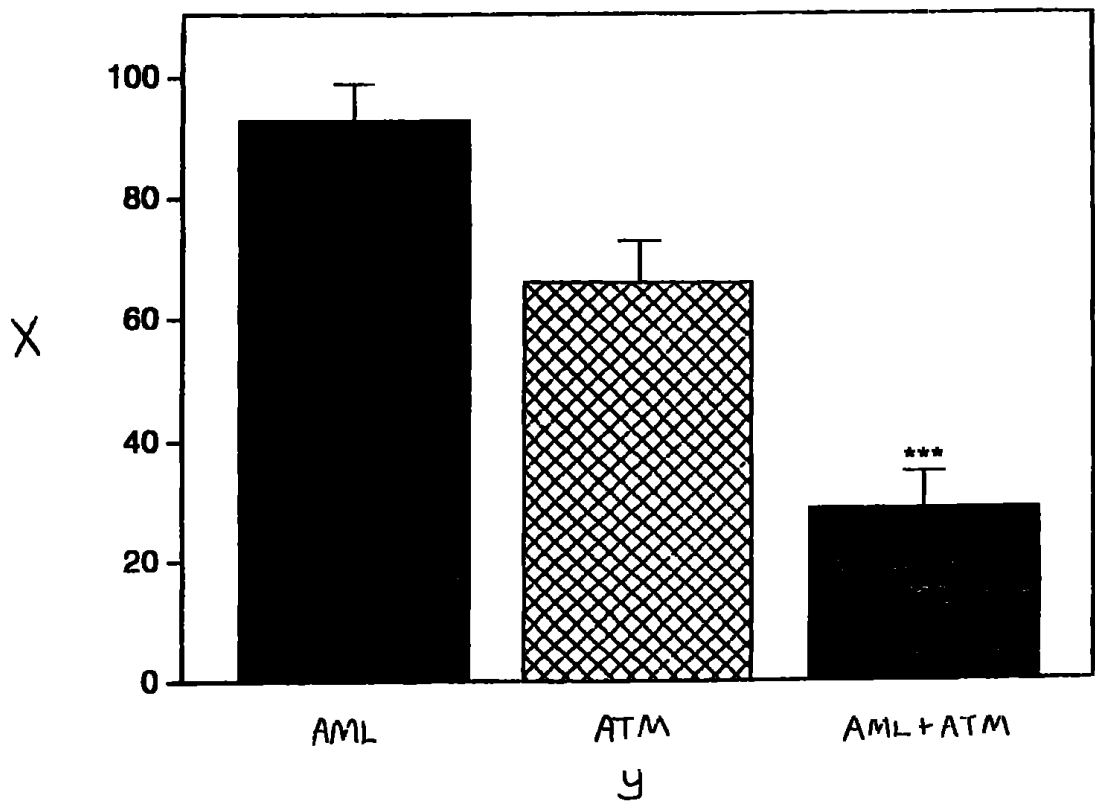


Figure 7B

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371**Computed Enthalpies of Formation for
Atorvastatin Metabolite Radicals***

Molecule	ΔH_f (kcal/mol)
Carbon radical	-209.50
Oxygen radical	-199.89
Nitrogen radical	-192.55
Methyl radical	-193.51
Phenyl radical	-176.05
Carbon/Oxygen Diradical	-182.07
Carbon/Nitrogen Diradical	-174.25

*The smaller (i.e., more negative) the ΔH_f value, the easier to abstract the H atom from that site.

Computed Enthalpies of Formation for Amlodipine Radicals*

Molecule	ΔH_f (kcal/mol)
Carbon radical	-164.28
Nitrogen radical	-148.27

*The smaller (i.e., more negative) the ΔH_f value, the easier to abstract the H atom from that site.

