

Señor

SUPERINTENDENTE DE INDUS

DIVISION DE NUEVAS CREAC

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Radicacion: SUPERINDUSTRIA Y COMERCIO
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Fecha (AMD): 2000-05-29 16:22:18

Tramite : 002 PATENTES D

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

1 REGISTRO/

Folios: 239

329 COMPLETOS

Re: P1.-MERCK & CO., INC .- Solicitud de Patente de Invención
para "DIHIDROXIACIDO ABIERTO Y SALES DE
INHIBIDORES DE LA HMG-CoA REDUCTASA".- Clase
A61.-Expediente número 00-016.008 .-

1. Me refiero a mi solicitud arriba nombrada de fecha 6 de Marzo de 2000.

2. Anexos me permito presentar a usted:

(1) Copias autenticas (3) de las primeras solicitudes de patente presentadas para el invento arriba nombrado respecto de las cuales reclamo prioridad, a saber:

(a) La solicitud estadinense número 60/123.227 de 8 de Marzo de 1999, junto con su traducción oficial, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(b) La solicitud estadinense número 09/264.744 de 9 de Marzo de 1999, junto con su traducción oficial, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(c) La solicitud estadinense número PCT/US00/02626 de 2 de Febrero de 2000, junto con su traducción oficial, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

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3. Copias debidamente autenticadas por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial del señor Eduardo Calado Noguera quien elaboró la traducción de las solicitudes estadinenses números 60/123.227, 09/264.744 y PCT/US00/02626 , respecto de las cuales se reivindica prioridad en el presente caso.

4. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,



JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DEL MINISTERIO DE
RELACIONES EXTERIORES

CERTIFICA

Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma del señor **EDUARDO CALADO NOGUERA**, como traductor e intérprete oficial para los Idiomas INGLES- ESPAÑOL, ESPAÑOL- INGLES, según resolución 541 del 27 de febrero de 1976.

La anterior certificación se expide a solicitud del interesado quien se identificó con cédula de ciudadanía 17.177.588 expedida en Bogotá.

Dada en Santa Fe de Bogotá, D.C., a los seis (6) de noviembre de 1997.

Blanchard
BLANCA ACOSTA DE GARCIA
Jefe Area de Legalizaciones (e)

COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTÁ, 25 ABR. 2000
PABLO MENDEZ SANCHEZ

COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTÁ, 22 MAR. 2000
COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTÁ, 26 NOV. 1997
PABLO MENDEZ SANCHEZ

1176

República de Colombia



Ministerio de Justicia y del Derecho

EL SECRETARIO GENERAL (E) DEL MINISTERIO DE
JUSTICIA Y DEL DERECHO

CERTIFICA:

Que por Resolución 541 del 27 de febrero de 1976, le fue expedida licencia para ejercer funciones de Traductor e Intérprete Oficial en los idiomas **INGLES** y **ESPAÑOL** al señor **EDUARDO CALADO NOGUERA**, identificado con la cédula de ciudadanía No. 17.177.588 expedida en Bogotá.

Que dicha Resolución se encuentra vigente en la fecha.

Se expide la presente certificación a solicitud del interesado.

Dada en Santa Fe de Bogotá, D.C., a

14 OCT. 1997

[Firma manuscrita]

ALVARO NAMEN VARGAS

COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTA 25 AGO. 1999
PABLO MENDEZ BARRANAS

COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTA 26 NOV. 1997

COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTA 25 ABR. 2000
PABLO MENDEZ BARRANAS

COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTA
HAGO CONSTAR QUE ESTA COPIA COINCIDE
con documento original que he tenido a la vista
sonido para autentica que he tenido a la vista
SANTA FE DE BOGOTA 04 NOV. 1997
PABLO MENDEZ BARRANAS

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Febrero 23, 2000
Traducción Oficial No. 0217
REF:MERCK & CO;INC
Patente No.: 60/123,227

Merck & Co; Inc
Caso - 204164

11897

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
OFICINA DE MARCAS Y PATENTES

Diciembre 28,1999

Por medio del presente documento se certifica que adjunto se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud: 60/123,227

Fecha de Registro: Marzo 08,1999

Autorizado por:

COMISIONADO DE MARCAS Y PATENTES

Firma: T. LAWRENCE

Funcionario Encargado de Certificaciones

Hay sello de la Oficina de Marcas y Patentes realizado de color dorado.

Eduardo Calado
Eduardo Calado
"TRAM" 103 1
Rev 8/11/99

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Número de Caso: 20416PV

Apellidos	Nombre	Domicilio(ciudad y Estado o país extranjero)
Vega	José M.	Trappe, PA 19426

ÁCIDOS -ABIERTOS DE DIHIDROXI Y SALES DE HMG-CO INHIBIDORES DE REDUCTASA.

Rahway

Estado: Nueva Jersey Código Postal: 07065 País: Estados Unidos

Eduardo Calado
Eduardo Calado Voguera
"TRABAJADOR OFICIAL"
"SIN FALTAS ENCLAVES"
RECEIVED JUN 19 1960

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PARTES DE LA SOLICITUD INCLUIDAS (Verificar de que todas apliquen)

- ☒ ESPECIFICACIONES [34] Número de Páginas
- ☐ GRÁFICA (S) [3] Número de Páginas
- ☐ Declaración de pequeña Empresa
- ☐ Otros (especificar)

FORMA DE PAGO DE HONORARIOS PARA LA SOLICITUD PROVISIONAL DE ESTA PATENTE (Señalar uno)

- ☐ Se adjunta un cheque o giro postal para gastos de honorarios de registro de la mencionada patente.
- ☒ El comisionado por la presente se encuentra autorizado a cobrar honorarios de registro y crédito al número de Cuenta Bancaria 13-2755.
- ☒ Honorarios provisionales para registro = \$150.00

La invención fue realizada por una agencia del Gobierno de los Estados Unidos o bajo contrato con una agencia del Gobierno de los Estados Unidos.

NO

Edward Palacios
FEDERAL BUREAU OF INVESTIGATION
UNITED STATES DEPARTMENT OF JUSTICE
WASHINGTON, D.C. 20535
REC-541 Febrero de 1966

12190

[] Si, el nombre de la Agencia del Gobierno de los Estados Unidos y número de contrato son los siguientes:

Atentamente,

FIRMA: Carol S. Quagliato

Fecha: 3/8/99

No. de REGISTRO -35,330

Teléfono: (732) 594-3809

CERTIFICADO DE ENVIÓ POSTAL

Fecha de envío: Marzo 8, 1999

Correo Inmediato Certificado No: EM35836315 US

Yo, por medio del presente documento certifico que ha sido enviado por Correo Certificado como Correo Postal al Destinatario y al Comisionado Asistente para Patentes, Box Patent Application, Washington, DC., 20231.

Firma: Enviado por: Irene Samis

Edwardo Calado
Edwardo Calado Noguera
"FIRMA FOR OFFICIAL"
MOL-ING-10
1999-03-08

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REIVINDICACIONES:

1. Un método para inhibir HMG-CoA reductasa, el cual consiste en un suministro oral terapéutico, de una cantidad eficaz de un compuesto seleccionado de un ácido-abierto de dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo, en una forma dosis farmacéutica de liberación retardada a un paciente que necesite dicho tratamiento en el cual la liberación substancial del compuesto da la forma de dosis es retardada hasta el transcurso de la dosis hasta el estómago.
2. El método de acuerdo a la Reivindicación 1, en el cual el compuesto es suministrado en una forma de dosis farmacéutica revestida entéricamente.
3. El método de acuerdo a la reivindicación 1 en el cual el compuesto se suministra de una forma de dosis farmacéutica con tiempo de liberación controlada, revestida y entérica.
4. El método de acuerdo a la Reivindicación 1 en el cual el compuesto se suministra en un dispositivo que consta de:

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(A) la parte central comprimida y preparada de una mezcla que consta de:

(i) una cantidad terapéuticamente eficaz del compuesto;

y

(ii) un polímero el cual sobre hidratación forma partículas microscópicas gelatinosas; y

(B) un revestimiento de polimerico impermeable al agua, insoluble en agua el cual consta de un polímero y plastificados, el cual se adhiere alrededor de la parte central, y el revestimiento tiene una pluralidad de formas abiertas que se exponen aproximadamente de 1 hasta alrededor de 75% de la superficie de la parte central; y donde el promedio de liberación del compuesto del dispositivo es una de las funciones y tamaño de número de aperturas.

5. El método de la Reivindicación 4 en la cual la liberación del dispositivo de la droga es entérico y revestido.

6. Un método para tratar la hipercolesteromia, la cual consta en el suministro oral de una cantidad terapéuticamente eficaz de un compuesto seleccionado de ácido abierto dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo, en una forma de dosis de liberación retardada

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12. El método de acuerdo a la Reivindicación 11 en la cual la enfermedad cardiovascular es una enfermedad coronaria.

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14. El método de acuerdo a la Reivindicación 13 en la cual la persona que recibe el compuesto tiene la enfermedad aterosclerótica.

15. El método de acuerdo a la Reivindicación 13 en la cual la persona que recibe el compuesto se encuentran en riesgo de desarrollar la enfermedad aterosclerótica.

16. El método de acuerdo a la Reivindicación 13 en al cual el caso de la enfermedad aterosclerótica es seleccionado de una enfermedad coronaria, y un caso cerebrovascular de claudicación intermitente.

17. El método de acuerdo a la reivindicación 16 en la cual el evento de la es seleccionado de una enfermedad coronaria, infarto del miocardio y procedimiento de revascularización coronaria.

18. El método de acuerdo a la reivindicación 17 en la cual el evento cerebrovascular es seleccionado de un accidente cerebrovascular y un ataque isquémico pasajero.

19. El método de acuerdo a la Reivindicación 1 en la cual el compuesto es una sal farmacéuticamente aceptable de un ácido abierto dihidroxi

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20. El método de acuerdo a la Reivindicación 19 en la cual el compuesto es una sal farmacéuticamente aceptable en forma del ácido abierto dihidroxi statin seleccionado de un grupo que consiste de lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin y cerevastatin.

21. El método de acuerdo a la reivindicación 20 en la cual el compuesto es una sal farmacéuticamente aceptable de la forma de ácido abierto dihidroxi de un statin seleccionado de un grupo que consiste de lovastatina y simvastatina.

22. El método de acuerdo a la Reivindicación 21 en la cual el compuesto es una sal farmacéuticamente aceptable de ácido abierto dihidroxi simvastatin.

23. El método de acuerdo a la Reivindicación 22 en la cual el compuesto es una forma de cristalino hidratado de la sal de calcio del ácido abierto simvastatin.

24. El método de acuerdo a la Reivindicación 23 en la cual el compuesto es una forma cristalina hidratada de sal de calcio de ácido abierto dihidroxi simvastatina el cual tiene un patrón polvo de difracción de rayos x obtenido

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28. Una composición farmacéutica de suministro oral la cual consta de una cantidad terapéuticamente eficaz de un compuesto seleccionado de un ácido abierto dihidroxi statin y una sal farmacéuticamente aceptable o éster de la misma y un portador farmacéuticamente aceptable, formulado en la forma de dosis de acción retardada en la cual la liberación del compuesto de la forma de dosis es retardada hasta que pase a través del estómago.

se a través del estómago.

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29. La composición farmacéutica de la reivindicación 28 en la cual la composición se encuentra totalmente revestida.

30. La composición farmacéutica de acuerdo a la composición 29 en la cual la composición es formulada en una forma de dosis farmacéutica de tiempo de liberación controlada, revestida y entérica.

31. La composición farmacéutica de acuerdo a la reivindicación 28 en el cual la composición formulada se suministra en un dispositivo que contiene la droga la cual consta de:

(A) la parte central comprimida y preparada de una mezcla que consta de:

(i) una cantidad terapéuticamente eficaz del compuesto;

y

(ii) un polímero el cual con la hidratación forma partículas microscópicas gelatinosas; y

(B) un revestimiento de polimérico impermeable al agua, insoluble en agua el cual consta de un polímero y plastificadores, el cual se adhiere alrededor de la parte central, y el revestimiento tiene una

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pluralidad de formas abiertas que se exponen aproximadamente de 1 hasta alrededor de 75% de la superficie de la parte central; y donde el promedio de liberación del compuesto del dispositivo es una de las funciones y tamaño de número de aperturas.

32. La composición farmacéutica de acuerdo a la reivindicación 31 en el cual el dispositivo de liberación de la droga es revestido y entérico.

33. Un proceso para la preparación de una composición de suministro oral la cual consta en mezclar el compuesto seleccionado de un ácido abierto de dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo con un portador en forma de dosis de acción retardada.

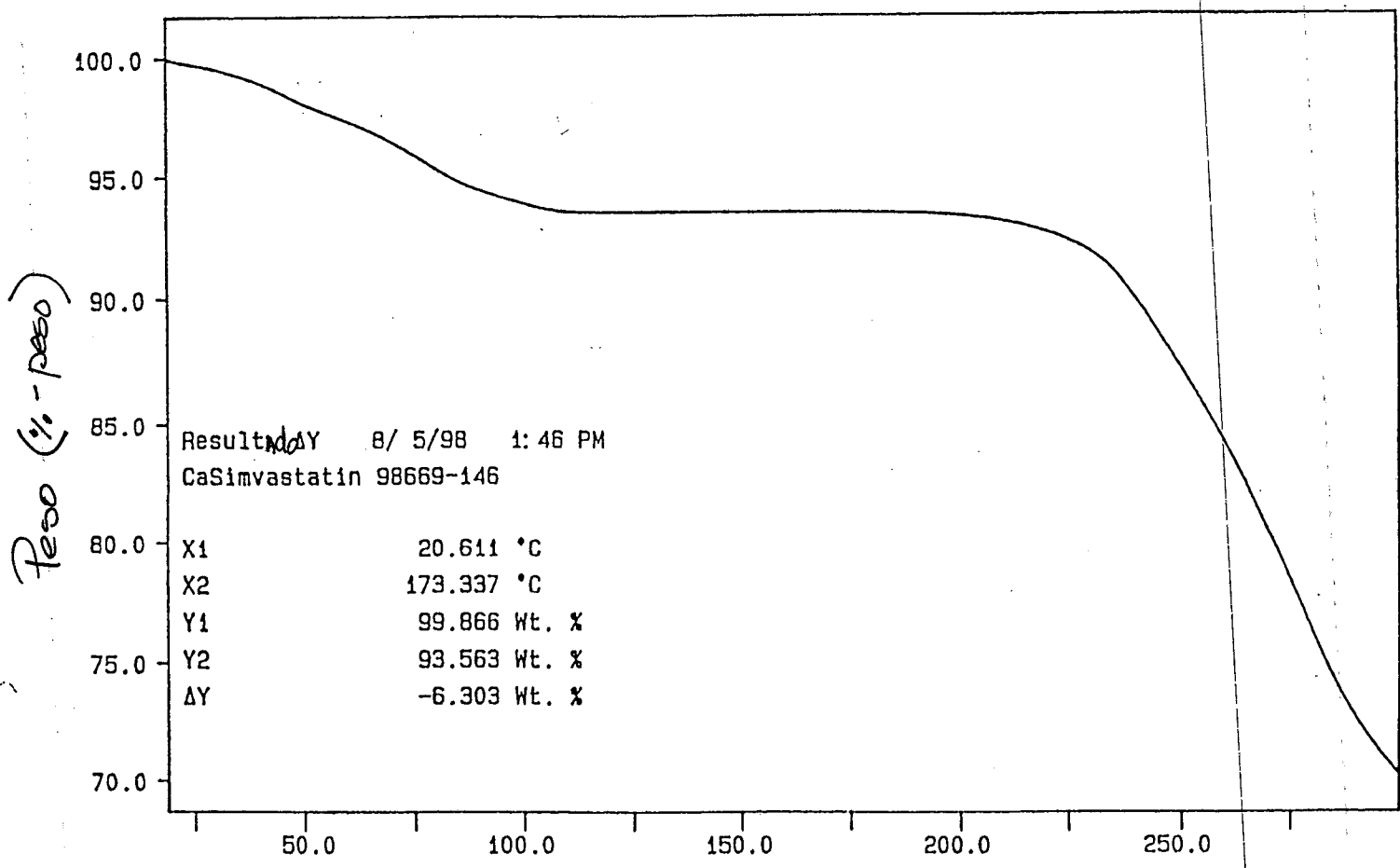
34. Una composición farmacéutica de suministro oral el cual es fabricado con la mezcla de una cantidad terapéuticamente eficaz de un compuesto seleccionado de un ácido abierto de dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo con un portador farmacéuticamente aceptable en una dosis de acción retardada.

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GRAFICA 1

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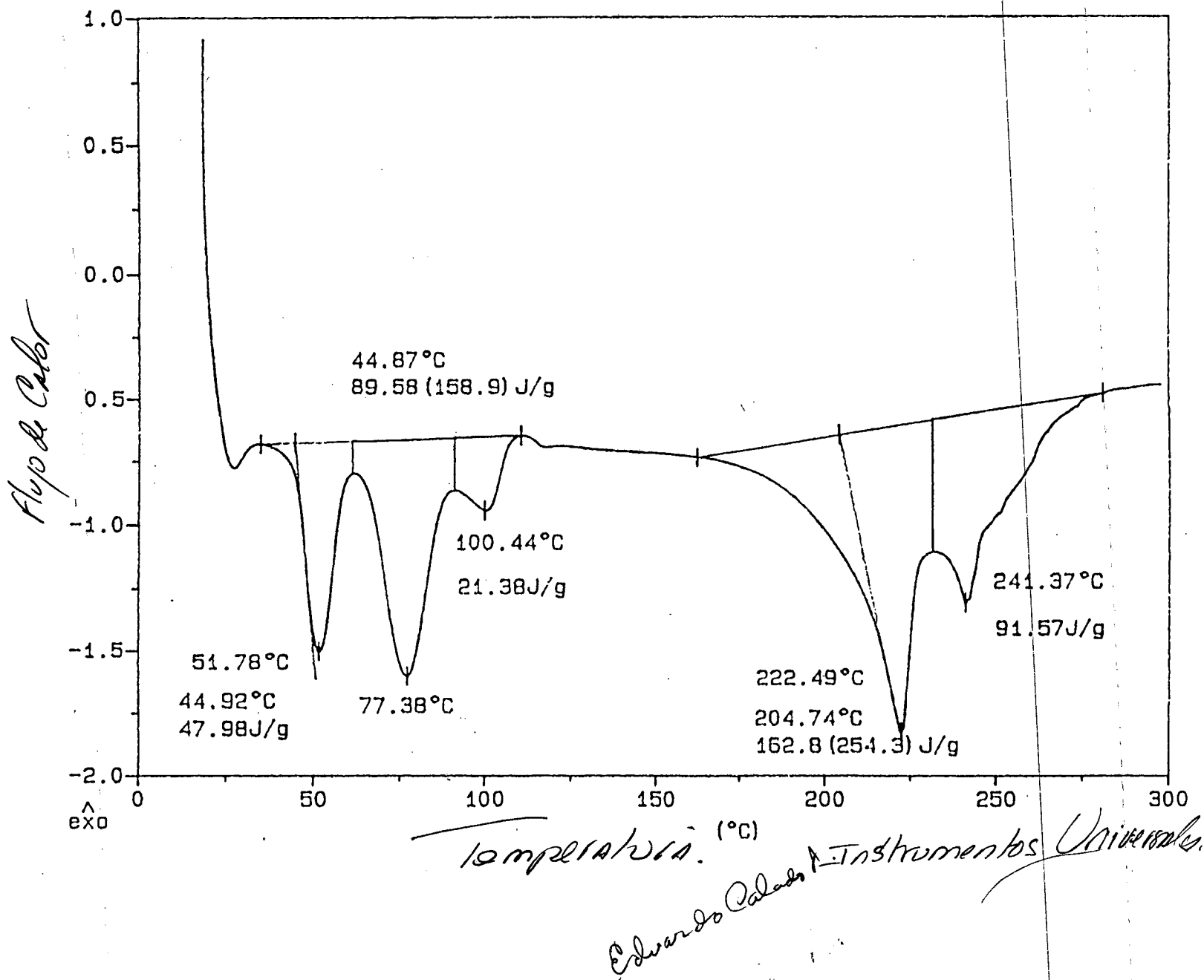
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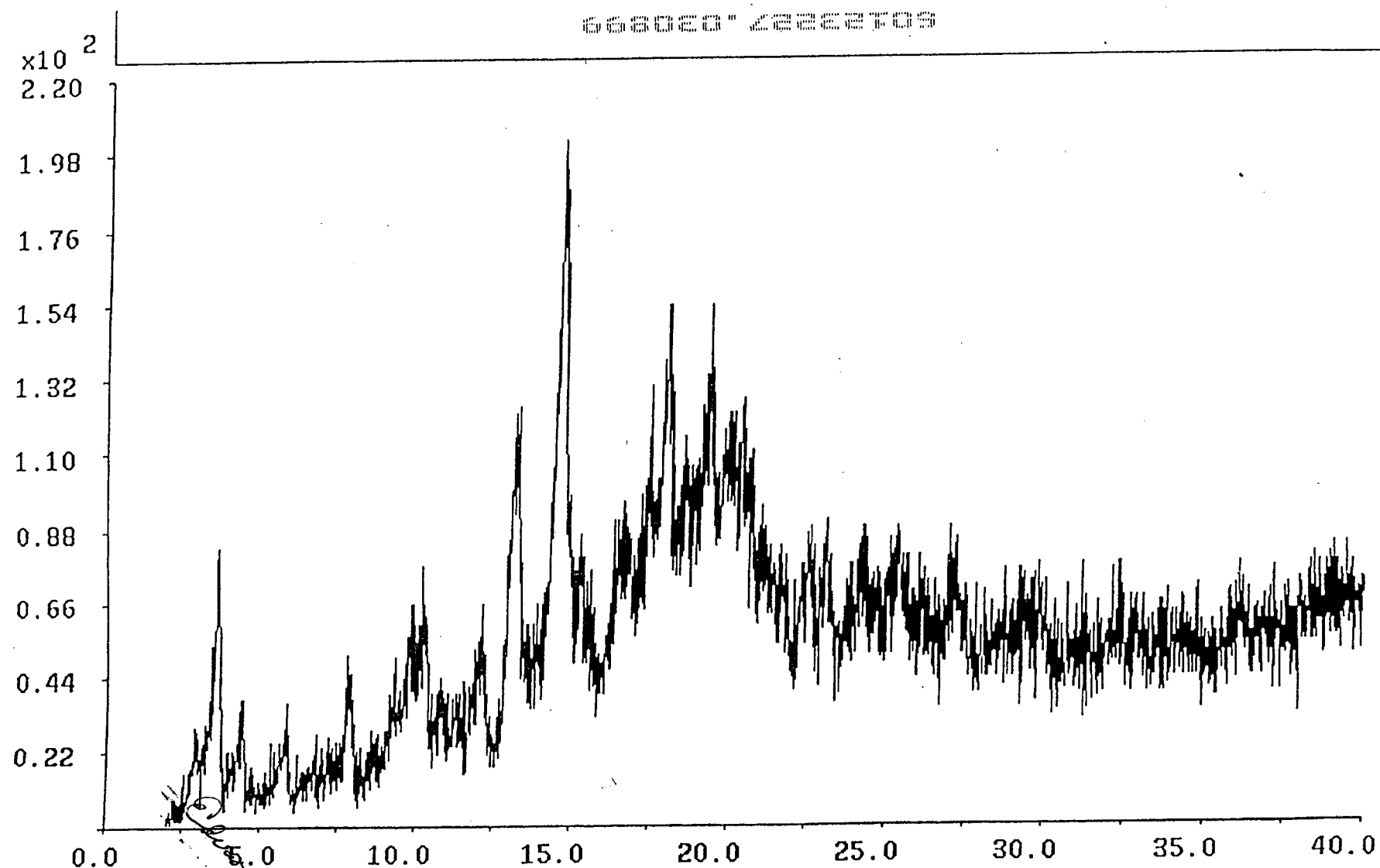
VRM
PERKIN-ELMER

Edmundo Calabrese
Sistema de Analisis serie termica
FARMACIA CALABRESE
TRABAJA Y OBTIENE
BENEFICIO PARA SI
Y PARA SU EMPRESA

GRAFICA 2

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GRAFICA 3

Quarta Colada

733

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PA 189828

**THE UNITED STATES OF AMERICA****TO ALL TO WHOM THESE PRESENTS SHALL COME:****UNITED STATES DEPARTMENT OF COMMERCE****United States Patent and Trademark Office****December 28, 1999**

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/123,227**FILING DATE: March 08, 1999**

**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

T. LAWRENCE**Certifying Officer**

Type a plus sign (+)
inside this box → ☐

Approved for use through 01/31/98. OMB 0651-0037
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PTO/SB/16 (3-97)

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (C).