Figure 8

211
372

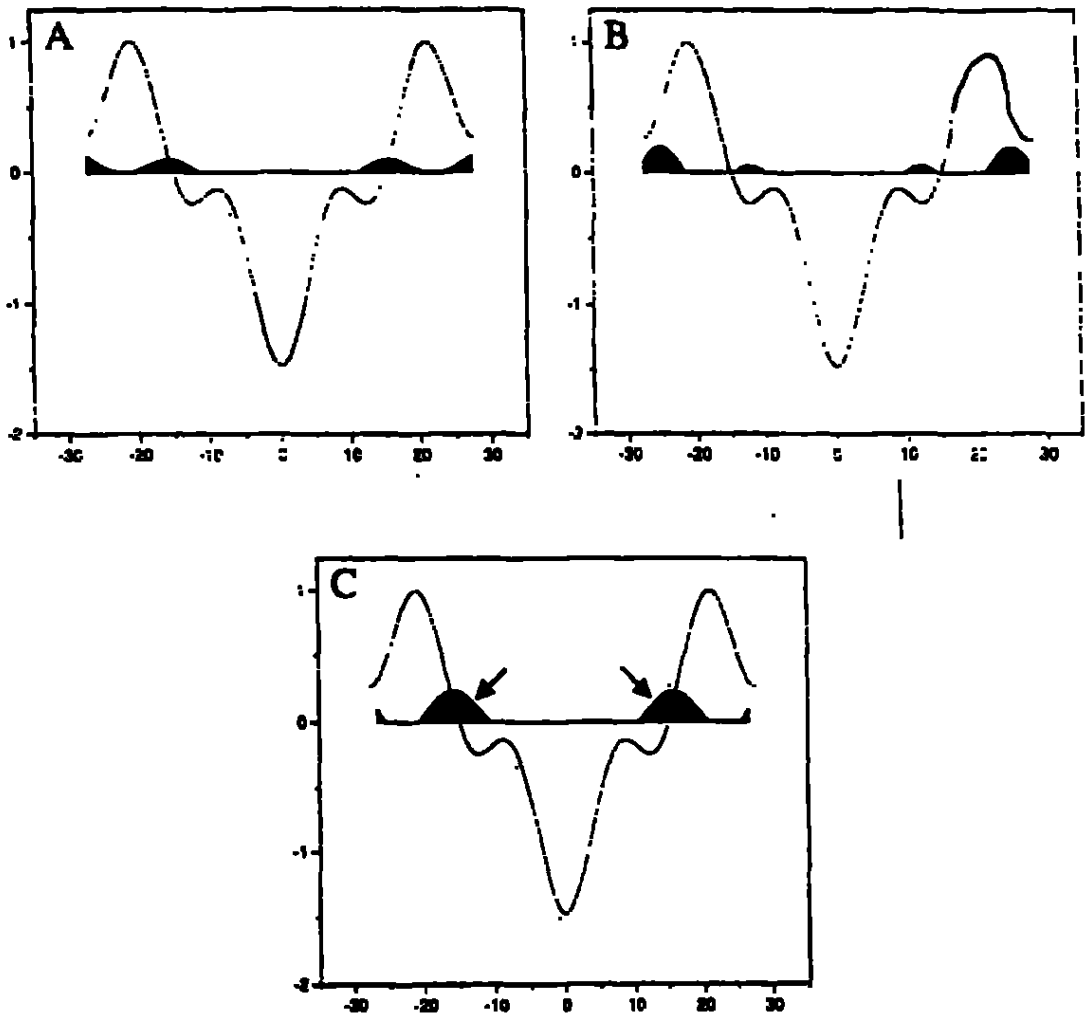


Figure 9

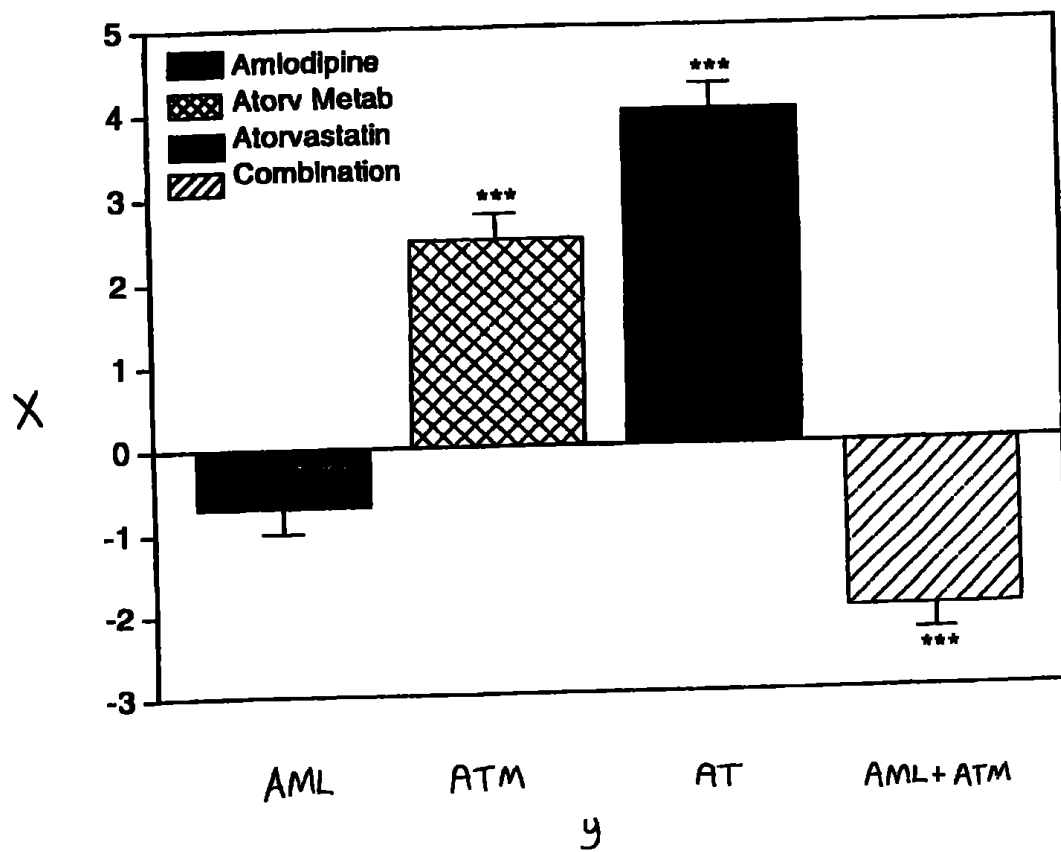


Figure 10

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(74) Agents: SPIEGEL, Allen, J. et al.; c/o Simpson, Alison,
Urquhart-Dykes & Lord, 30 Welbeck Street, London W1M
7PG (GB).

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(71) Applicant (*for all designated States except US*): PFIZER
PRODUCTS INC. [US/US]; Eastern Point Road, Groton,
CT 06340 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): CHANG, George
[US/US]; Pfizer Inc., Central Research Division, Eastern
Point Road, Groton, CT 06340 (US). HAMANAKA,
Ernest, Seichi [CA/US]; Pfizer Inc., Central Research
Division, Eastern Point Road, Groton, CT 06340 (US).

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WO 00/73271 A1

(54) Title: MUTUAL SALT OF AMLODIPINE AND ATORVASTATIN

(57) Abstract: This invention relates to a mutual salt of amlodipine and atorvastatin, pharmaceutical compositions thereof and methods of treating angina pectoris, atherosclerosis and combined hypertension and hyperlipidemia in mammals with such a mutual salt and compositions. This invention also relates to methods of managing cardiac risk in a mammal presenting with symptoms of cardiac risk, including humans by administering such a mutual salt and compositions.