CASE NUMBER 20416PV

INVENTOR(S)

Given Name (first and middle (if any))	Family Name or Surname	Residence (City and Either State or Foreign Country)
Jose M.	Vega	Trappe, PA 19426

☐ Additional inventors are being named on the __ separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE INHIBITORS

CORRESPONDENCE ADDRESS

Merck & Co., Inc.
Patent Department - RY60-30
P.O. Box 2000
Rahway

STATE	New Jersey	ZIP CODE	07065	COUNTRY	U.S.A.
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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	34	☐ Small Entity Statement
☒ Drawing(s)	Number of Sheets	3	☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

☐ A check or money order is enclosed to cover the filing fees

☒ The Commissioner is hereby authorized to charge filing fees or credit to Deposit Account Number:

13-2755

FILING FEE
AMOUNT (\$) \$150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted

SIGNATURE

Date 3/8/99

TYPED or PRINTED NAME Carol S. Quagliato

REGISTRATION NO. 35,330
(if appropriate)

TELEPHONE 732-594-3809

EXPRESS MAIL CERTIFICATE
DATE OF DEPOSIT March 8, 1999
EXPRESS MAIL NO. 3583 03157US

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS
BEING DEPOSITED WITH THE UNITED STATES POSTAL
SERVICE AS EXPRESS MAIL "POST OFFICE TO
ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN
AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER
FOR PATENTS, WASHINGTON, D.C. 20540

MAILED BY John Samuels
DATE March 8, 1999
Generated form No. P11, Merck & Co., Inc., 12/1/97

InTriplicate

DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE INHIBITORS

The instant invention relates to the use of dihydroxy open acid statins and salts thereof, which are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, in a delayed-release dosage formulation, and to a particular crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin referred to herein as compound I.

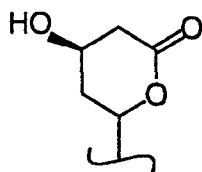
It has been clear for several decades that elevated blood cholesterol is a major risk factor for coronary heart disease (CHD), and many studies have shown that the risk of CHD events can be reduced by lipid-lowering therapy. Prior to 1987, the lipid-lowering armamentarium was limited essentially to a low saturated fat and cholesterol diet, the bile acid sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of these treatments have limited efficacy or tolerability, or both. With the introduction of lovastatin (MEVACOR®; see US Patent No. 4,231,938), the first inhibitor of HMG-CoA reductase to become available for prescription in 1987, for the first time physicians were able to obtain comparatively large reductions in plasma cholesterol with very few adverse effects.

In addition to the natural fermentation products, mevastatin and lovastatin, there are now a variety of semi-synthetic and totally synthetic HMG-CoA reductase inhibitors, including simvastatin (ZOCOR®; see US Patent No. 4,444,784), pravastatin sodium salt (PRAVACHOL®; see US Patent No. 4,346,227), fluvastatin sodium salt (LESCOL®; see US Patent No. 5,354,772), atorvastatin calcium salt (LIPITOR®; see US Patent No. 5,273,995) and cerivastatin sodium salt (also known as rivastatin; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors, are

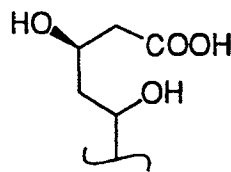
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- described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996). The HMG-CoA reductase inhibitors described above belong to a structural class of compounds which contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open-acid, and are often referred to as "statins." An illustration of the lactone portion of a statin and its corresponding open-acid form is shown below.



Lactone

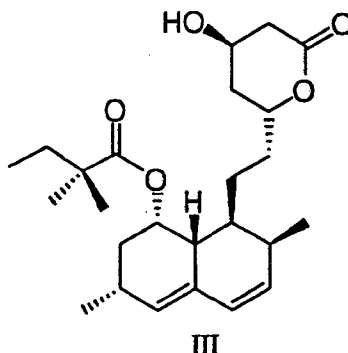
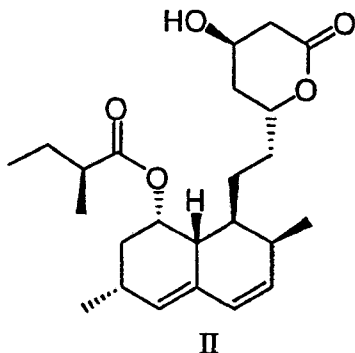


Dihydroxy Open-Acid

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- Salts of the dihydroxy open-acid can be prepared, and in fact, as noted above, several of the marketed statins are administered as the dihydroxy open acid salt forms. Lovastatin and simvastatin are marketed worldwide in their lactonized form. Lovastatin is shown as structural formula II, and simvastatin is shown as structural formula III, below.

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- The lactonized forms of the statins are not active inhibitors of HMG-CoA reductase, but the dihydroxy open acid forms are. It is known that condensation of the dihydroxy open acid form of statins to the

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corresponding lactonized form occurs under acidic conditions, that is at about pH 4 or under.

Therefore, due to the low gastric pH of the stomach, a statin conventionally administered by oral dosing in its lactone form will remain largely in its lactone form in the stomach. The vast majority of the drug will still be in the lactone form at the time of absorption from the intestine following oral dosing with the lactone. After absorption, the lactone enters the liver and it is in the hepatocytes that the lactone can be metabolized to the active open acid form, a reaction catalyzed by two hepatic esterases or "lactonases," one which is in the cytosolic and the other in the microsomal fraction. Once in the blood there is an additional plasma esterase which can also hydrolyze the lactone to the open acid. There may be some minimal chemical, i.e., non-enzymatic, hydrolysis that occurs in blood or in the liver; however, at the pH in blood and liver, there should not be any lactonization, i.e., conversion of open acid back to the lactone.

A statin conventionally administered by oral dosing in its dihydroxy open acid form or a pharmaceutically acceptable salt or ester thereof will tend to convert to its lactone form in the acidic environment of the stomach, so that a mixture of the open ring and the corresponding closed ring forms will co-exist there. For example, see M.J. Kaufman, International Journal of Pharmaceutics, 1990, 66(Dec 1), p. 97-106, which provides hydrolysis data that are used to simulate the extent of drug degradation that occurs in acidic gastric fluids following oral administration of several structurally related hypocholesterolemic agents, including simvastatin and lovastatin. Therefore, even after conventional oral dosing with a dihydroxy open acid statin or a salt or ester thereof, a mixture of the open acid and the corresponding lactone form of the drug would exist by the time of absorption from the intestine.

The preparation of the naturally occurring compound lovastatin and the semi-synthetic analog simvastatin leads to a mixture of the lactone and the open-ring dihydroxy acid forms. Several procedures have been published describing ways to make simvastatin from lovastatin, and most proceed through a lactone ring opening step at some point in the process and sometimes formation of a salt at the

139
108

resulting carboxy acid, and end with a ring-closing step in order to make the final simvastatin product. For example, U.S. Patent No. 4,820,850 describes a process for making simvastatin which involves opening the lactone ring of lovastatin and forming an alkyl-amide at the resulting
5 carboxy acid, followed by protection of the two hydroxy groups and methylation of the 8' acyl sidechain. After the methylation step, the hydroxy protecting groups are removed, the amide is hydrolyzed to the free acid and an ammonium salt of the free acid is formed, followed by a step to re-lactonize the ring. In U.S. Patent No. 4,444,784, the 8'-acyl
10 sidechain of lovastatin is removed and the lactone ring opened in the first step, followed by re-lactonization of the ring and protection of its hydroxy group. Next, the 8' position is acylated to introduce the simvastatin sidechain and a deprotection step is performed to obtain the simvastatin final product. In another process disclosed in U.S. Patent
15 No. 4,582,915, the potassium salt of the ring opened form of lovastatin is methylated at the 8' acyl sidechain, the free acid is then re-generated, and the dihydroxy open acid moiety is re-lactonized.

Several pharmaceutically acceptable salt forms of dihydroxy open acid statins are known in the art, as shown by the marketed salt
20 forms of pravastatin, fluvastatin, atorvastatin and cerivastatin described above. Some salt forms of dihydroxy open acid simvastatin have been previously described, for example the ammonium salt and the potassium salt which were used as intermediates in the synthetic processes described above. Chemical Abstracts also discloses a variety
25 of salt forms of dihydroxy open acid simvastatin, including a calcium salt having Registry No. 151006-18-7, which was referenced from a genus disclosed in U.S Patent No. 5,223,415, assigned to Merck & Co., Inc. Although there are no calcium salts exemplified in the patent, the general description of salt preparation taught in this patent would lead
30 to an amorphous calcium salt product.

Since becoming available, millions of doses of simvastatin have been administered and these drugs have developed an excellent safety record. However, as noted in the Physician's Desk Reference (PDR), in rare instances myopathy has been associated with the use of
35 all statins, including simvastatin. The mechanism for statin-related

140
109

myopathy is currently poorly understood. It is also known that many drugs, including certain statins such as simvastatin, are metabolised in the liver and intestine by the cytochrome P450 3A4 (CYP 3A4) enzyme system. As also noted in the PDR, there are adverse drug interaction concerns if a potent inhibitor of CYP3A4, such as itraconazole, and a CYP3A4-metabolized statin are used together, and some cases of myopathy were found to have occurred in patients taking such a drug combination. Simvastatin has been administered to over 20 million patients worldwide in the past 11 years and has been demonstrated to be remarkably safe. However, the very low risk of myopathy is substantially increased when simvastatin is given together with potent inhibitors of CYP3A4. This increased risk is believed to be related to the increased plasma levels of HMG-CoA reductase inhibitory activity resulting from the reduced metabolic elimination of simvastatin in the presence of a potent inhibitor of CYP3A4. While the overall safety record for simvastatin is exceptional, it would be desirable to further optimize its safety profile by reducing the potential for drug interactions with inhibitors of CYP3A4. It would also be desirable to further reduce the already low rate of occurrence of myopathy associated with the use of all statins.

Applicants have now discovered that dihydroxy open acid statins may be less reliant on CYP3A4 metabolism than their closed ring lactonized counterparts. The instant invention involves methods and pharmaceutical compositions for orally administering open-ring dihydroxy open acid statins and salts and esters thereof, which are HMG-CoA reductase inhibitors, in such a way so as to minimize conversion to their lactonized counterparts. This allows for delivery of a dihydroxy open acid statin without its lactone counterpart directly to the absorptive mucosa of the small intestine thus allowing for absorption of the open acid statin into the portal circulation, penetration by active open acid statin into hepatocytes to achieve enhanced efficacy, and systemic exposure consisting of open acid moieties. More particularly, delayed-release of an orally administered dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof, for example dihydroxy open acid simvastatin or a salt thereof, until after passage through the

141
110

stomach reduces the amount of lactone formed and absorbed in the body. Maintaining the statin in its open acid form in the body thereby reduces the potential for drug interactions between statins whose metabolism is CYP3A4-mediated and other active agents which inhibit the CYP3A4
5 enzymatic pathway. Moreover, maintaining the statin in its open acid form in the body may have additional clinical benefits for all statins, even for those statins that are not significantly metabolized by the CYP3A4 enzymatic pathway.

In addition, a novel crystalline hydrated form of the
10 calcium salt of dihydroxy open acid simvastatin has now been discovered to be a pharmaceutically suitable salt form having desirable physical properties for formulation into an anti-hypercholesterolemic drug composition.

15 SUMMARY OF THE INVENTION

One object of the instant invention is to provide a method for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, comprising orally administering a therapeutically effective
20 amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

25 One embodiment of the first object is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is a gel extrusion module (GEM) drug delivery device.

Another embodiment of the first object is to provide the above-described method wherein the delayed-release pharmaceutical
30 dosage form is an enterically coated pharmaceutical dosage form. An additional aspect of this embodiment is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is an enterically coated time controlled-release pharmaceutical dosage form. Yet another aspect of this embodiment is to provide the above-described

142
111

method wherein the delayed-release pharmaceutical dosage form is an enterically coated gel extrusion module (GEM) drug delivery device.

The compound used for the above-described object and embodiments may particularly be dihydroxy open acid simvastatin and the pharmaceutically acceptable salts thereof, and more particularly a pharmaceutically acceptable salt thereof.

A second object of the instant invention is to provide novel HMG-CoA reductase inhibitors which are crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, and particularly the compound referred to herein as compound I.

Additional objects are to provide the use of the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, particularly compound I, for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, and also to provide pharmaceutical formulations, including conventional rapid-release, delayed-release and time controlled-release formulations, including the GEM drug delivery device and enterically coated dosage forms, that can be used with the compounds. A further object is to provide a process for making compound I. Additional objects will be evident from the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a thermogravimetry (TG) weight loss curve for compound I obtained under a nitrogen flow at a heating rate of 10°C/minute.

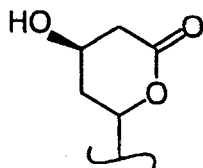
Figure 2 is a differential scanning calorimetry (DSC) curve for compound I obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup.

Figure 3 is an x-ray powder diffraction (XRPD) pattern for compound I. The XRPD pattern was obtained using CuK α radiation. The ordinate or Y-axis is x-ray intensity (cpm) and the abscissa or X-axis is the angle two-theta (2 θ) in degrees.

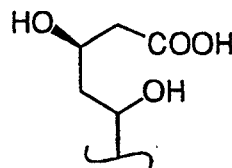
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DETAILED DESCRIPTION OF THE INVENTION

The term "statin(s)" as used herein is intended to be defined as inhibitors of HMG-CoA reductase which belong to a structural class of compounds that contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open acid, wherein the lactone portion of the statin and its corresponding dihydroxy open-acid form is shown below.



Lactone



Dihydroxy Open-Acid

- 10 All hydrates, solvates and polymorphic crystalline forms of HMG-CoA reductase inhibitors having the above-described lactone/dihydroxy open acid moiety are included within the scope of the term "statin(s)". Pharmaceutically acceptable salts and esters of the dihydroxy open-acid statins are included within the scope of the term "statin(s)".
- 15 Statins inhibit HMG-CoA reductase in their dihydroxy open acid form. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33.
- 20 The term "dihydroxy open acid statin(s)" is intended to be defined as statins which contain the dihydroxy open acid moiety, including pharmaceutically acceptable salts and esters thereof. The phrases "dihydroxy open acid statin(s)" and "dihydroxy open acid statin(s) and the pharmaceutically acceptable salts and esters thereof"
- 25 are used interchangeably herein and are both intended to encompass the open acid and salt and ester forms of the open acid of the statin, unless otherwise indicated. All hydrates, solvates and polymorphic crystalline forms are encompassed within the the scope of the term "dihydroxy open acid statin(s)."

144
113

Examples of dihydroxy open acid statins that may be used with the present invention include but are not limited to the dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof of: lovastatin (see US Patent No. 4,342,767); simvastatin (see US Patent No. 4,444,784), pravastatin, particularly the sodium salt thereof, fluvastatin particularly the sodium salt thereof; atorvastatin, particularly the calcium salt thereof; cerivastatin, particularly the sodium salt thereof, and nisvastatin also referred to as NK-104 (see PCT international publication number WO 97/23200). Pharmaceutically acceptable salts of dihydroxy open acid simvastatin, particularly the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, and more particularly the hydrated calcium salt of dihydroxy open acid simvastatin referred to herein as compound I, are preferred for use in the methods and compositions of this invention.

Herein, the term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, morpholine, 2,4,4-trimethyl-2-pentamine and tris(hydroxymethyl)aminomethane. Pharmaceutically acceptable esters at the carboxylic acid group can be made by treating a dihydroxy open acid statin with an alcohol. Examples of pharmaceutically acceptable esters of dihydroxy open acid statins include, but are not limited to, -C1-4 alkyl and -C1-4 alkyl substituted with phenyl-, dimethylamino-, and acetyl amino. "C1-4 alkyl" herein includes straight or branched aliphatic chains containing from 1 to 4 carbon atoms, for example methyl, ethyl, n-propyl, n-butyl, *iso*-propyl, *sec*-butyl and *tert*-butyl.

An object of this invention is to provide methods for reducing the amount of lactonized statin formed and absorbed in the

145
114

body after oral administration of a dihydroxy open acid statin in order to achieve enhanced clinical benefits. A way to achieve this is to administer the dihydroxy open acid statin in a delayed-release pharmaceutical dosage form. A delayed-release pharmaceutical dosage form as defined herein is an orally administerable pharmaceutical dosage form or device that does not release a substantial amount of the active compound until after the dosage form has passed through the stomach. Therefore, substantial release of the active compound would initially occur after entry into the duodenum. By "substantial release," it is intended that 90% or more by weight of the active agent in the delayed-release dosage form is released after entry into the duodenum, and that 10% or less by weight of the active agent in the delayed-release dosage form is released in the stomach. Particularly, the amount of active compound released in the stomach before entry into the duodenum is 5% or less by weight and more particularly 1% or less by weight.

It is to be understood that metabolism of the dihydroxy open acid statins will occur, primarily in the liver, after orally dosing in a delayed-release dosage form. However, since lactonization of the dihydroxy open acid statin would have been substantially avoided by use of a delayed release dosage form, the active and inactive metabolites that are formed will also be in the dihydroxy open acid form. In essence, if the dihydroxy open acid statin is administered in a delayed release dosage form, the internal exposure to lactonized parent compound and also to lactonized active and inactive metabolites will be minimized.

One example of a delayed-release dosage form is an enterically coated dosage form. The enteric coating will not dissolve in the acidic gastric environment, but will dissolve in the higher pH environment of the duodenum. An enterically coated dosage form will therefore not permit release of any significant amount of the active compound from the dosage form in the stomach, but, once the enteric coating dissolves in the duodenum, the active compound will be released. Suitable compositions for enteric coatings that can be used with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see L. Lachman, The Theory and Practice of Industrial Pharmacy, 3rd Ed., H. Liebermann and J. Kanig

145
115

contributors (Lea & Febiger, 1986). The pharmaceutical dosage form that is enterically coated can be a conventional rapid release dosage form or it can be a time controlled-release dosage form. Time controlled-release dosage forms are also well known in the pharmaceutical art, and are designed so as to slowly release the active compound in the body over a period of time, for example over a period of from about 6 to 24 hours. Use of a time controlled-release dosage form is preferred so as to lower the systemic exposure to the active statin.

An example of a delayed-release dosage form that also functions as a time controlled-release dosage form is described in U.S. Patent No. 5,366,738, herein incorporated by reference in its entirety. The controlled-release drug delivery device described in U.S. Patent No. 5,366,738 is known as a gel extrusion module (GEM) delivery device. The GEM device is a drug delivery device for the controlled in situ production and release of a dispersion containing a beneficial agent such as a pharmaceutical drug comprising:

- (A) a compressed core prepared from an admixture comprising:
 - (i) a therapeutically effective amount of the beneficial agent; and
 - (ii) a polymer which upon hydration forms gelatinous microscopic particles; and
- (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the beneficial agent from the device is a function of the number and size of the apertures.

In the GEM device, the polymer inside the compressed core is preferably selected from sodium polyacrylate, carboxypolymethylenes, and the pharmaceutically acceptable salts thereof, wherein the carboxypolymethylenes are prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and more preferably it is selected from carboxypolymethylenes prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and the

147
116

pharmaceutically acceptable salts thereof. Most preferably, CARBOPOL® 974P is used as the polymer inside the compressed core. In addition, the compressed core may also contain one or more polymer hydration modulating agents, anti-oxidants, lubricants, fillers and excipients. An optional subcoating may be applied to the compressed core prior to application of the water insoluble coating as an aid in the manufacturing process. The subcoating may be comprised of, for example, hydroxypropyl cellulose and hydroxypropylmethylcellulose.