-1-

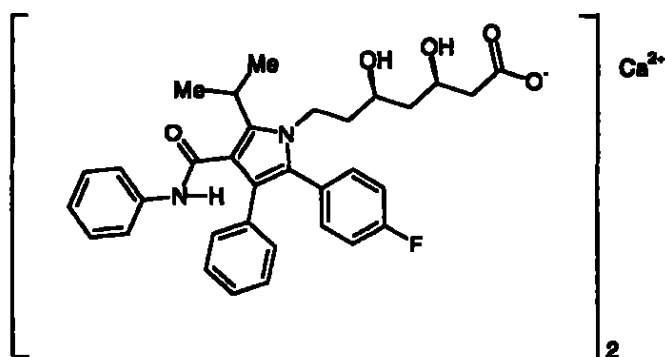
MUTUAL SALT OF AMLODIPINE AND ATORVASTATIN

This invention relates to a mutual salt of amlodipine and atorvastatin, pharmaceutical compositions thereof and methods of using said salt and/or said compositions to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans.

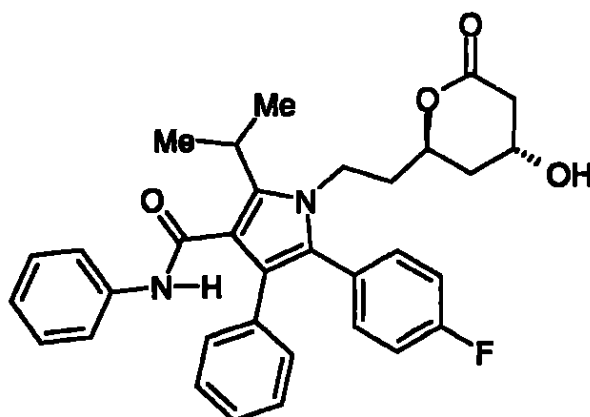
BACKGROUND OF THE INVENTION

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



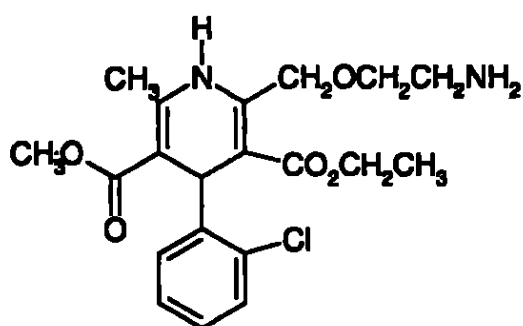
Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA. As such, atorvastatin calcium is a potent lipid lowering compound. The free carboxylic acid form of atorvastatin exists predominantly as the lactone of the formula



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

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

15



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 about 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.

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 the coronary arteries.

10 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
15 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
20 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
25 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
30 (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.

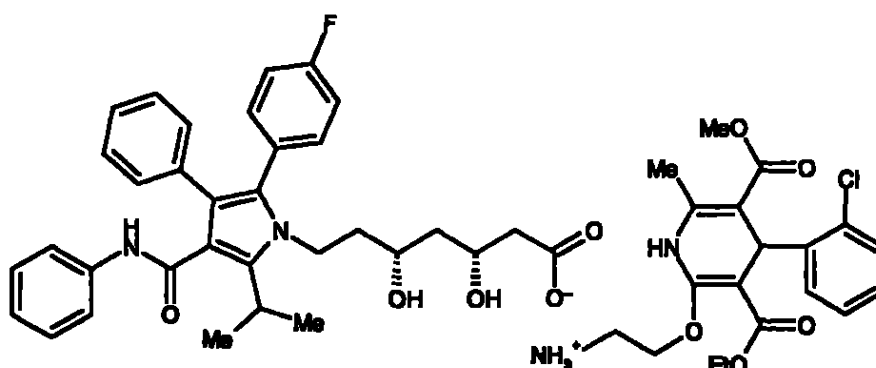
Krams et al., Journal of Human Hypertension (1995) (Suppl. 1), 53-59 disclose the use of calcium channel blockers, including amlodipine, to treat atherosclerosis. That reference further suggests that atherosclerosis can be treated with a combination of amlodipine and a lipid lowering agent. Human trials 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 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.

Commonly assigned International Patent Application Publication Number WO99/11259 discloses pharmaceutical compositions comprising a combination of amlodipine and atorvastatin.