The water insoluble, water impermeable polymeric coating is preferably comprised of (1) a polymer selected from polyvinyl chloride, cellulose acetate, cellulose acetate butyrate, ethylcellulose and combinations of these polymers; and (2) a plasticizer selected from diethylphthalate, dibutylsebacate and triethylcitrate. More preferably, the polymeric coating is comprised of cellulose acetate butyrate and triethyl citrate. The GEM device does not function as an osmotic drug delivery device, hence the release function of the device depends on passage of fluids from the external environment of the body to the internal environment of the compressed core through the formed apertures. It is intended that the terms "water insoluble, water impermeable" used to describe the polymeric coating define a coating which is essentially water insoluble and water impermeable, meaning that the polymeric coating allows minimal to no passage of water through the coating from the external environment of the body to the internal environment of the compressed core, except for the fluid passage that occurs through the drilled apertures, during the period of time the drug is being released from the GEM device in the body. Any minimal amount of water that does pass through the water insoluble, water impermeable polymeric coating is insubstantial and does not significantly contribute to the function of the GEM device, i.e. the release rate of the drug through the apertures. Rather the release rate of the drug from the GEM device is a function of the number and size of the apertures on the device.

For an elegant, aesthetically pleasing final product, an overcoat may finally be applied to the GEM delivery device containing colorants, waxes, and the like. The GEM device can also be enterically

148
117

coated. Even without enteric coating, extrusion of the polymer which carries the drug out from inside the compressed core of the GEM device does not occur to a substantial extent in the acidic pH of the stomach, therefore substantial release of the drug does not occur in the stomach.

- 5 Further details and examples of the GEM delivery device are described in US Patent No. 5,366,738.

The term "patient" includes mammals, especially humans, who take compound I for the prevention or treatment of a medical condition. Administering of the drug to the patient includes both self-
10 administration and administration to the patient by another person. The patient may be in need of treatment for an existing disease or medical condition, or may desire prophylactic treatment to prevent or reduce the risk for diseases and medical conditions affected by inhibition of HMG-CoA reductase.

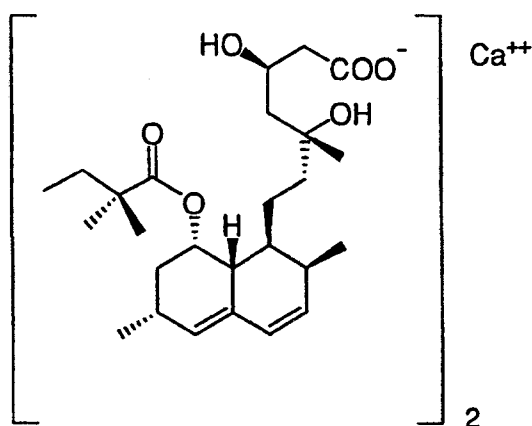
15 The term "therapeutically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term "prophylactically effective amount" is
20 intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

Particularly, the dosage a patient receives can be selected so as to
25 achieve the amount of LDL (low density lipoprotein) cholesterol lowering desired; the dosage a patient receives may also be titrated over time in order to reach a target LDL level. The dosage regimen utilizing a dihydroxy open acid statin is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of
30 the patient; the severity of the condition to be treated; the potency of the compound chosen to be administered; the route of administration; and the renal and hepatic function of the patient. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or

149
118

prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition.

The novel compounds of this invention are the crystalline hydrated forms of the calcium salt of dihydroxy open acid. A particular crystalline hydrated calcium salt of dihydroxy open acid is the one having an x-ray powder diffraction (XRPD) pattern obtained using CuK α radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å. For convenience, the crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin having the above-defined XRPD pattern will also be referred to herein as compound I. Compound I can be represented two-dimensionally as a hydrated form of the following structural formula Ia:



Ia

In addition to the XRPD pattern described above, compound I of the instant invention is further characterized by the thermogravimetry (TG) curve shown in Figure I. The TG curve for compound I was obtained under a nitrogen flow at a heating rate of 10°C/minute and is characterized by a 6.3% weight loss from ambient room temperature to a stable weight loss plateau at about 175°C. Additional weight losses due to the onset of decomposition of the compound are observed above about 190°C.

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119

Compound I is still further characterized by the differential scanning calorimetry (DSC) curve shown in Figure 2. The DSC curve for compound I was obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup, and is

5 characterized by three lower temperature endotherms with peak temperatures of 52, 77 and 100°C and associated heats of 48, 90 and 21 J/g, respectively, and two higher temperature endotherms due to decomposition with peak temperatures of 222 and 241°C and associated heats of 163 and 92 J/g.

10 Compound I of the instant invention is still further characterized by the ¹H NMR, ¹³C NMR and mass spectral data as given in Example 1 herein.

In the methods of treatment and prophylaxis described herein, as well as the pharmaceutical compositions and medicaments, a

15 dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof is employed. Preferably the compound employed is a pharmaceutically acceptable salt of a dihydroxy open acid statin, more preferably it is a pharmaceutically acceptable salt of dihydroxy open acid simvastatin, particularly a crystalline hydrated form of the calcium salt

20 of dihydroxy open acid simvastatin, and most preferably it is compound I. All hydrates, solvates and polymorphic crystalline forms of the above-described compounds and their use are encompassed within scope of the instant invention.

The instant invention provides methods for inhibiting

25 HMG-CoA reductase, and for treating lipid disorders including hypercholesterolemia, hypertriglyceridemia and hyperlipidemia, comprising administering a therapeutically effective amount of a dihydroxy open acid statin to a person in need of such treatment. Further provided are methods for preventing or reducing the risk of

30 developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a prophylactically or therapeutically effective amount, as appropriate, of a dihydroxy open acid statin to a mammal who is at risk of developing atherosclerosis or

35 who already has atherosclerotic disease.

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

A dihydroxy open acid statin may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom the potential for recurrence of such an event exists.

Accordingly, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of a prophylactically effective amount of a dihydroxy open acid statin to a patient at risk for such an event. The patient may already have atherosclerotic disease at the time of administration, or may be at risk for developing it.

Persons to be treated with the instant therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician practicing in the relevant fields of medicine. Such known risk factors include but are not limited

152
121

- to hypertension, smoking, diabetes, low levels of high density lipoprotein (HDL) cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: National Cholesterol
- 5 Education Program, Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), National Institute of Health, National Heart Lung and Blood Institute, NIH Publication No. 93-3095, September 1993; abbreviated version: Expert Panel on Detection, Evaluation, and
- 10 Treatment of High Blood Cholesterol in Adults, Summary of the second report of the national cholesterol education program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), JAMA, 1993, 269, pp. 3015-23. People who are identified as having one or more of the above-noted risk
- 15 factors are intended to be included in the group of people considered at risk for developing atherosclerotic disease. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within the group of people considered to be at risk for having an atherosclerotic disease
- 20 event.

- The oral dosage amount of the dihydroxy open acid statin, particularly a salt of a dihydroxy open acid statin such as simvastatin, and more particularly a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin such as compound I, is from about 1 to
- 25 200 mg/day, and more preferably from about 5 to 160 mg/day. However, dosage amounts will vary depending on factors as noted above, including the potency of the particular compound. Although the active drug of the present invention may be administered in divided doses, for example from one to four times daily, a single daily dose of the active drug is
- 30 preferred.. As examples, the daily dosage amount may be selected from, but not limited to, 5 mg, 10 mg, 20 mg, 25 mg, 40 mg, 50 mg, 75 mg, 80 mg, 150 mg and 160 mg.

The active drug employed in the instant therapy can be administered in such oral forms as tablets, capsules, pills, powders,

153
122

granules, elixirs, tinctures, suspensions, syrups, and emulsions. Oral formulations are preferred.

Oral delayed-release formulations are employed with the dihydroxy open acid statins. Examples of suitable formulations include
5 but are not limited to enterically coated pharmaceutical dosage forms such as enterically coated conventional pharmaceutical dosage forms and enterically coated time-controlled release dosage forms, the GEM delivery device, and an enterically coated GEM delivery device.

For the crystalline hydrated forms of the calcium salt of
10 dihydroxy open acid simvastatin, for example compound I, administration of the active drug can be via any pharmaceutically acceptable route and in any pharmaceutically acceptable dosage form. This includes the use of oral conventional rapid-release, time controlled-release and delayed-release (such as described above) pharmaceutical
15 dosage forms. An oral time controlled-release dosage formulation of the instant drug is preferred, and particularly the GEM controlled-release drug delivery device described in U.S. Patent No. 5,366,738, herein incorporated by reference in its entirety. Additional suitable
20 pharmaceutical compositions for use with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

In the methods of the present invention, the active drug is typically administered in admixture with suitable pharmaceutical
25 diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

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

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calcium stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, 5 disintegrating agents and coloring and flavoring agents can also be incorporated into the mixture. Stabilizing agents such as antioxidants, for example butylated hydroxyanisole (BHA), 2,6-di-tert-butyl-4-methylphenol (BHT), propyl gallate, sodium ascorbate, citric acid, and calcium metabisulphite, can also be added to stabilize the dosage forms; 10 the use of at least one stabilizing agent is preferred with the instant composition, and preferably an antioxidant is employed with dihydroxy open acid simvastatin or a salt thereof, and particularly compound I. Other suitable components include gelatin, sweeteners, natural and synthetic gums such as acacia, tragacanth or alginates, 15 carboxymethylcellulose, polyethylene glycol, waxes and the like.

The active drug can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, 20 stearylamine or phosphatidylcholines.

Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl- 25 pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, 30 polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The instant invention also encompasses a process for 35 preparing a pharmaceutical composition comprising combining a

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124

dihydroxy open acid statin with a pharmaceutically acceptable carrier. Also encompassed is the pharmaceutical composition which is made by combining a dihydroxy open acid statin with a pharmaceutically acceptable carrier.

- 5 Additional active agents may be used in combination with the dihydroxy open acid statin in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration of the active agents. One or more additional active agents may be administered with a
- 10 dihydroxy open acid statin. The additional active agent or agents can be cholesterol lowering compounds. Examples of additional active agents which may be employed include but are not limited to HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme
- 15 A: cholesterol acyltransferase (ACAT) inhibitors; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, including micronized fenofibrate, and gemfibrozil; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation
- 20 inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPAR γ) agonists including the compounds commonly referred to as glitazones, including those compounds included within the structural class known as thiazolidinediones as well as those PPAR γ
- 25 agonists outside the thiazolidinedione structural class); PPAR dual α/γ agonists; vitamin B₆ (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B₁₂ (also known as cyanocobalamin); beta-blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt
- 30 and the methylglucamine salt; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

- A therapeutically effective amount of a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin, for example compound I, can be used for the preparation of a medicament useful for
- 35 inhibiting HMG-CoA reductase, as well as for treating and/or reducing

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the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, such as preventing or reducing the risk of developing atherosclerotic disease, halting or slowing the progression of atherosclerotic disease once it has become clinically manifest, and preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event. For example, the medicament may be comprised of about 1 mg to 200 mg of a crystalline hydrated form of dihydroxy open acid simvastatin, or more particularly about 5 mg to 160 mg.

A therapeutically effective amount of a dihydroxy open acid statin can be used for the preparation of a medicament adapted for delayed-release that is useful for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, as described above.

The medicament comprised of a dihydroxy open acid statin, for example compound I, may also be prepared with one or more additional active agents, such as those described supra.

Simvastatin is a semi-synthetic product which can be made from the natural product lovastatin. Processes for preparing lovastatin and simvastatin are well documented in the published literature. For example, U.S. Patent No. 4,231,938, herein incorporated by reference, describes a fermentation and isolation process for obtaining lovastatin using the microorganism *Aspergillus terreus*. U.S. Patent No.'s 4,444,784, 4,820,850, 4,916,239 and 4,582,915, herein all incorporated by reference, describe methods for making simvastatin.

Preparation of Compound I

Compound I of the instant invention can generally be prepared as follows. Simvastatin and its dihydroxy open acid counterpart, including compound I, tend to form oxidative by-products; therefore, to minimize the formation of such by-products, it is preferred that the procedures used to make compound I are performed under an inert atmosphere such as nitrogen. Although compound I can be obtained without using an inert atmosphere, the purity of the desired product will not be optimized.

159
126

Hydrolysis of the lactone ring of simvastatin can be accomplished by treating simvastatin with at least one equivalent, and preferably a slight excess of one equivalent, of an aqueous base. If more than a slight excess of base is used, the excess base is preferably

5 neutralized before proceeding to the salt formation step in order to prevent formation of insoluble calcium hydroxide or calcium carbonate by-product. The base employed for the hydrolysis can be an aqueous solution of a metal hydroxide or metal carbonate, for example but not

10 limited to sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate and potassium carbonate. Sodium hydroxide is preferred. The hydrolysis can be performed in water, an aqueous-protic organic solvent mixture, or an aqueous-aprotic organic solvent mixture. Suitable protic organic solvents include but are not limited to methanol (MeOH), ethanol (EtOH), isopropyl alcohol, propanol and

15 tetrahydrofuran (THF). Examples of suitable aprotic organic solvents include but are not limited to *tert*-butyl methyl ether (MTBE) and toluene. An aqueous ethanol solvent mixture is preferred.

After the hydrolysis reaction is complete, the pH of the reaction mixture is adjusted to 6 to 9, preferably 7 to 8.5, by addition of an

20 acid. In this pH range, the dihydroxy open acid simvastatin will exist as a metal salt, for example as the sodium salt if the base used in the hydrolysis step is sodium hydroxide or sodium carbonate. Any acid that is capable of forming a soluble calcium salt such as calcium chloride or calcium citrate, is suitable. A soluble calcium salt is intended to be a

25 salt that is soluble in the solvent system employed in the instant process. Preferably a mineral acid is employed, particularly HCl.

The resulting pH-adjusted reaction mixture containing the metal salt of dihydroxy open acid simvastatin is next combined with a solution of about 0.50 to 0.55 equivalents of calcium acetate hydrate

30 $[\text{Ca}(\text{OAc})_2 \cdot \text{Ca} \cdot x\text{H}_2\text{O}]$ in an aqueous-protic organic solvent mixture, such as water-EtOH. The pH-adjusted reaction mixture can be added to the calcium acetate hydrate solution, or the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture. The addition can occur all at once, or optionally it can be performed in portions over time

35 with periods of aging. For example, a small portion, e.g., about one-

158
127

quarter, of the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture over a short period of time, for example over about 30 minutes, and then the resulting mixture can be allowed to age for an additional short period of time at room temperature, optionally
5 followed by a further period of aging at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C, after which the remaining calcium acetate hydrate solution can be added in portions over several hours at a temperature up to about 50°C,
10 for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C.

Whether the pH-adjusted reaction mixture and the calcium acetate hydrate solution are combined at once or in portions, the
15 resulting slurry must be aged until turnover of the resulting amorphous calcium salt of dihydroxy open acid simvastatin to the crystalline product is complete, usually for at least several hours. Complete turnover to the crystalline product can be assessed by standard techniques in the art, for example, by examining a sample of the product
20 under a microscope. This aging step can be performed at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C. During the aging period or periods, the use of lower temperatures will lead to crystallized product; however,
25 it has been found that as the temperature drops, the rate of crystal turnover becomes slower, making the procedure less time-efficient.

If necessary, the slurry is then allowed to cool to room temperature and is collected by suction filtration, and the recovered solid
30 is suction dried under a moist atmosphere (about 40 to 70% relative humidity), preferably a moist inert atmosphere such as nitrogen. The final step of suction filtration in the recovery of compound I should be done under a moist atmosphere, and preferably a moist inert atmosphere in order to minimize oxidative by-products. If an additional step of adding an antioxidant to compound I is performed, as described

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128

below, then the final suction filtration is the one performed after combining the antioxidant with compound I.

As noted above, compound I has a tendency to oxidize upon contact with air, and one way to minimize oxidation is to perform the reaction sequence under an inert atmosphere. Additionally, an antioxidant such as BHA, BHT, ascorbic acid, or calcium metabisulphite can be combined with compound I. This is simply done by agitating a slurry of compound I with the antioxidant and recovering the resulting solid by suction filtration.

Abbreviations which may appear herein are as follows: EtOH is ethanol; HPLC is high performane liquid chromatography; min. is minutes; h is hour(s); D.I. is de-ionized; NMR is nuclear magnetic resonance; EI MS is electron impact mass spectrum; HR-EI MS is high resolution electron impact mass spectrum; RH is relative humidity.

EXAMPLE 1

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I)

A 22 L four-necked round bottom flask was equipped with a temperature probe, a N₂ inlet, an addition funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H₂O was added and the solution was purged with N₂ for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry was purged with N₂ for 5 min. Then 5N NaOH (198 mL) was added at room temperature. After about 1 hour, the hydrolysis reaction was complete as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (approx. 65 mL). A solution of Ca(OAc)₂·H₂O (116.6 g, 0.662 mol) in 4.0 L of 60% EtOH-H₂O was purged with nitrogen for 5 min. A 1.0 L portion of this solution was added to solution of the sodium salt over 30 min. The resulting slurry was aged at room temperature for 30 min, and then at 30 to 35°C for 1-2 h.

The rest of Ca(OAc)₂ in EtOH-water was added over approx. 30 min at 30 to 35°C. The slurry was aged at 30 to 35 °C for 5 hours under

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129

atmosphere of N₂. The slurry was cooled to room temperature and was collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H₂O, 4 L 20% EtOH-H₂O, followed by 6 L x 3 of D.I. water. The solid was suction dried under an atmosphere of moist N₂ (40 to 70% relative humidity) at room temperature for 4 days. Crystalline hydrated calcium salt of dihydroxy open acid simvastatin was obtained as a white powder.

The calcium salt was delumped with a single pass through a cleaned QUADRO™ COMIL® (Model 197S).

HPLC CONDITIONS

Column: YMC Basic 4.6 mm x 25 cm
 Detector: ABS 757 1AU/volt output
 Sample solvent: EtOH/CH₃CN/H₂O (1:1:1)
 Column temp: 25 °C (Anal. Dept. runs samples at 5 °C to prevent formation of simvastatin on column).
 Flow rate: 1.5 mL / min.
 Wavelength: 238 and 210 nm

Gradient:

Time (min.)	%CH ₃ CN	%H ₂ O (10 mM K ₂ HPO ₄ -KH ₂ PO ₄ , pH = 6.5)
0.00	30	70
20.00	45	55
34.00	70	30
39.00	70	30
39.50	30	70
43.00	30	70

Retention time of simvastatin open acid: 17.07 min.
 Retention time of simvastatin: 32.90 min.

SPECTRAL DATA

161
130

¹H NMR (400 MHz, CD₃OD), δ 5.97 (d, J = 9.6 Hz, 1 H), 5.77 (dd, J = 9.6, 5.2 Hz, 1 H), 5.49 (m, 1 H), 5.33 (m, 1 H), 4.17 (m, 1 H), 3.70 (m, 1 H), 2.44 - 2.35 (m, 2 H), 2.42 (dd, J = 15.7, 3.6 Hz, 1 H), 2.31 - 2.27 (m, 1 H), 2.29 (dd, J = 15.7, 8.4 Hz, 1 H), 2.00 (ddd, J = 15.7, 7.6, 2.4 Hz, 1 H), 1.93 (m, 1 H),
5 1.68 (m, 1 H), 1.61 - 1.55 (m, 2 H), 1.55 (m, 2 H), 1.42 (m, 1 H), 1.32 (m, 1 H), 1.19 (m, 1 H), 1.12 (s, 6 H), 1.08 (d, J = 7.2 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 3 H), 0.84 (t, J = 7.6 Hz, 3 H) ppm.

¹³C NMR (100.55 MHz, CD₃OD), δ 182.3, 179.3, 134.1, 133.2, 130.3, 129.6,
10 72.5, 69.8, 45.1, 44.4, 44.1, 38.8, 38.3, 36.4, 34.3, 33.9, 32.0, 28.6, 25.9, 25.37, 25.36, 23.7, 14.3, 9.9 ppm

EI MS: m/e: 437 (M+H), 419(M+H-H₂O), 303.

HR-EI MS: Calcd. for C₂₅H₃₈O₅ 418.2719; Found: 418.2712.

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EXAMPLE 2

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) with BHA

A 22 L three-necked round bottom flask was equipped with a
20 temperature probe, a N₂ inlet, an additional funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H₂O was added and purged with N₂ for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry purged with N₂ for 5 min. 198 mL of 5N NaOH (0.993 mol, 1.05 equiv.) was then added at room temperature. The hydrolysis reaction is usually complete
25 in 1 h. as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (about 65 mL).

A solution of Ca(OAc)₂·H₂O (91.7 g, 0.520 mol, 0.55 equiv.) in 4.0 L of 60% EtOH-H₂O was purged with nitrogen for 5 min. 1.0 L of this solution was added to reaction solution over 30 min. The slurry was aged at room
30 temperature for 30 min, and then at 30 to 35 °C for 1-2 h. The rest of the Ca(OAc)₂ in EtOH-water was added in portions over 3h hours at 30-35°C. The slurry was allowed to age at 30 to 35 °C for 5 h under an atmosphere of N₂. The slurry was allowed to cool to room temperature and was

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162
131

collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H₂O, 4 L 20% EtOH-H₂O, followed by 6 L x 3 of D.I. water. The solid was suction dried under atmosphere of moist N₂ (40 to 70% RH) at room temperature to give 1.7 Kg of wet cake.