SUMMARY OF THE INVENTION

This invention is directed to a compound which is an atorvastatin salt of amlodipine. It is to be understood that the phrase "amlodipine salt of atorvastatin" is synonymous with the phrase "atorvastatin salt of amlodipine." Those phrases are used interchangeably throughout this specification and appendant claims.

This invention is particularly directed to an atorvastatin salt of amlodipine which is a compound of formula I,



I

This invention is still more particularly directed to a compound of formula I wherein the carbon atom at the 4-position of the dihydropyridine ring has the (R)-configuration, e.g., 7-[2-(4-fluoro-phenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoate salt with 2-(2-amino-ethoxymethyl)-4(R)-(2-chloro-phenyl)-6-methyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester.

This invention is also more particularly directed to a compound of formula I wherein the carbon atom at the 4-position of the dihydropyridine ring has the (S)-configuration, 7-[2-(4-fluoro-phenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoate salt with 2-(2-amino-ethoxymethyl)-4(S)-(2-chloro-phenyl)-6-methyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester.

This invention is also directed to pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to methods of treating angina pectoris in a mammal suffering from angina pectoris comprising administering to said mammal an angina pectoris treating effective amount of a compound of formula I.

This invention is also directed to methods of treating angina pectoris in a mammal suffering from angina pectoris comprising administering to said mammal an angina pectoris treating effective amount of a pharmaceutical composition comprising a mutual salt of amlodipine and atorvastatin and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to methods of treating hypertension and hyperlipidemia in a mammal suffering from hypertension and hyperlipidemia comprising administering to said mammal a hypertension and hyperlipidemia treating effective amount of a compound of formula I.

This invention is also directed to methods of treating hypertension and hyperlipidemia in a mammal suffering from hypertension and hyperlipidemia comprising administering to said mammal a hypertension and hyperlipidemia treating effective amount of a pharmaceutical composition comprising a mutual salt of amlodipine and atorvastatin and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to methods of treating atherosclerosis in a mammal suffering from atherosclerosis comprising administering to said mammal an antiatherosclerosis effective amount of a compound of formula I. This invention is particularly directed to those cases where said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques, including wherein said atherosclerotic plaque formation is slowed in coronary arteries, carotid arteries or in the peripheral arterial system. This invention is also particularly directed to those cases where said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques, including wherein said regression occurs in the coronary arteries, in the carotid arteries and/or in the peripheral arterial system.

This invention is also directed to methods of treating atherosclerosis in a mammal suffering from atherosclerosis comprising administering to said mammal an antiatherosclerosis effective amount of a pharmaceutical composition comprising a mutual salt of amlodipine and atorvastatin and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to methods of managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, comprising administering to said mammal a cardiac risk treating effective amount of a compound of formula I.

This invention is also directed to methods of managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, comprising administering to said mammal a cardiac risk treating effective amount of a pharmaceutical composition comprising a mutual salt of amlodipine and atorvastatin and a
5 pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions comprising an amount of a compound of formula I and amlodipine or a pharmaceutically acceptable salt thereof, e.g., amlodipine besylate. This invention is also directed to methods of treating diseases and conditions in mammals comprising administering to said
10 mammals, e.g., humans, such a pharmaceutical composition. Diseases and conditions which may be treated with such pharmaceutical compositions include angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and cardiac risk.

This invention is also directed to pharmaceutical compositions comprising an
15 amount of a compound of formula I and atorvastatin or a pharmaceutically acceptable salt thereof, e.g., the hemicalcium salt of atorvastatin. This invention is also directed to methods of treating diseases and conditions in mammals comprising administering to said mammals, e.g., humans, such pharmaceutical compositions. Diseases and conditions which may be treated with such pharmaceutical compositions include
20 angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and cardiac risk.

This invention is also directed to methods of delivering amlodipine *in vivo* by administering to a mammal, e.g., a human, a compound of formula I.

This invention is also directed to methods of delivering atorvastatin *in vivo* by
25 administering to a mammal, e.g., a human, a compound of formula I.