5 The above wet cake was placed in a clean 20 L three necked flask under atmosphere of nitrogen. A solution of BHA (2.603 g, 0.2 wt % equiv) in degassed 15% EtOH H₂O (8.5 L) was added, followed by addition of degassed water (2.55 L), and the slurry was agitated at room temperature for 1 to 2 h. The solid was collected by suction filtration
10 under atmosphere of moist N₂ with no washing to give 1.49 Kg wet cake. The solid was suction dried under atmosphere of moist N₂ (40 to 70% RH) at room temperature for 4 days. The calcium salt was obtained as a white powder (94% yield, 99.4%A at 238 nm, 0.2wt% BHA, KF = 7.3 %wt).

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

163
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WHAT IS CLAIMED IS:

1. A method for inhibiting HMG-CoA reductase comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.
2. The method of claim 1 wherein the compound is administered in an enterically coated pharmaceutical dosage form.
3. The method of claim 1 wherein the compound is administered in an enterically coated time controlled-release pharmaceutical dosage form.
4. The method of claim 1 wherein the compound is administered in a drug delivery device comprised of:
- (A) a compressed core prepared from an admixture comprising:
- (i) a therapeutically effective amount of the compound; and
- (ii) a polymer which upon hydration forms gelatinous microscopic particles; and
- (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;
- and wherein the release rate of the compound from the device is a function of the number and size of the apertures.
5. The method of claim 4 wherein the drug delivery device is enterically coated.

164
133

6. A method of treating hypercholesterolemia comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

7. A method for preventing or reducing the risk of developing atherosclerotic disease comprising orally administering a prophylactically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a person at risk of developing atherosclerotic disease wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

8. The method of Claim 7 wherein the atherosclerotic disease is selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

9. The method of Claim 8 wherein the cardiovascular disease is coronary heart disease.

10. A method for treating atherosclerotic disease comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

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

165
134

12. The method of Claim 11 wherein the cardiovascular disease is coronary heart disease.

5 13. A method for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical
10 dosage form to a person at risk of having an atherosclerotic disease event wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

15 14. The method of Claim 13 wherein the person receiving the compound has atherosclerotic disease.

15 15. The method of Claim 13 wherein the person receiving the compound is at risk of developing atherosclerotic disease.

20 16. The method of Claim 13 wherein the atherosclerotic disease event is selected from a coronary heart disease event, a cerebrovascular event and intermittent claudication.

25 17. The method of Claim 16 wherein the coronary heart disease event is selected from coronary heart disease death, myocardial infarction, and coronary revascularization procedures.

30 18. The method of Claim 17 wherein the cerebrovascular event is selected from a cerebrovascular accident and a transient ischemic attack.

19. The method of claim 1 wherein the compound is a pharmaceutically acceptable salt of a dihydroxy open acid statin.

168
135

20. The method of claim 19 wherein the compound is a pharmaceutically acceptable salt of the dihydroxy open acid form of a statin selected from the group consisting of lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin and cerivastatin.

5

21. The method of claim 20 wherein the compound is a pharmaceutically acceptable salt of the dihydroxy open acid form of a statin selected from the group consisting of lovastatin and simvastatin.

10

22. The method of claim 21 wherein the compound is a pharmaceutically acceptable salt of dihydroxy open acid simvastatin.

15

23. The method of claim 22 wherein the compound is a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin.

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24. The method of claim 23 wherein the compound is a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin having an x-ray powder diffraction pattern obtained using CuK α radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å.

25

25. The method of claim 1 wherein 10% or less by weight of the compound in the delayed-release dosage form is released in the stomach.

30

26. The method of claim 1 wherein 5% or less by weight of the compound in the delayed-release dosage form is released in the stomach.

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27. The method of claim 1 wherein 1% or less by weight of the compound in the delayed-release dosage form is released in the stomach.

167
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28. An orally administrable pharmaceutical composition comprising a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof and a pharmaceutically acceptable carrier,
5 formulated in a delayed-release dosage form wherein release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

29. The pharmaceutical composition of claim 28 wherein
10 the composition is enterically coated.

30. The pharmaceutical composition of claim 29 wherein
the composition is formulated in an enterically coated time controlled-
release pharmaceutical dosage form.
15

31. The pharmaceutical composition of claim 28 wherein
the composition is formulated in a drug delivery device comprised of:
(A) a compressed core prepared from an admixture comprising:
20 (i) a therapeutically effective amount of the compound;
and
(ii) a polymer which upon hydration forms gelatinous
microscopic particles; and
(B) a water insoluble, water impermeable polymeric coating
comprising a polymer and a plasticizer, which surrounds and
25 adheres to the core, the coating having a plurality of formed
apertures exposing between about 1 and about 75% of the core
surface;
and wherein the release rate of the compound from the device is a
function of the number and size of the apertures.

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32. The pharmaceutical composition of claim 31 wherein
the drug delivery device is enterically coated.

33. A process for preparing an orally administrable
35 pharmaceutical composition comprising combining a compound

~~169~~
138

TITLE OF THE INVENTION

DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE INHIBITORS

5 ABSTRACT OF THE DISCLOSURE

The instant invention provides methods and pharmaceutical compositions for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, comprising orally

10 administering a therapeutically effective amount of a compound selected
from a dihydroxy open acid statin and a pharmaceutically acceptable
salt or ester thereof in a delayed-release pharmaceutical dosage form to
a patient in need of such treatment wherein substantial release of the
compound from the dosage form is delayed until after passage of the
15 dosage form through the stomach.

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139

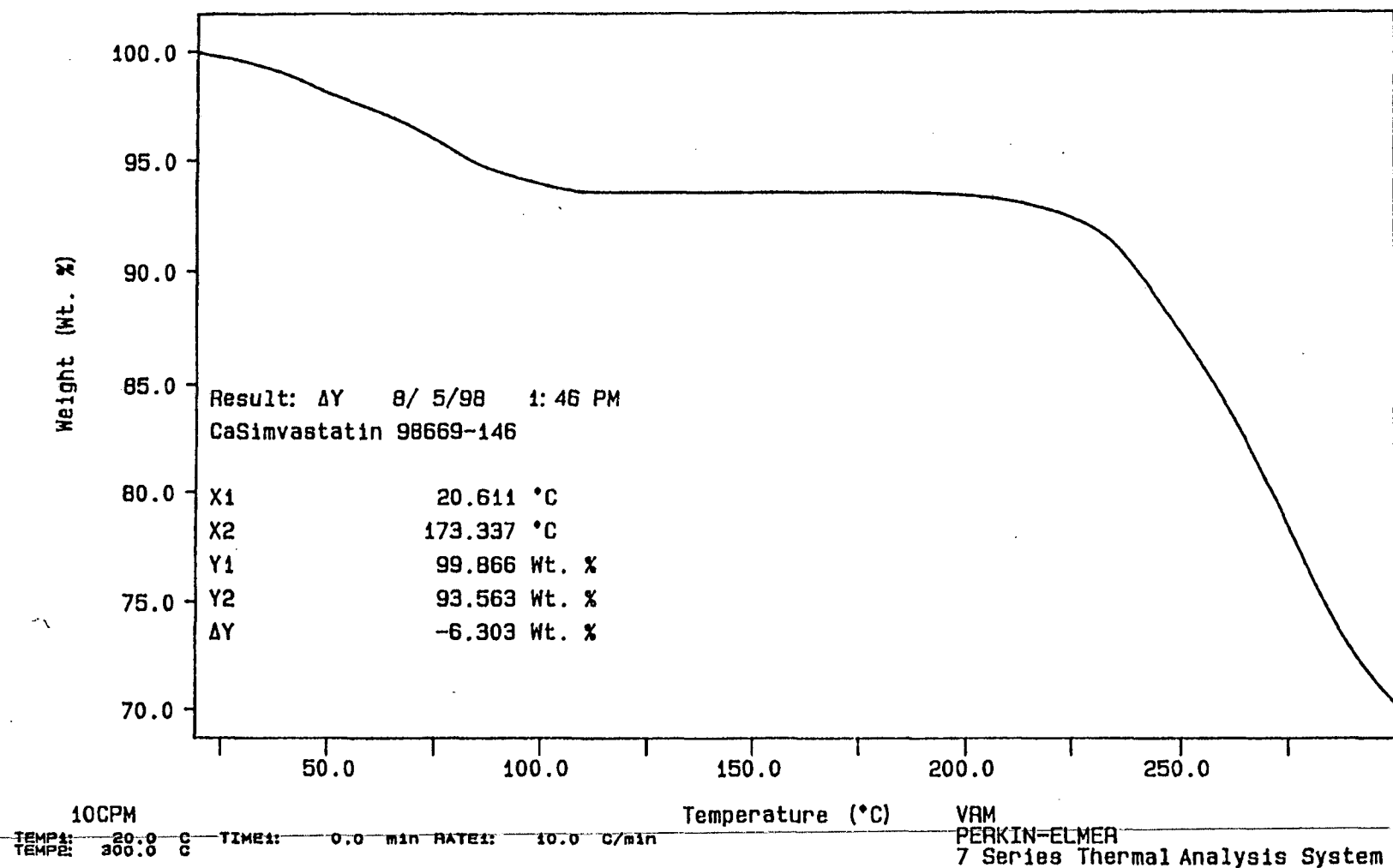
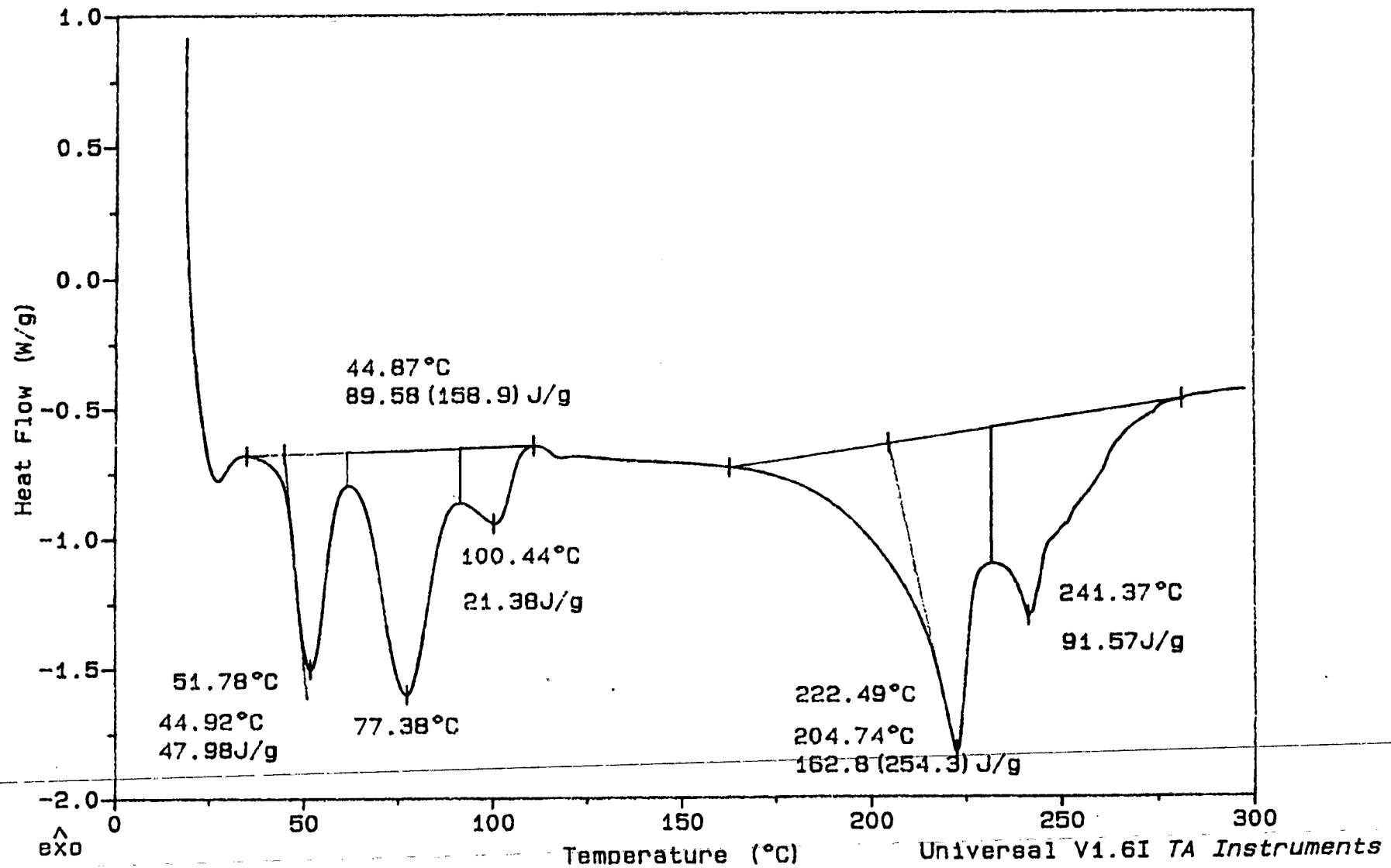


Figure 1.

139

Figure 2: 668020" 42222709

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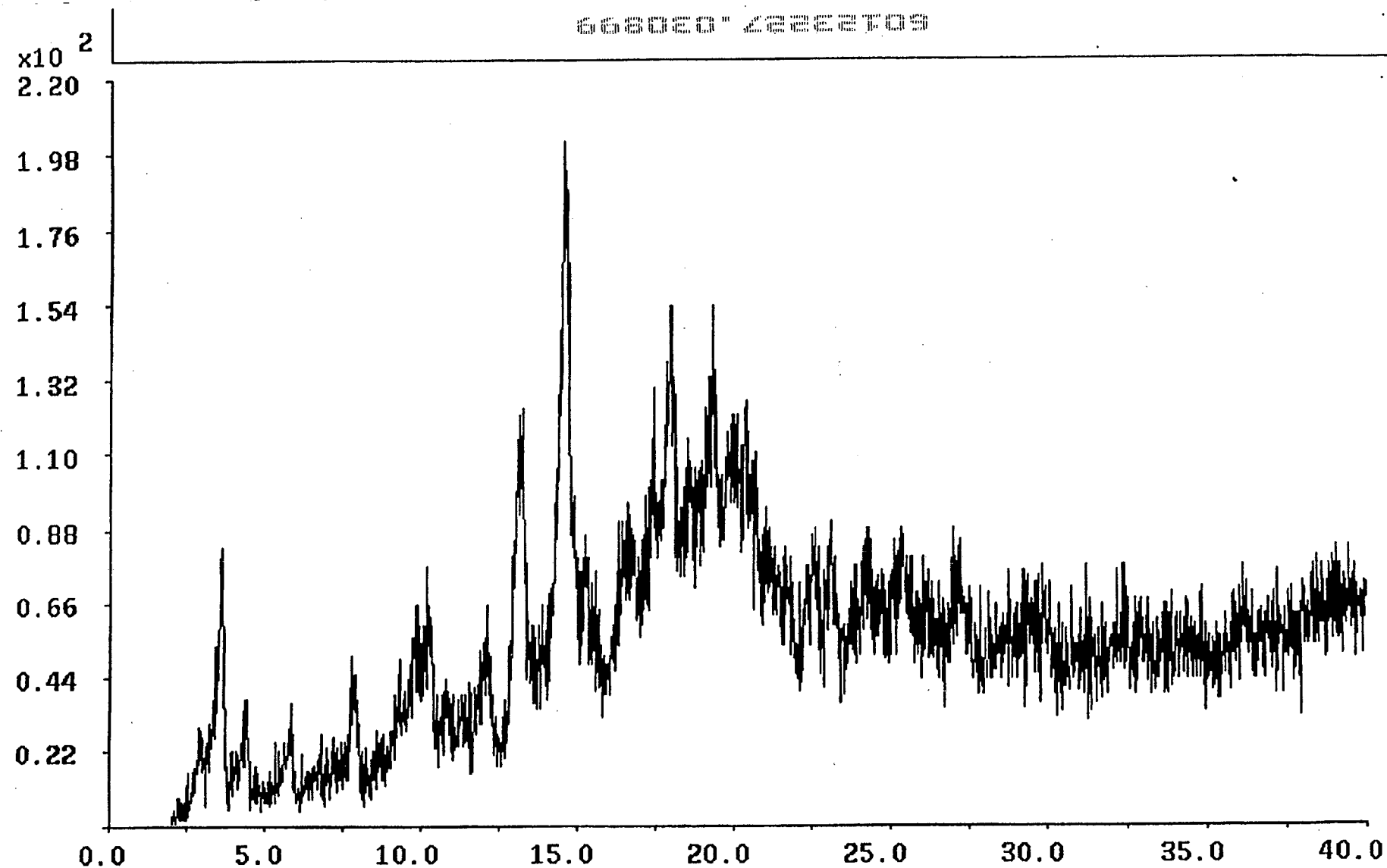


Figure 3.

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Febrero 23, 2000
Traducción Oficial No. 0218
REF:MERCK & CO;INC
Patente No.: 09/264,744

Merck & Co; Inc
Caso - 204164

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
OFICINA DE MARCAS Y PATENTES

Febrero 07, 2000

Por medio del presente documento se certifica que adjunto se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud:09/264,744

Fecha de Registro: Marzo 09,1999

Autorizado por:

COMISIONADO DE MARCAS Y PATENTES

Firma: H. PHILLIPS

Funcionario Encargado de Certificaciones

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Edwards
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Rev. 8-87 Febrero de 1996

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TRAMITE UTIL PARA SOLICITUD DE PATENTE

(solo para solicitudes no provisionales bajo el codigo 37 CFR 1.53 (b))

No. de Caso :20416

Número Total de páginas: 42

Primer nombre del inventor o solicitante identificado:

JOSE M.VEGA.

No de envio de Correo Postal Certificado al Destinatario

EM358363497

ELEMENTOS PARA LA SOLICITUD

(Ver capítulo MPEP 600 referente a los contenidos en la solicitud de patentes)

1. ☒ Formulario para trámites de honorarios
2. ☒ Especificaciones Páginas en total [34]
3. ☒ Gráfica (s) (35 USC 113) Páginas en total [3]
4. Declaración Juramentada Páginas en total []
 - a. [] Ultimo documento ejecutado (original y copia)
 - b. [] Copia de solicitud anterior 37 CFR 1.63 (d)
(para continuidad/divisoria llenar el espacio 14)
 - i. SUPRESION DE INVENTOR (ES)

Documento firmado con supresión adjunta

Inventor(es) nombrados en solicitud anterior

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P.O. Box 541 - February 2006

176
144

Ver 37. CFR 1.63 (d) (2) y 1.33(b)

5. Incorporación por referencia (aplicable si el espacio 4b se encuentra marcado)

La totalidad de la información de la solicitud anterior de la cual una copia juramentada o declaración se adjunta bajo el espacio número 4b, se considera como parte de la información de la presente solicitud y por lo tanto se incorpora mediante referencia en la misma.

6. Secuencia de presentación de nucleotido o Secuencia de Amino Acidos
(si aplica y es necesario)

- a. ____ Copia legible en Computador
b. ____ Documento impreso (igual a la copia del computador)
c. ____ Certificado que verifique la identidad de las copias anteriores

Enviar Correo a la Siguiete Dirección:

Assistant Commissioner for Patents

Box Patent Application

Washington , DC 20231

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Edwardo Calado N.
Edwardo Calado Noguera
DIRECTOR GENERAL
REGISTRO DE MARCAS
Rev. 541 1.5.99 de 19.6

177
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7. ☐ Traspaso de Documentos (Caratula y Documento (s))

8. ☐ 37 CFR 3.73(b) Declaración PODER []

Cuando hay un apoderado

9. ☐ Declaracion sobre información del
documento (IDS)PTO-1449 Copias Citaciones IDS []

10. ☐ Correcciones Preliminares

11. [X] Postal con Timbre prepago (MPEP 503)

Debe ser especificado por ítemes)

12. ☐ Copia Certificada de Documentos de Prioridad

Si se reivindica prioridad extranjera

13. ☐ Otros

Declaración (no firmada)

14. SI EXISTE UNA SOLICITUD A CONTINUACION (Marcar el
espacio apropiado y suministre la información requerida

☐ Continuación ☐ Divisoria ☐ Continuación en parte (CIP)

☒ No de solicitud anterior

Eduardo Calado
Eduardo Calado Noguera
"TRADUCTOR OFICIAL"
10-1-2006

15. DIRECCION DE CORRESPONDENCIA

178
146

[X] No. de cliente o etiqueta con código de barra

Cliente Número: 000210

___ Dirección de Correspondencia a continuación

Nombre Carol S. Quagliato

Dirección Merck & Co., Inc., P.O.Box 2000

Ciudad Rahway Estado Nueva Jersey Código Postal: 07065-0907

País USA Teléfono (732) 594-3809 Fax (732)-594-4720

No. de Envío Correo Postal : EM358363497 US

Fecha de depósito: Marzo 9, 1999

Yo, por medio del presente documento certifico que este ha sido enviado por Correo Certificado bajo el Código 37 de Regulaciones Federales § 1.10 como Correo Postal al Destinatario y al Comisionado Asistente para Patentes, Box Patent Application, Washington, DC., 20231.

Enviado por: IRENE SAMIT

Fecha: Marzo 9, 1999

Edwards Calado K.
Edwards Calado Neguera
"INTELECTUAL PROPERTY"
NO. 12 100 100 100 100
Rev. 341 100 100 100 100

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147

REIVINDICACIONES:

1. Un método para inhibir HMG-CoA reductasa, el cual consiste en un suministro oral terapéutico, de una cantidad eficaz de un compuesto seleccionado de un ácido-abierto de dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo, en una forma dosis farmacéutica de liberación retardada a un paciente que necesite dicho tratamiento en el cual la liberación substancial del compuesto da la forma de dosis es retardada hasta el transcurso de la dosis hasta el estómago.

2. El método de acuerdo a la Reivindicación 1, en el cual el compuesto es suministrado en una forma de dosis farmacéutica revestida entéricamente.

3. El método de acuerdo a la reivindicación 1 en el cual el compuesto se suministra de una forma de dosis farmacéutica con tiempo de liberación controlada, revestida y entérica.

4. El método de acuerdo a la Reivindicación 1 en el cual el compuesto se suministra en un dispositivo que consta de:

Edwardo Calado Nogueira
"IRADIADOR OFICIAL"
MÉDICO ESPECIALISTA
R. N. 1.111.011.111.0

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(A) la parte central comprimida y preparada de una mezcla que consta de:

(i) una cantidad terapéuticamente eficaz del compuesto;

y

(ii) un polímero el cual sobre hidratación forma partículas microscópicas gelatinosas; y

(B) un revestimiento de polimerico impermeable al agua, insoluble en agua el cual consta de un polímero y plastificados, el cual se adhiere alrededor de la parte central, y el revestimiento tiene una pluralidad de formas abiertas que se exponen aproximadamente de 1 hasta alrededor de 75% de la superficie de la parte central; y donde el promedio de liberación del compuesto del dispositivo es una de las funciones y tamaño de número de aperturas.

5. El método de la Reivindicación 4 en la cual la liberación del dispositivo de la droga es entérico y revestido.

6. Un método para tratar la hipercolesteromia, la cual consta en el suministro oral de una cantidad terapéuticamente eficaz de un compuesto seleccionado de ácido abierto dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo, en una forma de dosis de acción retardada

Calado
Eduardo Calado
OFFICIAL
Rev

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para un paciente que necesite de dicho tratamiento en el cual la liberación del compuesto del dispositivo de dosis se retarda hasta que la droga pase por el estomago.

7. Un método para prevenir o reducir el riesgo de desarrollar la enfermedad aterosclerótica la cual consiste en suministrar oralmente una cantidad eficaz profiláctica del compuesto seleccionado de un ácido abierto dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo en una forma de dosis farmaceutica de liberación retardada, a una persona que se encuentre en riesgo de desarrollar la enfermedad aterosclerótica en el cual la liberación substancial del compuesto de la forma de dosis se retarda hasta que esta haya pasado a través del estómago.

8. El método de acuerdo a la Reivindicación 7 en la cual la enfermedad aterosclerótica es seleccionada de una enfermedad cardiovascular, enfermedad cerebrovascular y una enfermedad del vaso periférico.

9. El método de acuerdo a la Reivindicación 8 en la cual la enfermedad cardiovascular es una enfermedad coronaria.

10. Un método para tratar la enfermedad aterosclerótica la cual consta en suministrar oralmente una cantidad eficaz del compuesto seleccionado de

Eduardo
Eduardo Calado Segura
"TRADUCCIONES" 6

187
156

un ácido abierto dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo en una dosis farmacéutica de liberación retardada a un paciente que necesite dicho tratamiento en el cual la liberación substancial del compuesto de la forma de dosis es retardada hasta que pase la dosis a través del estómago.

11. El método de acuerdo a la Reivindicación 10 en la cual la enfermedad aterosclorotica es seleccionada de una enfermedad cardiovascular, enfermedad cerebrovascular y una enfermedad de vaso periférico.

12. El método de acuerdo a la Reivindicación 11 en la cual la enfermedad cardiovascular es una enfermedad coronaria.

13. Un método para prevenir o reducir el riesgo que ocurra o vuelva a repetirse la enfermedad aterosclerótica la cual consiste en suministrar oralmente una cantidad eficaz terapéutica del compuesto seleccionado de un ácido abierto dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo, en una forma de dosis farmacéutica de liberación retardada, a una persona que se encuentre en riesgo de desarrollar la enfermedad aterosclerótica en el cual la liberación substancial del compuesto de la forma de dosis se retarda hasta que esta haya pasado a través del estómago.

Edmundo C. Noguera
"TRADUCTOR OFICIAL"
ESPAÑOL-INGLES
P. 106

183
151

14. El método de acuerdo a la Reivindicación 13 en la cual la persona que recibe el compuesto tiene la enfermedad aterosclerótica.

15. El método de acuerdo a la Reivindicación 13 en la cual la persona que recibe el compuesto se encuentran en riesgo de desarrollar la enfermedad aterosclerótica.

16. El método de acuerdo a la Reivindicación 13 en al cual el caso de la enfermedad aterosclerótica es seleccionado de una enfermedad coronaria, y un caso cerebrovascular de claudicación intermitente.

17. El método de acuerdo a la reivindicación 16 en la cual el evento de la es seleccionado de una enfermedad coronaria, infarto del miocardio y procedimiento de revascularización coronaria.

18. El método de acuerdo a la reivindicación 17 en la cual el evento cerebrovascular es seleccionado de un accidente cerebrovascular y un ataque isquémico pasajero.

19. El método de acuerdo a la Reivindicación 1 en la cual el compuesto es una sal farmacéuticamente aceptable de un ácido abierto dihidroxi statin.

Eduardo Calado Neguera
"FIRMADO POR OFICIAL"
NORMA ESTÁNDAR-INGLES
Rev. 19. Febrero de 1996

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24. El método de acuerdo a la Reivindicación 23 en la cual el compuesto es una forma cristalina hidratada de sal de calcio de ácido abierto dihidroxi simvastatina el cual tiene un patrón polvo de difracción de rayos x obtenido

ene un patrón polvo de
Edwardo Calado
 Edwardo Calado Vagueria
 1911-1912
 1913
 1914
 1915
 1916

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de radiaciones CuKa caracterizadas en que las reflexiones en los espacios-d
de 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60,
3.93, 3.84, 3.67, 3.51 y 3.28A.

25. El método de acuerdo a la reivindicación 1 en el cual 10% o menos
por el peso del compuesto es en dosis de acción retardada la cual se libera
en el estómago.

26. El método de acuerdo a la Reivindicación 1 en el cual 5% o menos
del peso del compuesto en la forma de dosis de acción retardada la cual se
libera en el estómago.

27. El método de acuerdo a la Reivindicación 1 en la cual 1% o menos
por el peso del compuesto es en forma de dosis de acción retardada la cual
se libera en el estómago.

28. Una composición farmacéutica de suministro oral la cual consta de
una cantidad terapéuticamente eficaz de un compuesto seleccionado de un
ácido abierto dihidroxi statin y una sal farmacéuticamente aceptable o éster
de la misma y un portador farmacéuticamente aceptable, formulado en la
forma de dosis de acción retardada en la cual la liberación del compuesto
de la forma de dosis es retardada hasta que pase a través del estómago.

Edwardo Calvo
Edwardo Calvo Soguer
"TRADUCTOR OFICIAL"
ING. QUÍMICO

29. La composición farmacéutica de la reivindicación 28 en la cual la composición se encuentra totalmente revestida.

30. La composición farmacéutica de acuerdo a la composición 29 en la cual la composición es formulada en una forma de dosis farmacéutica de tiempo de liberación controlada, revestida y entérica.

31. La composición farmacéutica de acuerdo a la reivindicación 28 en el cual la composición formulada se suministra en un dispositivo que contiene la droga la cual consta de:

(A) la parte central comprimida y preparada de una mezcla que consta de:

(i) una cantidad terapéuticamente eficaz del compuesto;

y

(ii) un polímero el cual con la hidratación forma partículas microscópicas gelatinosas; y

(B) un revestimiento de polimérico impermeable al agua, insoluble en agua el cual consta de un polímero y plastificados, el cual se adhiere alrededor de la parte central, y el revestimiento tiene una

el revestimiento tiene

187/155

pluralidad de formas abiertas que se exponen aproximadamente de 1 hasta alrededor de 75% de la superficie de la parte central; y donde el promedio de liberación del compuesto del dispositivo es una de las funciones y tamaño de número de aperturas.

32. La composición farmacéutica de acuerdo a la reivindicación 31 en el cual el dispositivo de liberación de la droga es totalmente revestido.

33. Un proceso para la preparación de una composición de suministro oral la cual consta en mezclar el compuesto seleccionado de un ácido abierto de dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo con un portador en forma de dosis de acción retardada.

34. Una composición farmacéutica de suministro oral el cual es fabricado con la mezcla de una cantidad terapéuticamente eficaz de un compuesto seleccionado de un ácido abierto de dihidroxi statin y una sal farmacéuticamente aceptable o éster del mismo con un portador farmacéuticamente aceptable en una dosis de acción retardada.

Edwards Calado
FARMACIA CALADO
CALLE 100 N. 100
CALLE 100 N. 100
CALLE 100 N. 100

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Caso:No: 20416

**DECLARACION Y PODER
PARA LA SOLICITUD DE PATENTES DE LOS ESTADOS
UNIDOS**

Yo en mi calidad de abajo mencionado inventor, por la presente declaro:

☒ Yo creo ser el único y primer inventor

☐ primero y co-inventor con los demás inventores menciuonados a continuación:

El cual se reivindica pidiendo la solicitud de patente de invención con el título:

“ÁCIDOS -ABIERTOS DE DIHIDROXI Y SALES DE HMG-CO INHIBIDORES DE
REDUCTASA.”

cuya especificaciones:

(Indique uno)

☒ se encuentra adjuntas a la presente.

☐ Fué registrado en _____ como

No Serial de la Solicitud _____

Edvarado Palacios
Edvarado Palacios "Voguera"
"TRANSLADOR OFICIAL"
BUREAU OF PATENT TRANSLATIONS
WASHINGTON, D.C.
1966

189
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y fué revisado en _____
(si aplica)

Yo por medio del presente documento declaro que he revisado y
entiendo el contenido de las especificaciones anteriormente
mencionadas, incluyendo las reivindicaciones.

Yo tengo conocimiento sobre mi obligación de revelar toda
información que sea parte del material patentable tal como lo define
el Artículo 37 C.F.R. §1.56.

Yo por la presente reivindico beneficios de prioridad bajo el Título
35, del Código de regulaciones Federales de los Estados Unidos,
Sección 119 (a) -(d) de cualquiera de la solicitud(es) extranjera para
patente (s) o certificado como inventor o § 365 (a) de cualquier
Solicitud para Patente Internacional con una fecha de registro
anterior de aquella solicitud que aparece en la cual se reivindica
prioridad.

Solicitudes extranjeras con una fecha de registro anterior (es)			Prioridades Reivindicadas	
_____	_____	_____	[]	[]
(Nombre)	(Pais)	Día/Mes/año de registro	Si	No
_____	_____	_____	[]	[]
(Nombre)	(Pais)	Día/Mes/año de registro	Si	No

Eduardo Calado
Eduardo Calado Noguera
"INVENTOR OFICIAL"
BOGOTÁ, COLOMBIA
12 de febrero

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(Fecha de registro)

Armas y Patentes tal con
Eduardo Calado Vagueria
"FRASES OFICIALES"
"FRASES OFICIALES"
"FRASES OFICIALES"

19159

define la norma del Código 37 C.F.R. §1.56 el cual se hizo efectiva entre las fechas de registro de la solicitud anterior y la fecha de registro Internacional PCT de esta solicitud.

(No Serial Solicitud) (Fecha de Registro) (Estatus)(patentado,pendiente,
abandonado)

No. de Caso _____

(No Serial Solicitud) (Fecha de Registro) (Estatus)(patentado,pendiente,
abandonado)

No. de Caso _____

(No Serial Solicitud) (Fecha de Registro) (Estatus)(patentado,pendiente,
abandonado)

No. de Caso _____

Como Inventor, yo por la presente nombro al (los) siguiente (s)
abogados y /o representante (s) para procesar esta solicitud y llevar a
cabo toda transacción de negocios en la Oficina de Marcas y Patentes
relacionadas con la presente:

Carol S. Quagliato

No. Registro: 35,330

Melvin Winokur

No. Registro: 32,763

Edw. de la Cruz
Eduardo de la Cruz
"DIRECTOR OFICIAL"
19159

192
160

Carol S. Quagliato
Patent Department
Merck & Co., Inc
P.O. Box 2000
Rahway, NJ 07065-0907
Teleefono: (732) 594-3809

Yo, por la presente afirmo que toda declaración presentada es de mi entero conocimiento, fiel y verdadera y tengo presente que toda falsa declaración es castigada mediante una multa o el encarcelamiento, o ambos, bajo la Sección 1001 del Título 18 del Código de los Estados Unidos, y que cualquier declaración puede comprometer la validez de esta solicitud o de cualquier patente expedida inmediatamente después.

Yo, por la presente afirmo que toda declaración presentada es de mi entero conocimiento, fiel y verdadera y tengo presente que toda falsa declaración es castigada mediante una multa o el encarcelamiento, o ambos, bajo la Sección 1001 del Título 18 del Código de los Estados Unidos, y que cualquier declaración puede

Edw. Calado
"REGISTRADOR OFICIAL"
"SECRETARIO OFICIAL"
"SECRETARIO OFICIAL"
"SECRETARIO OFICIAL"

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161

comprometer la validez de esta solicitud o de cualquier patente expedida inmediatamente después.

También doy fe y conocimiento de que revelación, información y cifras anteriormente mencionadas en la especificación de la solicitud y reivindicaciones son absolutamente verdaderas.

Nombre completo: Jose N. Vega

No hay firma del inventor:

Fecha:

Ciudadanía: USA

Residence: Trappe, Pa 19426

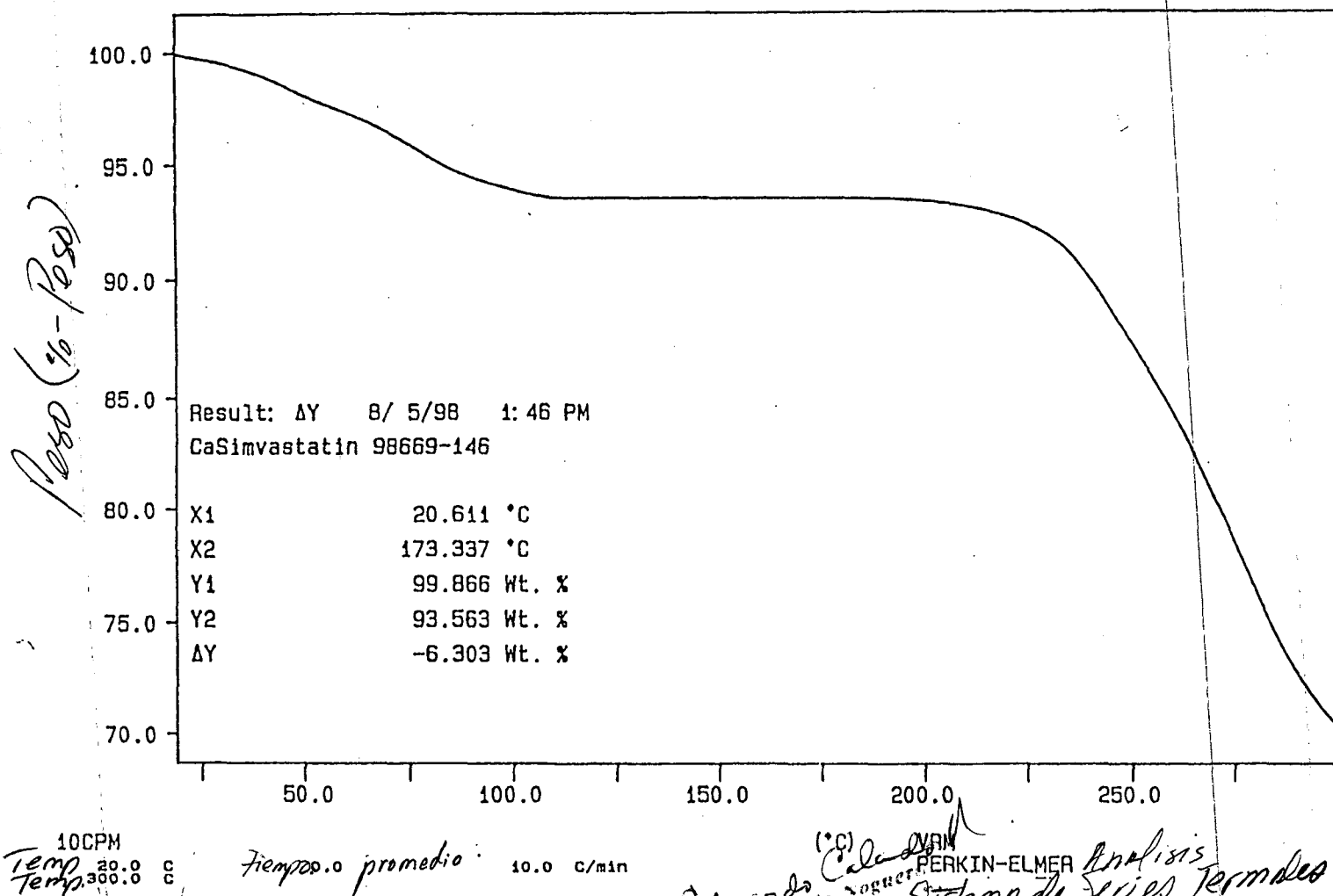
Dirección Correo Postal: 10 Sentry Parkway, Blue Bell, Pa 19422

Edwards Calado
Eduardo Calado Saguera
"FIRMA OFICIAL"
COMISIONADOS
1986

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GRAFICA 1

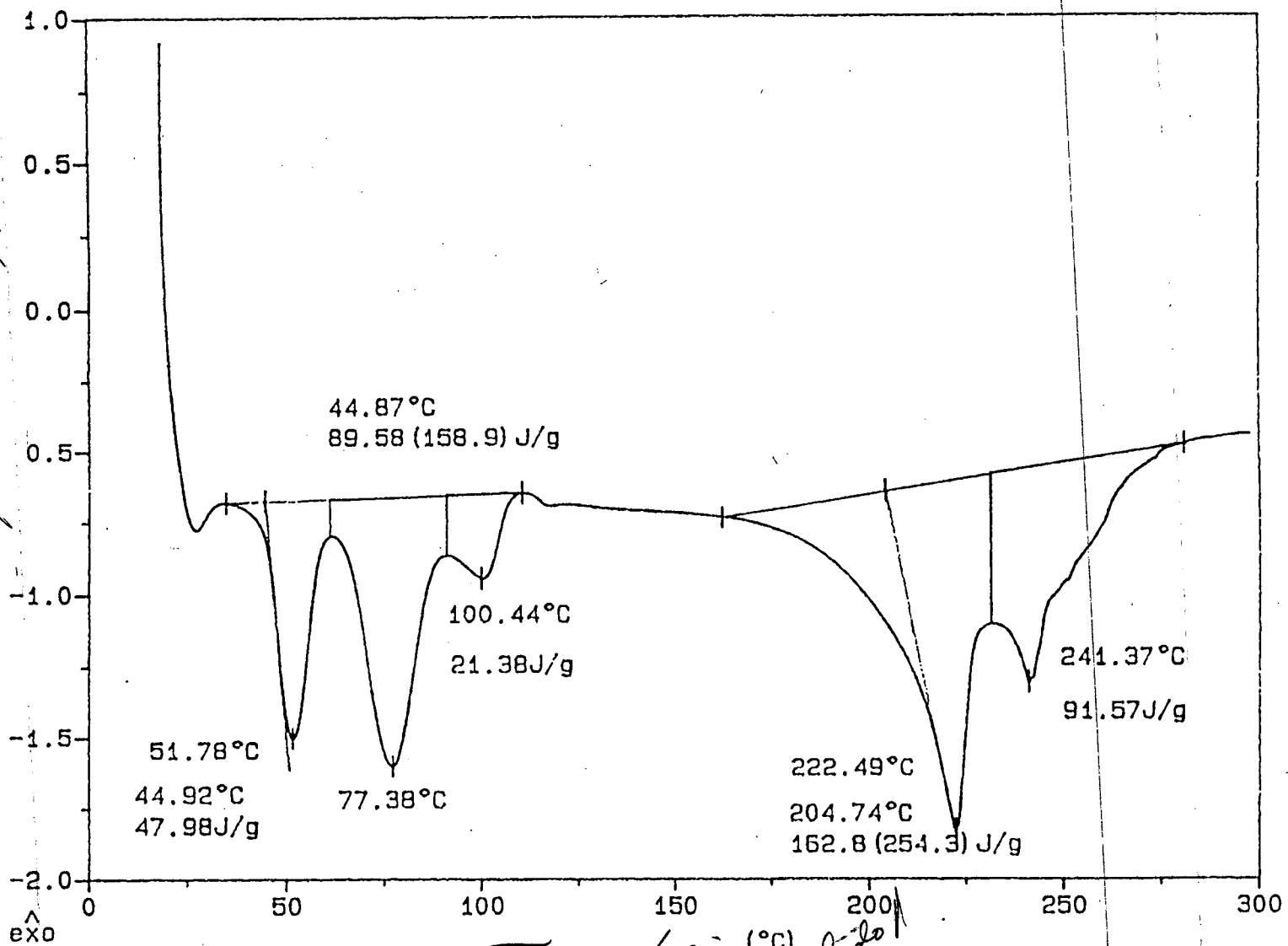
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Edwards Calorimetric Analysis
Perkin-Elmer
STRATEGIC THERMAL ANALYSIS
SYSTEM