This invention is also directed to methods of treating a mammal comprising administering to said mammal an amount of a compound of formula I and an amount of amlodipine or a pharmaceutically acceptable salt thereof.

This invention is also directed to methods of treating a mammal comprising
30 administering to said mammal an amount of a compound of formula I and an amount of atorvastatin or a pharmaceutically acceptable salt thereof.

This invention is also directed to methods of treating a mammal with amlodipine comprising administering to said mammal a compound of formula I.

This invention is also directed to methods of treating a mammal with atorvastatin comprising administering to said mammal a compound of formula 1.

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
5 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
10 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 combination of this invention.

15 Where used herein and in the appendant claims, 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 and/or cardiac ischaemia. Cardiac risk is calculated using the Framingham Risk Equation as set forth above. The term "cardiac risk management" means that the risk of future adverse cardiac
20 events is substantially reduced.

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DETAILED DESCRIPTION OF THE INVENTION

The mutual salt of amlodipine and atorvastatin of this invention and pharmaceutical compositions thereof may be readily prepared as set forth in the following description and in the Examples below.

5 Specifically, the mutual salt of atorvastatin and amlodipine is prepared by dissolving the free base of amlodipine in an appropriate reaction inert solvent and adding the resulting solution to a solution of the free acid of atorvastatin in an appropriate reaction inert solvent. As used herein, the expressions "reaction inert solvent" and "inert solvent" refer to a solvent or mixture of solvents which does not
10 interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product. Preferred solvents for amlodipine include but are not limited to acetone, water/acetone mixtures, alcoholic solvents such as methanol and ethanol. An especially preferred solvent for amlodipine is a one to one mixture of water and acetone. Preferred solvents for
15 atorvastatin include but are not limited to ethyl acetate, toluene, acetone and alcoholic solvents such as methanol and ethanol. An especially preferred solvent for atorvastatin is ethyl acetate. The reaction mixture is stirred vigorously at ambient temperature. Crystallization is accomplished by the addition of less polar solvents such as toluene (20ml) to afford the mutual salt of amlodipine and atorvastatin. It will
20 be understood by a person skilled in the art that amlodipine is a racemic mixture of two enantiomers and that the salt formed using the racemic mixture of amlodipine will result in a diastereomeric mixture of the salt of amlodipine and atorvastatin. An optically pure form of the salt of amlodipine and atorvastatin can be prepared using the same procedure set forth above but substituting the (R)-enantiomer of amlodipine
25 for the racemic mixture or by substituting the (S)-enantiomer of amlodipine for the racemic mixture.

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.
30 4,879,303, which is incorporated herein by reference. Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers.

The R and S enantiomers of amlodipine may be prepared as described by Arrowsmith et al., J. Med. Chem., 1986, 29, 1696.

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Atorvastatin may readily be prepared as described in U.S. Patent No. 4,881,893, 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.

5 In addition, the mutual salt of amlodipine and atorvastatin of this invention may occur as a hydrate or as a solvate. Said hydrates and solvates are also within the scope of this invention.

The mutual salt, pharmaceutical compositions 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
10 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, the mutual salt, compositions and methods, by virtue of their action as antiatherosclerotics, antianginals, antihypertensives and
15 antihyperlipidemics, are useful in the management of cardiac risk.

The utility of the salt and compositions 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 the Mutual Salt of Amlodipine and Atorvastatin
on the Treatment of Atherosclerosis

This study is a prospective randomized evaluation of the effect of a combination of a mutual salt of amlodipine and atorvastatin on the
25 progression/regression of coronary and carotid artery disease. The study is used to show that a mutual salt 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 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 (10 mgs) and placebo or a mutual salt of amlodipine and atorvastatin (about 5 to 160 mgs). All doses set forth in this protocol are per day doses. The amount of amlodipine besylate, atorvastatin calcium and mutual salt of amlodipine and atorvastatin may be varied as required. Generally, a subject will begin taking 10 mg and the amount will be titrated down to as little as 5 mg as determined by the clinical physician.