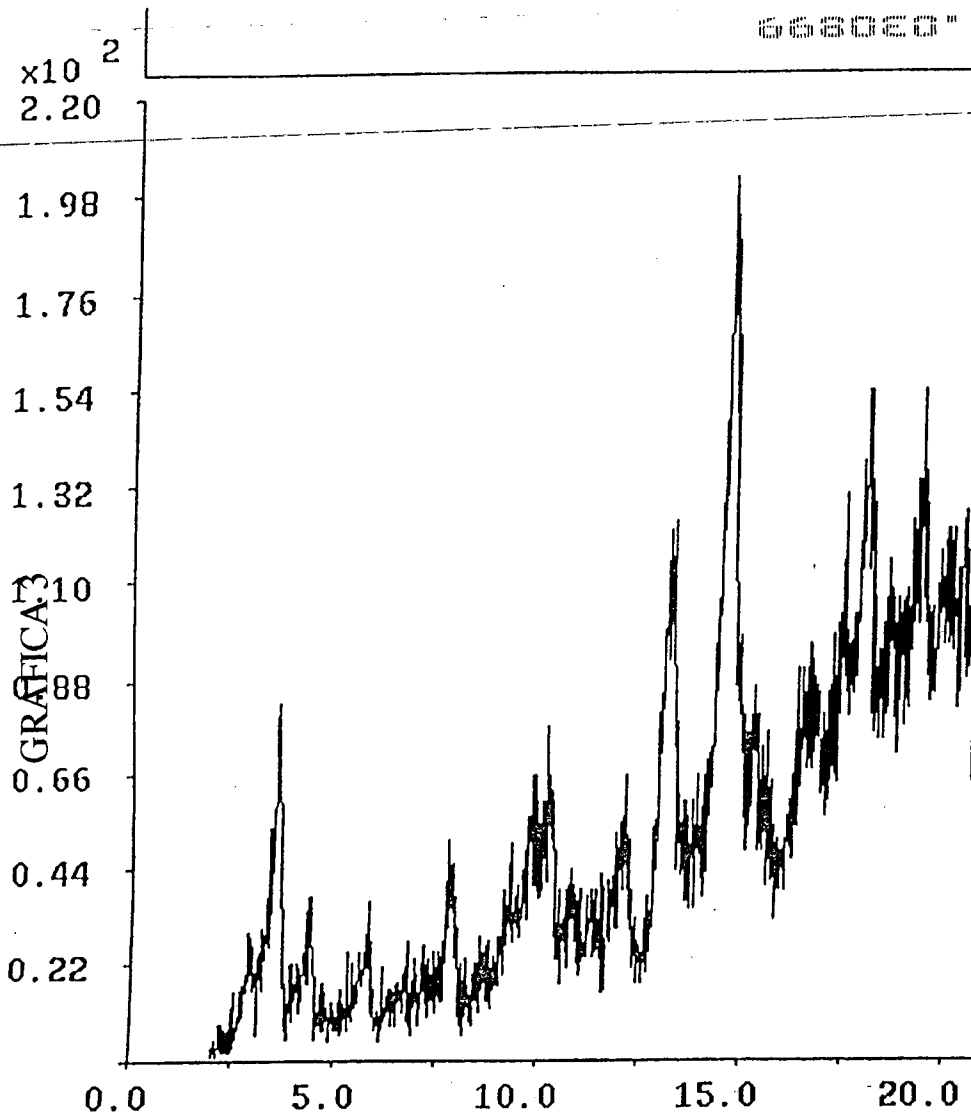
GRAFICA 2

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Temperatura (°C)
Eduardo Calvo

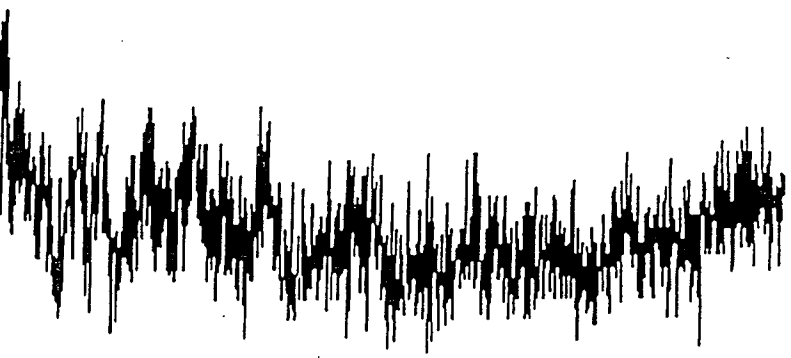
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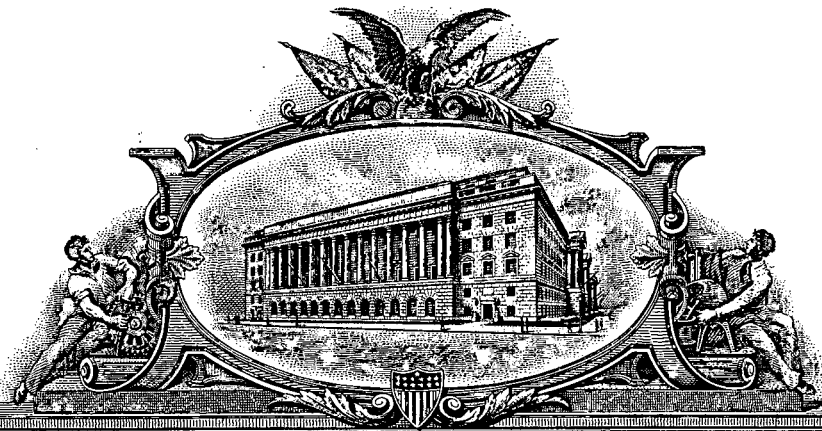
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Edwards Calves



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 07, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/264,744

FILING DATE: *March 09, 1999*



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

H. Phillips
H. PHILLIPS
Certifying Officer

03/09/99



JCS30 U.S. PTO

Please type a plus sign (+) inside this box ☐

PTO/SB/05 (12/97)

**UTILITY
PATENT
APPLICATION
TRANSMITTAL**

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. 20416

Total Pages 42

First Named Inventor or Application Identifier

Jose M. Vega

Express Mail Label No.

EM358363497US

JCS11 U.S. PTO
09/26/94

03/09/99

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☒ Fee Transmittal Form
(Submit an original, and a duplicate for fee processing)
2. ☒ Specification [Total Pages 34]
3. ☒ Drawing(s) (35 USC 113) [Total Sheets 3]
4. Oath or Declaration [Total Pages]
 - a. ☐ Newly executed (original or copy)
 - b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 14 completed)
[Note Box 5 below]
 - i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33 (b).
5. ☐ Incorporation By Reference (useable if Box 4b is checked). The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
 - a. ☐ Computer Readable Copy
 - b. ☐ Paper Copy (identical to computer copy)
 - c. ☐ Statement verifying identity of above copies

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231**ACCOMPANYING APPLICATION PARTS**

7. ☐ Assignment papers (cover sheet & document(s))
8. ☐ 37 CFR 3.73(b) Statement (when there is an assignee) ☐ Power of Attorney
9. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
10. ☐ Preliminary Amendment
11. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
12. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
13. ☒ Other:
Declaration (unsigned)

14. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. ____/____**15. CORRESPONDENCE ADDRESS**☒ Customer Number or Bar Code Label

Customer No. 000210

(Insert Customer No. or Attach bar code here)

NAME	Carol S. Quagliato				
ADDRESS	Merck & Co., Inc., P. O. Box 2000				
CITY	Rahway	STATE	NJ	ZIP CODE	07065-0907
COUNTRY	USA	TELEPHONE	732-594-3809	FAX	732-594-4720

(computer generated form No. U6 - Merck & Co., Inc., 12/97)

EXPRESS MAIL CERTIFICATE

DATE OF DEPOSIT March 9, 1999

EXPRESS MAIL NO. EM358363497US

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, BOX PATENT APPLICATION, WASHINGTON, D.C. 20231.

MAILED BY

DATE

March 9, 1999

TITLE OF THE INVENTION
DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE
INHIBITORS.

5 FIELD OF THE INVENTION

The instant invention relates to the use of dihydroxy open acid statins and salts thereof, which are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, in a delayed-release dosage formulation, and to a particular crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin referred to herein as compound I.

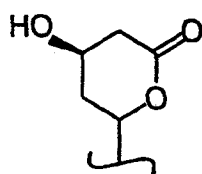
BACKGROUND OF THE INVENTION

It has been clear for several decades that elevated blood cholesterol is a major risk factor for coronary heart disease (CHD), and many studies have shown that the risk of CHD events can be reduced by lipid-lowering therapy. Prior to 1987, the lipid-lowering armamentarium was limited essentially to a low saturated fat and cholesterol diet, the bile acid sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of these treatments have limited efficacy or tolerability, or both. With the introduction of lovastatin (MEVACOR®; see US Patent No. 4,231,938), the first inhibitor of HMG-CoA reductase to become available for prescription in 1987, for the first time physicians were able to obtain comparatively large reductions in plasma cholesterol with very few adverse effects.

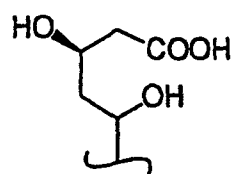
In addition to the natural fermentation products, mevastatin and lovastatin, there are now a variety of semi-synthetic and totally synthetic HMG-CoA reductase inhibitors, including simvastatin (ZOCOR®; see US Patent No. 4,444,784), pravastatin sodium salt (PRAVACHOL®; see US Patent No. 4,346,227), fluvastatin sodium salt (LESCOL®; see US Patent No. 5,354,772), atorvastatin calcium salt (LIPITOR®; see US Patent No. 5,273,995) and cerivastatin sodium salt (also known as rivastatin; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors, are

200
168

described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996). The HMG-CoA reductase inhibitors described above belong to a structural class of compounds which contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open-acid, and are often referred to as "statins." An illustration of the lactone portion of a statin and its corresponding open-acid form is shown below.

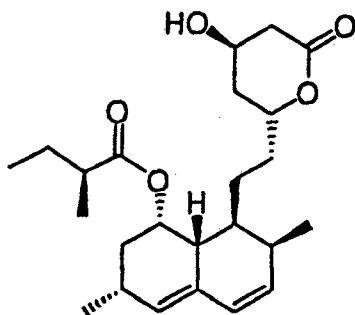


Lactone

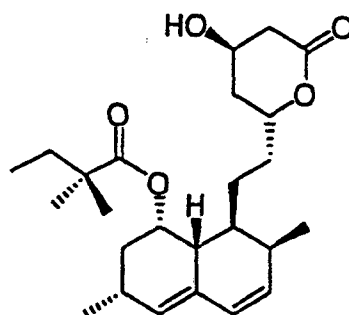


Dihydroxy Open-Acid

Salts of the dihydroxy open-acid can be prepared, and in fact, as noted above, several of the marketed statins are administered as the dihydroxy open acid salt forms. Lovastatin and simvastatin are marketed worldwide in their lactonized form. Lovastatin is shown as structural formula II, and simvastatin is shown as structural formula III, below.



II



III

The lactonized forms of the statins are not active inhibitors of HMG-CoA reductase, but the dihydroxy open acid forms are. It is known that condensation of the dihydroxy open acid form of statins to the

201
169

corresponding lactonized form occurs under acidic conditions, that is at about pH 4 or under.

Therefore, due to the low gastric pH of the stomach, a statin conventionally administered by oral dosing in its lactone form will

- 5 remain largely in its lactone form in the stomach. The vast majority of the drug will still be in the lactone form at the time of absorption from the intestine following oral dosing with the lactone. After absorption, the lactone enters the liver and it is in the hepatocytes that the lactone can be metabolized to the active open acid form, a reaction catalyzed by
- 10 two hepatic esterases or "lactonases," one which is in the cytosolic and the other in the microsomal fraction. Once in the blood there is an additional plasma esterase which can also hydrolyze the lactone to the open acid. There may be some minimal chemical, i.e., non-enzymatic, hydrolysis that occurs in blood or in the liver; however, at the pH in blood
- 15 and liver, there should not be any lactonization, i.e., conversion of open acid back to the lactone.

- A statin conventionally administered by oral dosing in its dihydroxy open acid form or a pharmaceutically acceptable salt or ester thereof will tend to convert to its lactone form in the acidic environment
- 20 of the stomach, so that a mixture of the open ring and the corresponding closed ring forms will co-exist there. For example, see M.J. Kaufman, International Journal of Pharmaceutics, 1990, 66(Dec 1), p. 97-106, which provides hydrolysis data that are used to simulate the extent of drug degradation that occurs in acidic gastric fluids following oral
- 25 administration of several structurally related hypocholesterolemic agents, including simvastatin and lovastatin. Therefore, even after conventional oral dosing with a dihydroxy open acid statin or a salt or ester thereof, a mixture of the open acid and the corresponding lactone form of the drug would exist by the time of absorption from the intestine.

- 30 The preparation of the naturally occurring compound lovastatin and the semi-synthetic analog simvastatin leads to a mixture of the lactone and the open-ring dihydroxy acid forms. Several procedures have been published describing ways to make simvastatin from lovastatin, and most proceed through a lactone ring opening step at
- 35 some point in the process and sometimes formation of a salt at the

202
170

resulting carboxy acid, and end with a ring-closing step in order to make the final simvastatin product. For example, U.S. Patent No. 4,820,850 describes a process for making simvastatin which involves opening the lactone ring of lovastatin and forming an alkyl-amide at the resulting carboxy acid, followed by protection of the two hydroxy groups and methylation of the 8' acyl sidechain. After the methylation step, the hydroxy protecting groups are removed, the amide is hydrolyzed to the free acid and an ammonium salt of the free acid is formed, followed by a step to re-lactonize the ring. In U.S. Patent No. 4,444,784, the 8'-acyl sidechain of lovastatin is removed and the lactone ring opened in the first step, followed by re-lactonization of the ring and protection of its hydroxy group. Next, the 8' position is acylated to introduce the simvastatin sidechain and a deprotection step is performed to obtain the simvastatin final product. In another process disclosed in U.S. Patent No. 4,582,915, the potassium salt of the ring opened form of lovastatin is methylated at the 8' acyl sidechain, the free acid is then re-generated, and the dihydroxy open acid moiety is re-lactonized.

Several pharmaceutically acceptable salt forms of dihydroxy open acid statins are known in the art, as shown by the marketed salt forms of pravastatin, fluvastatin, atorvastatin and cerivastatin described above. Some salt forms of dihydroxy open acid simvastatin have been previously described, for example the ammonium salt and the potassium salt which were used as intermediates in the synthetic processes described above. Chemical Abstracts also discloses a variety of salt forms of dihydroxy open acid simvastatin, including a calcium salt having Registry No. 151006-18-7, which was referenced from a genus disclosed in U.S. Patent No. 5,223,415, assigned to Merck & Co., Inc. Although there are no calcium salts exemplified in the patent, the general description of salt preparation taught in this patent would lead to an amorphous calcium salt product.

Since becoming available, millions of doses of simvastatin have been administered and these drugs have developed an excellent safety record. However, as noted in the Physician's Desk Reference (PDR), in rare instances myopathy has been associated with the use of all statins, including simvastatin. The mechanism for statin-related

203
171

myopathy is currently poorly understood. It is also known that many drugs, including certain statins such as simvastatin, are metabolised in the liver and intestine by the cytochrome P450 3A4 (CYP 3A4) enzyme system. As also noted in the PDR, there are adverse drug interaction concerns if a potent inhibitor of CYP3A4, such as itraconazole, and a CYP3A4-metabolized statin are used together, and some cases of myopathy were found to have occurred in patients taking such a drug combination. Simvastatin has been administered to over 20 million patients worldwide in the past 11 years and has been demonstrated to be remarkably safe. However, the very low risk of myopathy is substantially increased when simvastatin is given together with potent inhibitors of CYP3A4. This increased risk is believed to be related to the increased plasma levels of HMG-CoA reductase inhibitory activity resulting from the reduced metabolic elimination of simvastatin in the presence of a potent inhibitor of CYP3A4. While the overall safety record for simvastatin is exceptional, it would be desirable to further optimize its safety profile by reducing the potential for drug interactions with inhibitors of CYP3A4. It would also be desirable to further reduce the already low rate of occurrence of myopathy associated with the use of all statins.

Applicants have now discovered that dihydroxy open acid statins may be less reliant on CYP3A4 metabolism than their closed ring lactonized counterparts. The instant invention involves methods and pharmaceutical compositions for orally administering open-ring dihydroxy open acid statins and salts and esters thereof, which are HMG-CoA reductase inhibitors, in such a way so as to minimize conversion to their lactonized counterparts. This allows for delivery of a dihydroxy open acid statin without its lactone counterpart directly to the absorptive mucosa of the small intestine thus allowing for absorption of the open acid statin into the portal circulation, penetration by active open acid statin into hepatocytes to achieve enhanced efficacy, and systemic exposure consisting of open acid moieties. More particularly, delayed-release of an orally administered dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof, for example dihydroxy open acid simvastatin or a salt thereof, until after passage through the

204
172

stomach reduces the amount of lactone formed and absorbed in the body. Maintaining the statin in its open acid form in the body thereby reduces the potential for drug interactions between statins whose metabolism is CYP3A4-mediated and other active agents which inhibit the CYP3A4 enzymatic pathway. Moreover, maintaining the statin in its open acid form in the body may have additional clinical benefits for all statins, even for those statins that are not significantly metabolized by the CYP3A4 enzymatic pathway.

In addition, a novel crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin has now been discovered to be a pharmaceutically suitable salt form having desirable physical properties for formulation into an anti-hypercholesterolemic drug composition.

SUMMARY OF THE INVENTION

One object of the instant invention is to provide a method for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

One embodiment of the first object is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is a gel extrusion module (GEM) drug delivery device.

Another embodiment of the first object is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is an enterically coated pharmaceutical dosage form. An additional aspect of this embodiment is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is an enterically coated time controlled-release pharmaceutical dosage form. Yet another aspect of this embodiment is to provide the above-described

method wherein the delayed-release pharmaceutical dosage form is an enterically coated gel extrusion module (GEM) drug delivery device.

The compound used for the above-described object and embodiments may particularly be dihydroxy open acid simvastatin and the pharmaceutically acceptable salts thereof, and more particularly a pharmaceutically acceptable salt thereof.

A second object of the instant invention is to provide novel HMG-CoA reductase inhibitors which are crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, and particularly the compound referred to herein as compound I.

Additional objects are to provide the use of the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, particularly compound I, for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, and also to provide pharmaceutical formulations, including conventional rapid-release, delayed-release and time controlled-release formulations, including the GEM drug delivery device and enterically coated dosage forms, that can be used with the compounds. A further object is to provide a process for making compound I. Additional objects will be evident from the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a thermogravimetry (TG) weight loss curve for compound I obtained under a nitrogen flow at a heating rate of 10°C/minute.

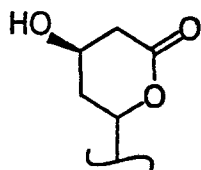
Figure 2 is a differential scanning calorimetry (DSC) curve for compound I obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup.

Figure 3 is an x-ray powder diffraction (XRPD) pattern for compound I. The XRPD pattern was obtained using CuK α radiation. The ordinate or Y-axis is x-ray intensity (cpm) and the abscissa or X-axis is the angle two-theta (2 θ) in degrees.

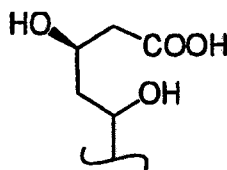
206
174

DETAILED DESCRIPTION OF THE INVENTION

The term "statin(s)" as used herein is intended to be defined as inhibitors of HMG-CoA reductase which belong to a structural class of compounds that contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open acid, wherein the lactone portion of the statin and its corresponding dihydroxy open-acid form is shown below.



Lactone



Dihydroxy Open-Acid

All hydrates, solvates and polymorphic crystalline forms of HMG-CoA reductase inhibitors having the above-described lactone/dihydroxy open acid moiety are included within the scope of the term "statin(s)". Pharmaceutically acceptable salts and esters of the dihydroxy open-acid statins are included within the scope of the term "statin(s)".

Statins inhibit HMG-CoA reductase in their dihydroxy open acid form. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33.

The term "dihydroxy open acid statin(s)" is intended to be defined as statins which contain the dihydroxy open acid moiety, including pharmaceutically acceptable salts and esters thereof. The phrases "dihydroxy open acid statin(s)" and "dihydroxy open acid statin(s) and the pharmaceutically acceptable salts and esters thereof" are used interchangeably herein and are both intended to encompass the open acid and salt and ester forms of the open acid of the statin, unless otherwise indicated. All hydrates, solvates and polymorphic crystalline forms are encompassed within the the scope of the term "dihydroxy open acid statin(s)."

204
175

Examples of dihydroxy open acid statins that may be used with the present invention include but are not limited to the dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof of: lovastatin (see US Patent No. 4,342,767); simvastatin (see US Patent No. 4,444,784), pravastatin, particularly the sodium salt thereof; fluvastatin particularly the sodium salt thereof; atorvastatin, particularly the calcium salt thereof; cerivastatin, particularly the sodium salt thereof, and nisvastatin also referred to as NK-104 (see PCT international publication number WO 97/23200). Pharmaceutically acceptable salts of dihydroxy open acid simvastatin, particularly the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, and more particularly the hydrated calcium salt of dihydroxy open acid simvastatin referred to herein as compound I, are preferred for use in the methods and compositions of this invention.

Herein, the term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, morpholine, 2,4,4-trimethyl-2-pentamine and tris(hydroxymethyl)aminomethane. Pharmaceutically acceptable esters at the carboxylic acid group can be made by treating a dihydroxy open acid statin with an alcohol. Examples of pharmaceutically acceptable esters of dihydroxy open acid statins include, but are not limited to, -C₁₋₄ alkyl and -C₁₋₄ alkyl substituted with phenyl-, dimethylamino-, and acetylamino. "C₁₋₄ alkyl" herein includes straight or branched aliphatic chains containing from 1 to 4 carbon atoms, for example methyl, ethyl, n-propyl, n-butyl, iso-propyl, sec-butyl and tert-butyl.

An object of this invention is to provide methods for reducing the amount of lactonized statin formed and absorbed in the

200
176

body after oral administration of a dihydroxy open acid statin in order to achieve enhanced clinical benefits. A way to achieve this is to administer the dihydroxy open acid statin in a delayed-release pharmaceutical dosage form. A delayed-release pharmaceutical dosage form as defined herein is an orally administerable pharmaceutical dosage form or device that does not release a substantial amount of the active compound until after the dosage form has passed through the stomach. Therefore, substantial release of the active compound would initially occur after entry into the duodenum. By "substantial release," it is intended that 90% or more by weight of the active agent in the delayed-release dosage form is released after entry into the duodenum, and that 10% or less by weight of the active agent in the delayed-release dosage form is released in the stomach. Particularly, the amount of active compound released in the stomach before entry into the duodenum is 5% or less by weight and more particularly 1% or less by weight.

It is to be understood that metabolism of the dihydroxy open acid statins will occur, primarily in the liver, after orally dosing in a delayed-release dosage form. However, since lactonization of the dihydroxy open acid statin would have been substantially avoided by use of a delayed release dosage form, the active and inactive metabolites that are formed will also be in the dihydroxy open acid form. In essence, if the dihydroxy open acid statin is administered in a delayed release dosage form, the internal exposure to lactonized parent compound and also to lactonized active and inactive metabolites will be minimized.