The subjects are monitored for a one to three year period, generally three years being preferred. B-mode carotid ultrasound assessment of carotid artery

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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.

5 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.

10 The primary objective of this study is to show that the mutual salt of amlodipine 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.

15 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
20 averages is determined to arrive at the average mean segment diameter. The mean segment diameter of subjects taking the mutual salt of atorvastatin and amlodipine 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
25 atherosclerosis, respectively.

 The secondary objective of this study is to show that the mutual salt of amlodipine and atorvastatin 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
30 of time. The intimal-medial thickness of subjects taking the mutual salt of atorvastatin and amlodipine 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.

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

5 Effect of the Mutual Salt of Amlodipine and Atorvastatin
 on the Treatment of Angina

This study is a double blind, parallel arm, randomized study to show the effectiveness of a mutual salt of amlodipine and atorvastatin in the treatment of symptomatic angina.

10 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 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
15 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
20 subjects are evaluated to complete the study. Subjects are screened for compliance with the entry criteria, set forth above, 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
25 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
30 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 mutual salt of amlodipine and atorvastatin (about 5 to 160 mg). 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 of the compounds and compositions of this invention, and to determine the dosage amounts of the compounds and compositions 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 photoemission tomography (PET).

The utility of the mutual salts and compositions of the present invention as medical agents in the treatment of hypertension and hyperlipidemia in mammals (e.g., humans) suffering from a combination of hypertension and hyperlipidemia is

demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below.

Effect of the Mutual Salt of Amlodipine and Atorvastatin
on the Treatment of Subjects Having Both
Hypertension and Hyperlipidemia

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This study is a double blind, parallel arm, randomized study to show the effectiveness of a mutual salt of amlodipine and atorvastatin in controlling both hypertension and hyperlipidemia in subjects who have mild, moderate, or severe hypertension and hyperlipidemia.

10

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

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

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

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.

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 proportion of the total caloric intake. The term "washed out" where used in connection with this protocol, 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 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; (2) a fixed dose of atorvastatin calcium, generally about 10 to 80mg; or (3) a mutual salt of amlodipine and atorvastatin (about 5 to 160 mgs). Subjects remain on these doses for a minimum of six weeks, and generally for no more than eight weeks. The subjects return to the testing center at the conclusion of the six to eight weeks so that the baseline evaluations can be repeated. The blood pressure of the subject at the conclusion of the study is compared with the blood pressure of the subject upon entry. The lipid screen measures the total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apoB, VLDL (very low density lipoprotein) and other components of the lipid profile of the subject. Improvements in the values obtained after treatment relative to pretreatment values indicate the utility of the drug combination.

The utility of the mutual salts and compositions 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 the Mutual Salt of Amlodipine and Atorvastatin
on Subjects at Risk of Future
Cardiovascular Events

This study is a double blind, parallel arm, randomized study to show the effectiveness of the mutual salt of amlodipine and atorvastatin 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 mutual salt 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 in the hypertension and hyperlipidemia screen 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.

5 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) a mutual salt of amlodipine and atorvastatin (about 5 to 160 mgs). 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
10 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 the mutual salt of amlodipine and atorvastatin in the treatment of angina pectoris, atherosclerosis, hypertension and hyperlipidemia together, and the management of cardiac risk, also
15 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
20 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,
25 and in the appendant claims, are daily doses.

 In general, in accordance with this invention, the mutual salt of amlodipine and atorvastatin is generally administered in a dosage of about 2.5 mg to about 20 mg.

 The mutual salt of the present invention is generally administered in the form
30 of a pharmaceutical composition comprising the mutual salt of this invention together with a pharmaceutically acceptable carrier, vehicle or diluent. Thus, the mutual salt of this invention can be administered in any conventional oral, parenteral or transdermal dosage form.

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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 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.

The mutual salt of this invention may also be administered in a controlled release composition such as a slow release or a fast release formulation. Such controlled release dosage formulations of the mutual salts 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 skilled in the art after an evaluation of 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 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 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, Easton, Pa., 19th Edition (1995).