One example of a delayed-release dosage form is an enterically coated dosage form. The enteric coating will not dissolve in the acidic gastric environment, but will dissolve in the higher pH environment of the duodenum. An enterically coated dosage form will therefore not permit release of any significant amount of the active compound from the dosage form in the stomach, but, once the enteric coating dissolves in the duodenum, the active compound will be released. Suitable compositions for enteric coatings that can be used with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see L. Lachman, The Theory and Practice of Industrial Pharmacy, 3rd Ed., H. Liebermann and J. Kanig

209
177

contributors (Lea & Febiger, 1986). The pharmaceutical dosage form that is enterically coated can be a conventional rapid release dosage form or it can be a time controlled-release dosage form. Time controlled-release dosage forms are also well known in the pharmaceutical art, and are designed so as to slowly release the active compound in the body over a period of time, for example over a period of from about 6 to 24 hours. Use of a time controlled-release dosage form is preferred so as to lower the systemic exposure to the active statin.

An example of a delayed-release dosage form that also functions as a time controlled-release dosage form is described in U.S. Patent No. 5,366,738, herein incorporated by reference in its entirety. The controlled-release drug delivery device described in U.S. Patent No. 5,366,738 is known as a gel extrusion module (GEM) delivery device. The GEM device is a drug delivery device for the controlled in situ production and release of a dispersion containing a beneficial agent such as a pharmaceutical drug comprising:

- (A) a compressed core prepared from an admixture comprising:
 - (i) a therapeutically effective amount of the beneficial agent; and
 - (ii) a polymer which upon hydration forms gelatinous microscopic particles; and
- (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the beneficial agent from the device is a function of the number and size of the apertures.

In the GEM device, the polymer inside the compressed core is preferably selected from sodium polyacrylate, carboxypolymethylenes, and the pharmaceutically acceptable salts thereof, wherein the carboxypolymethylenes are prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and more preferably it is selected from carboxypolymethylenes prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and the

210
178

pharmaceutically acceptable salts thereof. Most preferably, CARBOPOL® 974P is used as the polymer inside the compressed core. In addition, the compressed core may also contain one or more polymer hydration modulating agents, anti-oxidants, lubricants, fillers and excipients. An optional subcoating may be applied to the compressed core prior to application of the water insoluble coating as an aid in the manufacturing process. The subcoating may be comprised of, for example, hydroxypropyl cellulose and hydroxypropylmethylcellulose.

The water insoluble, water impermeable polymeric coating is preferably comprised of (1) a polymer selected from polyvinyl chloride, cellulose acetate, cellulose acetate butyrate, ethylcellulose and combinations of these polymers; and (2) a plasticizer selected from diethylphthalate, dibutylsebacate and triethylcitrate. More preferably, the polymeric coating is comprised of cellulose acetate butyrate and triethyl citrate. The GEM device does not function as an osmotic drug delivery device, hence the release function of the device depends on passage of fluids from the external environment of the body to the internal environment of the compressed core through the formed apertures. It is intended that the terms "water insoluble, water impermeable" used to describe the polymeric coating define a coating which is essentially water insoluble and water impermeable, meaning that the polymeric coating allows minimal to no passage of water through the coating from the external environment of the body to the internal environment of the compressed core, except for the fluid passage that occurs through the drilled apertures, during the period of time the drug is being released from the GEM device in the body. Any minimal amount of water that does pass through the water insoluble, water impermeable polymeric coating is insubstantial and does not significantly contribute to the function of the GEM device, i.e. the release rate of the drug through the apertures. Rather the release rate of the drug from the GEM device is a function of the number and size of the apertures on the device.

For an elegant, aesthetically pleasing final product, an overcoat may finally be applied to the GEM delivery device containing colorants, waxes, and the like. The GEM device can also be enterically

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179

coated. Even without enteric coating, extrusion of the polymer which carries the drug out from inside the compressed core of the GEM device does not occur to a substantial extent in the acidic pH of the stomach, therefore substantial release of the drug does not occur in the stomach.

- 5 Further details and examples of the GEM delivery device are described in US Patent No. 5,366,738.

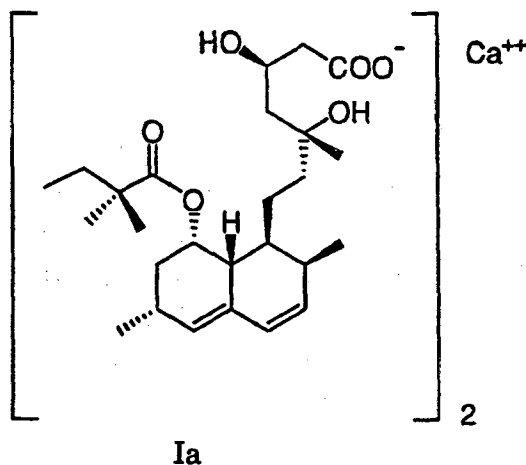
The term "patient" includes mammals, especially humans, who take compound I for the prevention or treatment of a medical condition. Administering of the drug to the patient includes both self-
10 administration and administration to the patient by another person. The patient may be in need of treatment for an existing disease or medical condition, or may desire prophylactic treatment to prevent or reduce the risk for diseases and medical conditions affected by inhibition of HMG-CoA reductase.

- 15 The term "therapeutically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term "prophylactically effective amount" is
20 intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician. Particularly, the dosage a patient receives can be selected so as to
25 achieve the amount of LDL (low density lipoprotein) cholesterol lowering desired; the dosage a patient receives may also be titrated over time in order to reach a target LDL level. The dosage regimen utilizing a dihydroxy open acid statin is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of
30 the patient; the severity of the condition to be treated; the potency of the compound chosen to be administered; the route of administration; and the renal and hepatic function of the patient. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or

212
180

prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition.

The novel compounds of this invention are the crystalline hydrated forms of the calcium salt of dihydroxy open acid. A particular crystalline hydrated calcium salt of dihydroxy open acid is the one having an x-ray powder diffraction (XRPD) pattern obtained using $\text{CuK}\alpha$ radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å. For convenience, the crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin having the above-defined XRPD pattern will also be referred to herein as compound I. Compound I can be represented two-dimensionally as a hydrated form of the following structural formula Ia:



In addition to the XRPD pattern described above, compound I of the instant invention is further characterized by the thermogravimetry (TG) curve shown in Figure I. The TG curve for compound I was obtained under a nitrogen flow at a heating rate of 10°C/minute and is characterized by a 6.3% weight loss from ambient room temperature to a stable weight loss plateau at about 175°C. Additional weight losses due to the onset of decomposition of the compound are observed above about 190°C.

213
181

Compound I is still further characterized by the differential scanning calorimetry (DSC) curve shown in Figure 2. The DSC curve for compound I was obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup, and is characterized by three lower temperature endotherms with peak temperatures of 52, 77 and 100°C and associated heats of 48, 90 and 21 J/g, respectively, and two higher temperature endotherms due to decomposition with peak temperatures of 222 and 241°C and associated heats of 163 and 92 J/g.

Compound I of the instant invention is still further characterized by the ¹H NMR, ¹³C NMR and mass spectral data as given in Example 1 herein.

In the methods of treatment and prophylaxis described herein, as well as the pharmaceutical compositions and medicaments, a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof is employed. Preferably the compound employed is a pharmaceutically acceptable salt of a dihydroxy open acid statin, more preferably it is a pharmaceutically acceptable salt of dihydroxy open acid simvastatin, particularly a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin, and most preferably it is compound I. All hydrates, solvates and polymorphic crystalline forms of the above-described compounds and their use are encompassed within scope of the instant invention.

The instant invention provides methods for inhibiting HMG-CoA reductase, and for treating lipid disorders including hypercholesterolemia, hypertriglyceridemia and hyperlipidemia, comprising administering a therapeutically effective amount of a dihydroxy open acid statin to a person in need of such treatment. Further provided are methods for preventing or reducing the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a prophylactically or therapeutically effective amount, as appropriate, of a dihydroxy open acid statin to a mammal who is at risk of developing atherosclerosis or who already has atherosclerotic disease.

2/4
182

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

A dihydroxy open acid statin may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom the potential for recurrence of such an event exists.

Accordingly, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of a prophylactically effective amount of a dihydroxy open acid statin to a patient at risk for such an event. The patient may already have atherosclerotic disease at the time of administration, or may be at risk for developing it.

Persons to be treated with the instant therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician practicing in the relevant fields of medicine. Such known risk factors include but are not limited

215
183

to hypertension, smoking, diabetes, low levels of high density lipoprotein (HDL) cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: National Cholesterol

- 5 Education Program, Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), National Institute of Health, National Heart Lung and Blood Institute, NIH Publication No. 93-3095, September 1993; abbreviated version: Expert Panel on Detection, Evaluation, and
- 10 Treatment of High Blood Cholesterol in Adults, Summary of the second report of the national cholesterol education program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), JAMA, 1993, 269, pp. 3015-23. People who are identified as having one or more of the above-noted risk
- 15 factors are intended to be included in the group of people considered at risk for developing atherosclerotic disease. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within the group of people considered to be at risk for having an atherosclerotic disease
- 20 event.

- 25 The oral dosage amount of the dihydroxy open acid statin, particularly a salt of a dihydroxy open acid statin such as simvastatin, and more particularly a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin such as compound I, is from about 1 to
- 30 200 mg/day, and more preferably from about 5 to 160 mg/day. However, dosage amounts will vary depending on factors as noted above, including the potency of the particular compound. Although the active drug of the present invention may be administered in divided doses, for example from one to four times daily, a single daily dose of the active drug is preferred.. As examples, the daily dosage amount may be selected from, but not limited to, 5 mg, 10 mg, 20 mg, 25 mg, 40 mg, 50 mg, 75 mg, 80 mg, 150 mg and 160 mg.

The active drug employed in the instant therapy can be administered in such oral forms as tablets, capsules, pills, powders,

246
189

granules, elixirs, tinctures, suspensions, syrups, and emulsions. Oral formulations are preferred.

Oral delayed-release formulations are employed with the dihydroxy open acid statins. Examples of suitable formulations include but are not limited to enterically coated pharmaceutical dosage forms such as enterically coated conventional pharmaceutical dosage forms and enterically coated time-controlled release dosage forms, the GEM delivery device, and an enterically coated GEM delivery device.

For the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, for example compound I, administration of the active drug can be via any pharmaceutically acceptable route and in any pharmaceutically acceptable dosage form. This includes the use of oral conventional rapid-release, time controlled-release and delayed-release (such as described above) pharmaceutical dosage forms. An oral time controlled-release dosage formulation of the instant drug is preferred, and particularly the GEM controlled-release drug delivery device described in U.S Patent No. 5,366,738, herein incorporated by reference in its entirety. Additional suitable pharmaceutical compositions for use with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

In the methods of the present invention, the active drug is typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

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

217
185

calcium stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, 5 disintegrating agents and coloring and flavoring agents can also be incorporated into the mixture. Stabilizing agents such as antioxidants, for example butylated hydroxyanisole (BHA), 2,6-di-tert-butyl-4-methylphenol (BHT), propyl gallate, sodium ascorbate, citric acid, and calcium metabisulphite, can also be added to stabilize the dosage forms; 10 the use of at least one stabilizing agent is preferred with the instant composition, and preferably an antioxidant is employed with dihydroxy open acid simvastatin or a salt thereof, and particularly compound I. Other suitable components include gelatin, sweeteners, natural and synthetic gums such as acacia, tragacanth or alginates, 15 carboxymethylcellulose, polyethylene glycol, waxes and the like.

The active drug can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, 20 stearylamine or phosphatidylcholines.

Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl- 25 pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, 30 polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The instant invention also encompasses a process for 35 preparing a pharmaceutical composition comprising combining a

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dihydroxy open acid statin with a pharmaceutically acceptable carrier. Also encompassed is the pharmaceutical composition which is made by combining a dihydroxy open acid statin with a pharmaceutically acceptable carrier.

5 Additional active agents may be used in combination with the dihydroxy open acid statin in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration of the active agents. One or more additional active agents may be administered with a
10 dihydroxy open acid statin. The additional active agent or agents can be cholesterol lowering compounds. Examples of additional active agents which may be employed include but are not limited to HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, including micronized fenofibrate, and gemfibrozil; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPAR γ) agonists including the compounds commonly referred to as glitazones, including those compounds included within the structural class known as thiazolidinediones as well as those PPAR γ agonists outside the thiazolidinedione structural class); PPAR dual α/γ agonists; vitamin B₆ (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B₁₂ (also known as cyanocobalamin); beta-blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; and anti-oxidant vitamins such as
30 vitamin C and E and beta carotene.

A therapeutically effective amount of a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin, for example compound I, can be used for the preparation of a medicament useful for
35 inhibiting HMG-CoA reductase, as well as for treating and/or reducing

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the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, such as preventing or reducing the risk of developing atherosclerotic disease, halting or slowing the progression of atherosclerotic disease once it has become clinically manifest, and

5 preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event. For example, the medicament may be comprised of about 1 mg to 200 mg of a crystalline hydrated form of dihydroxy open acid simvastatin, or more particularly about 5 mg to 160 mg.

10 A therapeutically effective amount of a dihydroxy open acid statin can be used for the preparation of a medicament adapted for delayed-release that is useful for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, as described above.

15 The medicament comprised of a dihydroxy open acid statin, for example compound I, may also be prepared with one or more additional active agents, such as those described supra.

Simvastatin is a semi-synthetic product which can be made from the natural product lovastatin. Processes for preparing lovastatin and simvastatin are well documented in the published literature. For
20 example, U.S. Patent No. 4,231,938, herein incorporated by reference, describes a fermentation and isolation process for obtaining lovastatin using the microorganism *Aspergillus terreus*. U.S. Patent No.'s 4,444,784, 4,820,850, 4,916,239 and 4,582,915, herein all incorporated by
25 reference, describe methods for making simvastatin.

Preparation of Compound I

Compound I of the instant invention can generally be prepared as follows. Simvastatin and its dihydroxy open acid
30 counterpart, including compound I, tend to form oxidative by-products; therefore, to minimize the formation of such by-products, it is preferred that the procedures used to make compound I are performed under an inert atmosphere such as nitrogen. Although compound I can be obtained without using an inert atmosphere, the purity of the desired
35 product will not be optimized.

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Hydrolysis of the lactone ring of simvastatin can be accomplished by treating simvastatin with at least one equivalent, and preferably a slight excess of one equivalent, of an aqueous base. If more than a slight excess of base is used, the excess base is preferably neutralized before proceeding to the salt formation step in order to prevent formation of insoluble calcium hydroxide or calcium carbonate by-product. The base employed for the hydrolysis can be an aqueous solution of a metal hydroxide or metal carbonate, for example but not limited to sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate and potassium carbonate. Sodium hydroxide is preferred. The hydrolysis can be performed in water, an aqueous-protic organic solvent mixture, or an aqueous-aprotic organic solvent mixture. Suitable protic organic solvents include but are not limited to methanol (MeOH), ethanol (EtOH), isopropyl alcohol, propanol and tetrahydrofuran (THF). Examples of suitable aprotic organic solvents include but are not limited to *tert*-butyl methyl ether (MTBE) and toluene. An aqueous ethanol solvent mixture is preferred.

After the hydrolysis reaction is complete, the pH of the reaction mixture is adjusted to 6 to 9, preferably 7 to 8.5, by addition of an acid. In this pH range, the dihydroxy open acid simvastatin will exist as a metal salt, for example as the sodium salt if the base used in the hydrolysis step is sodium hydroxide or sodium carbonate. Any acid that is capable of forming a soluble calcium salt such as calcium chloride or calcium citrate, is suitable. A soluble calcium salt is intended to be a salt that is soluble in the solvent system employed in the instant process. Preferably a mineral acid is employed, particularly HCl.

The resulting pH-adjusted reaction mixture containing the metal salt of dihydroxy open acid simvastatin is next combined with a solution of about 0.50 to 0.55 equivalents of calcium acetate hydrate $[\text{Ca}(\text{OAc})_2 \cdot \text{Ca} \cdot x\text{H}_2\text{O}]$ in an aqueous-protic organic solvent mixture, such as water-EtOH. The pH-adjusted reaction mixture can be added to the calcium acetate hydrate solution, or the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture. The addition can occur all at once, or optionally it can be performed in portions over time with periods of aging. For example, a small portion, e.g., about one-

221
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quarter, of the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture over a short period of time, for example over about 30 minutes, and then the resulting mixture can be allowed to age for an additional short period of time at room temperature, optionally

5 followed by a further period of aging at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C, after which the remaining calcium acetate hydrate solution can be added in portions over several hours at a temperature up to about 50°C,

10 for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C.

Whether the pH-adjusted reaction mixture and the calcium acetate hydrate solution are combined at once or in portions, the

15 resulting slurry must be aged until turnover of the resulting amorphous calcium salt of dihydroxy open acid simvastatin to the crystalline product is complete, usually for at least several hours. Complete turnover to the crystalline product can be assessed by standard techniques in the art, for example, by examining a sample of the product

20 under a microscope. This aging step can be performed at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C. During the aging period or periods, the use of lower temperatures will lead to crystallized product; however,

25 it has been found that as the temperature drops, the rate of crystal turnover becomes slower, making the procedure less time-efficient.

If necessary, the slurry is then allowed to cool to room temperature and is collected by suction filtration, and the recovered solid is suction dried under a moist atmosphere (about 40 to 70% relative

30 humidity), preferably a moist inert atmosphere such as nitrogen. The final step of suction filtration in the recovery of compound I should be done under a moist atmosphere, and preferably a moist inert atmosphere in order to minimize oxidative by-products. If an additional step of adding an antioxidant to compound I is performed, as described

below, then the final suction filtration is the one performed after combining the antioxidant with compound I.

As noted above, compound I has a tendency to oxidize upon contact with air, and one way to minimize oxidation is to perform the reaction sequence under an inert atmosphere. Additionally, an antioxidant such as BHA, BHT, ascorbic acid, or calcium metabisulphite can be combined with compound I. This is simply done by agitating a slurry of compound I with the antioxidant and recovering the resulting solid by suction filtration.

Abbreviations which may appear herein are as follows: EtOH is ethanol; HPLC is high performane liquid chromatography; min. is minutes; h is hour(s); D.I. is de-ionized; NMR is nuclear magnetic resonance; EI MS is electron impact mass spectrum; HR-EI MS is high resolution electron impact mass spectrum; RH is relative humidity.

EXAMPLE 1

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I)

A 22 L four-necked round bottom flask was equipped with a temperature probe, a N₂ inlet, an addition funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H₂O was added and the solution was purged with N₂ for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry was purged with N₂ for 5 min. Then 5N NaOH (198 mL) was added at room temperature. After about 1 hour, the hydrolysis reaction was complete as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (approx. 65 mL). A solution of Ca(OAc)₂·H₂O (116.6 g, 0.662 mol) in 4.0 L of 60% EtOH-H₂O was purged with nitrogen for 5 min. A 1.0 L portion of this solution was added to solution of the sodium salt over 30 min. The resulting slurry was aged at room temperature for 30 min, and then at 30 to 35°C for 1-2 h.

The rest of Ca(OAc)₂ in EtOH-water was added over approx. 30 min at 30 to 35°C. The slurry was aged at 30 to 35 °C for 5 hours under

223
191

atmosphere of N₂. The slurry was cooled to room temperature and was collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H₂O, 4 L 20% EtOH-H₂O, followed by 6 L x 3 of D.I. water. The solid was suction dried under an atmosphere of moist N₂ (40 to 70%

5 relative humidity) at room temperature for 4 days. Crystalline hydrated calcium salt of dihydroxy open acid simvastatin was obtained as a white powder.

The calcium salt was delumped with a single pass through a cleaned QUADRO™ COMIL® (Model 197S).

HPLC CONDITIONS

Column: YMC Basic 4.6 mm x 25 cm
Detector: ABS 757 1AU/volt output
15 Sample solvent: EtOH/CH₃CN/H₂O (1:1:1)
Column temp: 25 °C (Anal. Dept. runs samples at 5 °C to prevent formation of simvastatin on column).
Flow rate: 1.5 mL / min.
Wavelength: 238 and 210 nm

20 Gradient: %H₂O (10 mM K₂HPO₄-

Time (min.) %CH₃CN KH₂PO₄, pH = 6.5

0.00 30 70

20.00 45 55

25 34.00 70 30

39.00 70 30

39.50 30 70

43.00 30 70

30 Retention time of simvastatin open acid: 17.07 min.

Retention time of simvastatin: 32.90 min.

SPECTRAL DATA

224
192

¹H NMR (400 MHz, CD₃OD), δ 5.97 (d, J = 9.6 Hz, 1 H), 5.77 (dd, J = 9.6, 5.2 Hz, 1 H), 5.49 (m, 1 H), 5.33 (m, 1 H), 4.17 (m, 1 H), 3.70 (m, 1 H), 2.44 - 2.35 (m, 2 H), 2.42 (dd, J = 15.7, 3.6 Hz, 1 H), 2.31 - 2.27 (m, 1 H), 2.29 (dd, J = 15.7, 8.4 Hz, 1 H), 2.00 (ddd, J = 15.7, 7.6, 2.4 Hz, 1 H), 1.93 (m, 1 H), 1.68 (m, 1 H), 1.61 - 1.55 (m, 2 H), 1.55 (m, 2 H), 1.42 (m, 1 H), 1.32 (m, 1 H), 1.19 (m, 1 H), 1.12 (s, 6 H), 1.08 (d, J = 7.2 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 3 H), 0.84 (t, J = 7.6 Hz, 3 H) ppm.

¹³C NMR (100.55 MHz, CD₃OD), δ 182.3, 179.3, 134.1, 133.2, 130.3, 129.6, 72.5, 69.8, 45.1, 44.4, 44.1, 38.8, 38.3, 36.4, 34.3, 33.9, 32.0, 28.6, 25.9, 25.37, 25.36, 23.7, 14.3, 9.9 ppm

EI MS: m/e: 437 (M+H), 419(M+H-H₂O), 303.