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 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
5 being treated.

EXAMPLE ONE

Mutual Salt of Amlodipine and Atorvastatin. To a solution of the free acid of atorvastatin (5.0g, 8.9mM) in ethyl acetate (300ml) is added the free base of racemic amlodipine (3.7g, 8.9mM) in (1:1) water-acetone (25ml,25ml) or methanol (25 ml)
10 with vigorous stirring at room temperature. Crystallization is accomplished by the addition of a less polar solvent such as toluene (20ml) to afford the diastereomeric mutual salt of amlodipine and atorvastatin.

It should be understood that the invention is not limited to the particular embodiments described herein, but that various changes and modifications may be
15 made without departing from the spirit and scope of this novel concept as defined by the following claims.

11. A method of claim 10 wherein said atherosclerosis is manifested by a slowing of the progression of atherosclerotic plaques.
12. A method of claim 10 wherein said atherosclerosis is manifested by a regression of atherosclerotic plaques.
- 5 13. A method of treating atherosclerosis in a mammal suffering from atherosclerosis comprising administering to said mammal an antiatherosclerosis effective amount of a pharmaceutical composition of claim 5.
14. A method of managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, comprising administering to said mammal a cardiac risk
10 treating effective amount of a compound of claim 1.
15. A method of managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, comprising administering to said mammal a cardiac risk treating effective amount of a pharmaceutical composition of claim 5.
16. A pharmaceutical composition comprising an amount of a compound
15 of claim 1 and amlodipine or a pharmaceutically acceptable salt thereof.
17. A pharmaceutical composition of claim 16 comprising amlodipine besylate.
18. A pharmaceutical composition comprising an amount of a compound of claim 1 and atorvastatin or a pharmaceutically acceptable salt thereof.
- 20 19. A pharmaceutical composition of claim 18 comprising the hemicalcium salt of atorvastatin.
20. A method of treating angina pectoris in a mammal suffering from angina pectoris comprising administering to said mammal an effective amount of a pharmaceutical composition of claim 16.
- 25 21. A method of treating angina pectoris in a mammal suffering from angina pectoris comprising administering to said mammal an effective amount of a pharmaceutical composition of claim 18.
22. A method of treating atherosclerosis in a mammal comprising administering to said mammal an atherosclerosis treating effective amount of a
30 pharmaceutical composition of claim 16.
23. A method of treating atherosclerosis in a mammal comprising administering to said mammal an atherosclerosis treating effective amount of a pharmaceutical composition of claim 18.

24. A method of managing cardiac risk in a mammal comprising administering to said mammal a cardiac risk treating effective amount of a pharmaceutical composition of claim 16.

5 25. A method of managing cardiac risk in a mammal comprising administering to said mammal a cardiac risk treating effective amount of a pharmaceutical composition of claim 18.

26. A method of treating a mammal suffering from hypertension and hyperlipidemia comprising administering to said mammal a hypertension and hyperlipidemia treating effective amount of a pharmaceutical composition of claim 16.

10 27. A method of treating a mammal suffering from hypertension and hyperlipidemia comprising administering to said mammal a hypertension and hyperlipidemia treating effective amount of a pharmaceutical composition of claim 18.

28. A method of delivering amlodipine *in vivo* by administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a mammal.

15 29. A method of claim 28 wherein said mammal is a human.

30. A method of delivering atorvastatin *in vivo* by administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a mammal.

31. A method of claim 30 wherein said mammal is a human.

20 32. A method of treating a mammal comprising administering to said mammal an amount of a compound of claim 1 and an amount of amlodipine or a pharmaceutically acceptable salt thereof.

33. A method of treating a mammal comprising administering to said mammal an amount of a compound of claim 1 and an amount of atorvastatin or a pharmaceutically acceptable salt thereof.

25 34. A method of treating a mammal with amlodipine comprising administering to said mammal a compound of claim 1.

35. A method of treating a mammal with atorvastatin comprising administering to said mammal a compound of claim 1.