HR-EI MS: Calcd. for C₂₅H₃₈O₅ 418.2719; Found: 418.2712.

EXAMPLE 2

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) with BHA

A 22 L three-necked round bottom flask was equipped with a temperature probe, a N₂ inlet, an additional funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H₂O was added and purged with N₂ for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry purged with N₂ for 5 min. 198 mL of 5N NaOH (0.993 mol, 1.05 equiv.) was then added at room temperature. The hydrolysis reaction is usually complete in 1 h. as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (about 65 mL).

A solution of Ca(OAc)₂·H₂O (91.7 g, 0.520 mol, 0.55 equiv.) in 4.0 L of 60% EtOH- H₂O was purged with nitrogen for 5 min. 1.0 L of this solution was added to reaction solution over 30 min. The slurry was aged at room temperature for 30 min, and then at 30 to 35 °C for 1-2 h. The rest of the Ca(OAc)₂ in EtOH-water was added in portions over 3h hours at 30-35°C. The slurry was allowed to age at 30 to 35 °C for 5 h under an atmosphere

of N_2 . The slurry was allowed to cool to room temperature and was collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH- H_2O , 4 L 20% EtOH- H_2O , followed by 6 L x 3 of D.I. water. The solid was suction dried under atmosphere of moist N_2 (40 to 70% RH) at room temperature to give 1.7 Kg of wet cake.

The above wet cake was placed in a clean 20 L three necked flask under atmosphere of nitrogen. A solution of BHA (2.603 g, 0.2 wt % equiv) in degassed 15% EtOH H_2O (8.5 L) was added, followed by addition of degassed water (2.55 L), and the slurry was agitated at room temperature for 1 to 2 h. The solid was collected by suction filtration under atmosphere of moist N_2 with no washing to give 1.49 Kg wet cake. The solid was suction dried under atmosphere of moist N_2 (40 to 70% RH) at room temperature for 4 days. The calcium salt was obtained as a white powder (94% yield. 99.4%A at 238 nm, 0.2wt% BHA, KF = 7.3 %wt).

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

226
194

WHAT IS CLAIMED IS:

1. A method for inhibiting HMG-CoA reductase comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

2. The method of claim 1 wherein the compound is administered in an enterically coated pharmaceutical dosage form.

3. The method of claim 1 wherein the compound is administered in an enterically coated time controlled-release pharmaceutical dosage form.

4. The method of claim 1 wherein the compound is administered in a drug delivery device comprised of:

(A) a compressed core prepared from an admixture comprising:

(i) a therapeutically effective amount of the compound; and

(ii) a polymer which upon hydration forms gelatinous microscopic particles; and

(B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the compound from the device is a function of the number and size of the apertures.

5. The method of claim 4 wherein the drug delivery device is enterically coated.

227
195

6. A method of treating hypercholesterolemia comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

7. A method for preventing or reducing the risk of developing atherosclerotic disease comprising orally administering a prophylactically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a person at risk of developing atherosclerotic disease wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

8. The method of Claim 7 wherein the atherosclerotic disease is selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

9. The method of Claim 8 wherein the cardiovascular disease is coronary heart disease.

10. A method for treating atherosclerotic disease comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

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

228
196

12. The method of Claim 11 wherein the cardiovascular disease is coronary heart disease.

5 13. A method for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical
10 dosage form to a person at risk of having an atherosclerotic disease event wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

15 14. The method of Claim 13 wherein the person receiving the compound has atherosclerotic disease.

15 15. The method of Claim 13 wherein the person receiving the compound is at risk of developing atherosclerotic disease.

20 16. The method of Claim 13 wherein the atherosclerotic disease event is selected from a coronary heart disease event, a cerebrovascular event and intermittent claudication.

25 17. The method of Claim 16 wherein the coronary heart disease event is selected from coronary heart disease death, myocardial infarction, and coronary revascularization procedures.

30 18. The method of Claim 17 wherein the cerebrovascular event is selected from a cerebrovascular accident and a transient ischemic attack.

19. The method of claim 1 wherein the compound is a pharmaceutically acceptable salt of a dihydroxy open acid statin.

229
197

20. The method of claim 19 wherein the compound is a pharmaceutically acceptable salt of the dihydroxy open acid form of a statin selected from the group consisting of lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin and cerivastatin.

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21. The method of claim 20 wherein the compound is a pharmaceutically acceptable salt of the dihydroxy open acid form of a statin selected from the group consisting of lovastatin and simvastatin.

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22. The method of claim 21 wherein the compound is a pharmaceutically acceptable salt of dihydroxy open acid simvastatin.

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23. The method of claim 22 wherein the compound is a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin.

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24. The method of claim 23 wherein the compound is a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin having an x-ray powder diffraction pattern obtained using CuK α radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å.

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25. The method of claim 1 wherein 10% or less by weight of the compound in the delayed-release dosage form is released in the stomach.

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26. The method of claim 1 wherein 5% or less by weight of the compound in the delayed-release dosage form is released in the stomach.

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27. The method of claim 1 wherein 1% or less by weight of the compound in the delayed-release dosage form is released in the stomach.

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198

28. An orally administrable pharmaceutical composition comprising a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof and a pharmaceutically acceptable carrier,
5 formulated in a delayed-release dosage form wherein release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

29. The pharmaceutical composition of claim 28 wherein
10 the composition is enterically coated.

30. The pharmaceutical composition of claim 29 wherein the composition is formulated in an enterically coated time controlled-release pharmaceutical dosage form.

31. The pharmaceutical composition of claim 28 wherein the composition is formulated in a drug delivery device comprised of:

- (A) a compressed core prepared from an admixture comprising:
- (i) a therapeutically effective amount of the compound; and
 - (ii) a polymer which upon hydration forms gelatinous microscopic particles; and
- (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the compound from the device is a function of the number and size of the apertures.

32. The pharmaceutical composition of claim 31 wherein the drug delivery device is enterically coated.

33. A process for preparing an orally administrable
35 pharmaceutical composition comprising combining a compound

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selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof with a pharmaceutically acceptable carrier in a delayed-release dosage form.

- 5 34. An orally administrable pharmaceutical composition made by combining a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof with a pharmaceutically acceptable carrier in a delayed-release dosage form.

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656000-11143200

TITLE OF THE INVENTION

DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE
INHIBITORS

5 ABSTRACT OF THE DISCLOSURE

The instant invention provides methods and
pharmaceutical compositions for inhibiting HMG-CoA reductase, as
well as for treating and/or reducing the risk for diseases and conditions
affected by inhibition of HMG-CoA reductase, comprising orally
10 administering a therapeutically effective amount of a compound selected
from a dihydroxy open acid statin and a pharmaceutically acceptable
salt or ester thereof in a delayed-release pharmaceutical dosage form to
a patient in need of such treatment wherein substantial release of the
compound from the dosage form is delayed until after passage of the
dosage form through the stomach.

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
DECLARATION AND POWER OF ATTORNEY**

Assistant Commissioner for Patents
Washington, D.C. 20231

As a below-named inventor, I hereby declare that I believe I am:

- ☒ the original, first and sole inventor; or
- ☐ an original, first and joint inventor along with the other inventors listed below, of the subject matter which is claimed and for which a patent is sought on the invention entitled
- DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE INHIBITORS

the specification of which ☒ is attached hereto;

☐ was filed on _____ as Application
Serial No. _____ and was amended
through _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended as indicated above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate for the same invention having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Country	Number	Date Filed	Attorney Docket

Priority Claimed

☐ ☐
Yes No

Country	Number	Date Filed	Attorney Docket

☐ ☐
Yes No

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202

Prior United States Filing

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

To Be Assigned	March 8, 1999	20416PV
Appln. Ser. No.	Filing Date	Attorney Docket
Appln. Ser. No.	Filing Date	Attorney Docket
Appln. Ser. No.	Filing Date	Attorney Docket
Appln. Ser. No.	Filing Date	Attorney Docket

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date(s) of the prior application(s) and the national or PCT international filing date of this application:

Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket

And I hereby appoint

Carol S. Quagliato

Melvin Winokur

Reg. No. 35,330

Reg. No. 32,763

Reg. No. _____

respectively and individually, as my attorneys or agents with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Please address all communications to:

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Telephone No. (732) 594- 3809

235
203

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Full name of joint inventor	
Inventor's Signature	
Date	
Residence	
Citizenship	
Post Office Address (if different from above)	

Full name of joint inventor	
Inventor's Signature	
Date	
Residence	
Citizenship	
Post Office Address (if different from above)	

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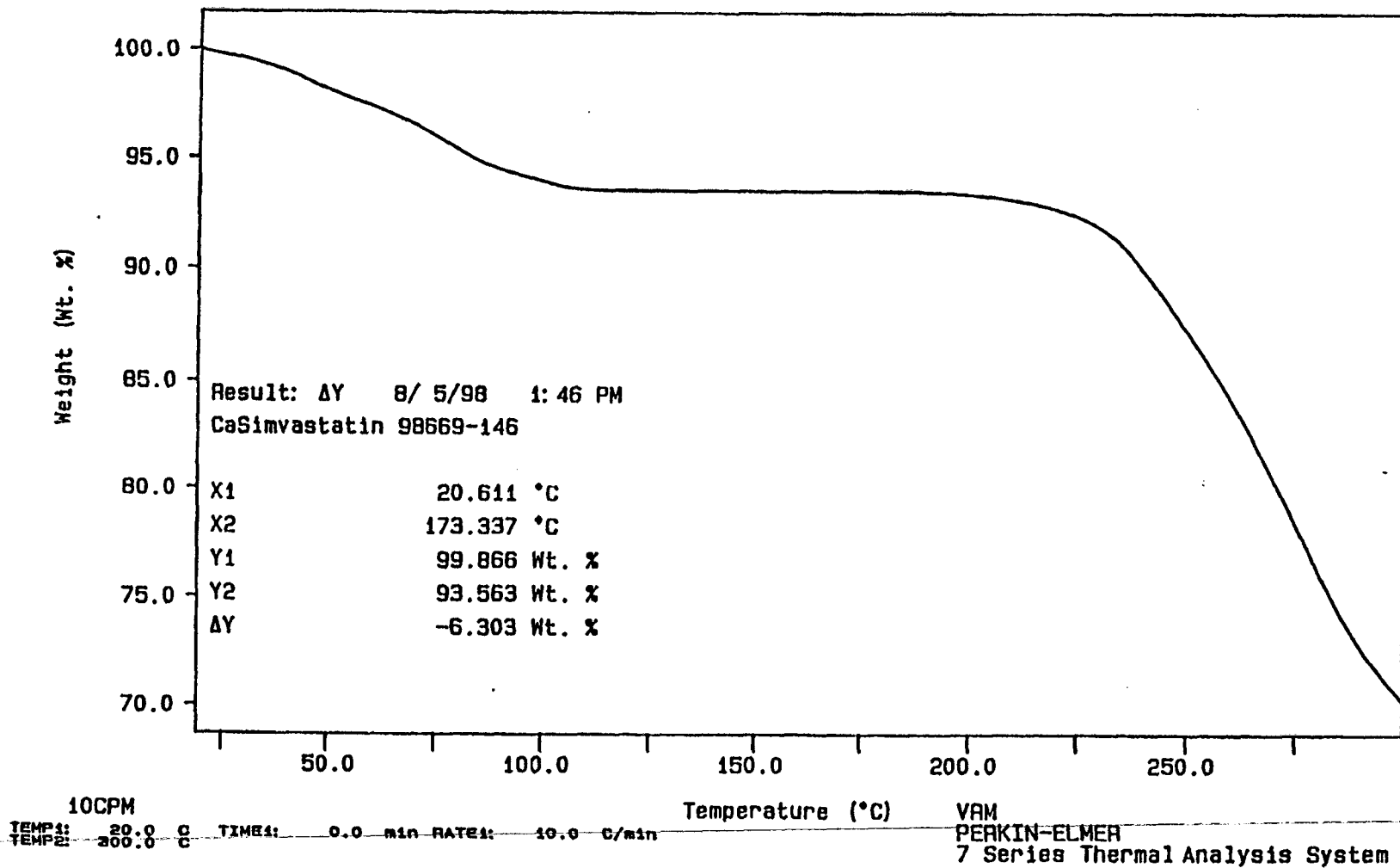
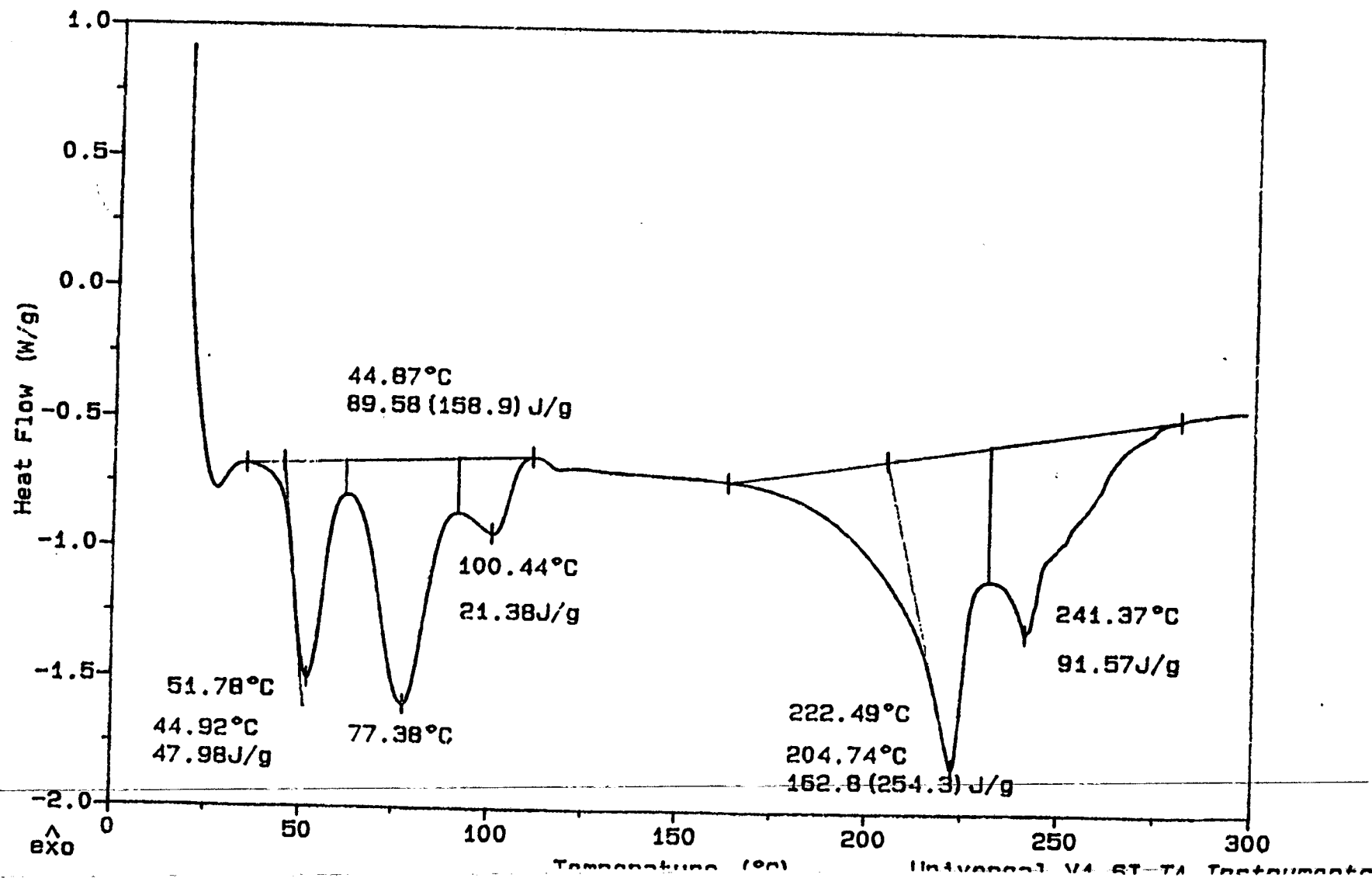


Figure 1.

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Figure 2
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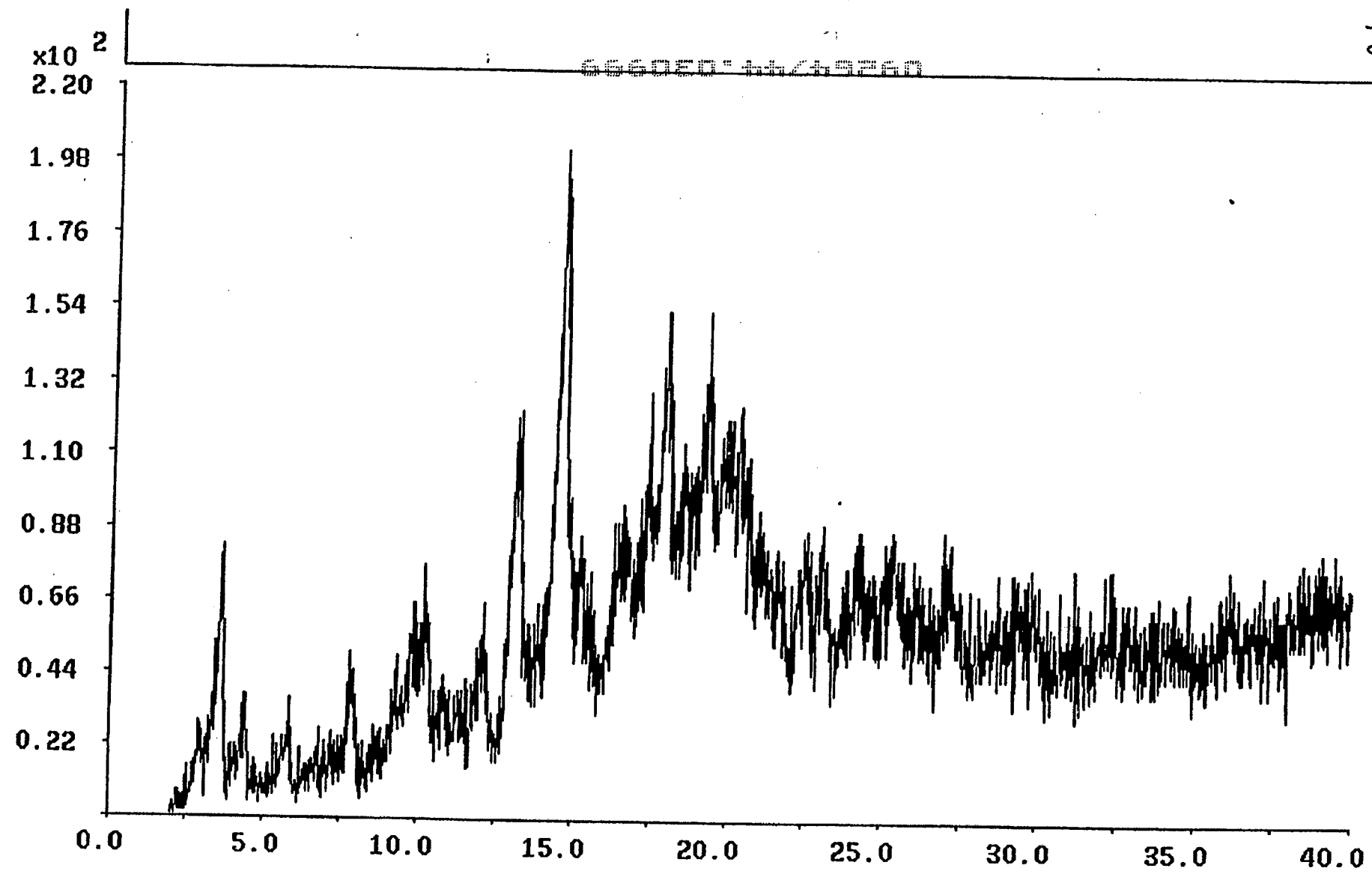


Figure 3.

206

Mayo 22, 2000
Traducción Oficial No. 0262
REF:MERCK & CO;INC
Patente No.:PCT/US 00/02626

Merck & Co; Inc
Caso - 00.016.008

240
207

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
OFICINA DE MARCAS Y PATENTES

Mayo 10, 2000

Por medio del presente documento se certifica que adjunto se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud:PCT/US00/02626

Fecha de Registro:Febrero 2, 2000

Autorizado por:

COMISIONADO DE MARCAS Y PATENTES

Firma:P. R. GRANT

Funcionario Encargado de Certificaciones

Hay sello de la Oficina de Marcas y Patentes realizado de color dorado.

Edwar de Colado
Edwar de Colado Noguera
DIRECTOR OFICIAL
MARCA Y PATENTES
Febrero 2 de 19 6

241
208

0 **Recibo y uso de Oficina solamente**

0-1 Solicitud Internacional No. PCT/US 00/02626

0-2 Fecha de Registro Internacional 02 Febrero 2000

0-3 Nombre de Oficina que recibe y "PCT
Solicitud Internacional" PCT-Solicitud
Internacional RO/US

0-4 Formulario - petición PCT/RO/101 PCT
Uso PCT Versión EASY 2.90
(actualizado el 15.12.1999)

0-5 Petición
El abajo escrito pide que la presente solicitud internacional sea
procesada de acuerdo a la Cooperación del Tratado de Patentes.

0-6 Oficina que Recibe (especificado por
el solicitante) Oficina de Marcas y
Patentes de los Estados Unidos
(USPTO) (RO/US)

0-7 Archivo de referencia del agente o
solicitante

PCT 20416Y

Edwards Calado
"SECRETARIO OFICIAL"
"ANOL-INGLES"
"1999-01-19-6"

242
209

I Título del invento SALES Y ÁCIDOS ABIERTOS DE
DIHIDROXI INHIBIDORES DE
REDUCTASE HMG-CO

II Solicitante

II-1 Esta persona es: Solamente el solicitante
II-2 Solicitante para: Todos los Estados a excepción US
II-4 Nombre: MERCK & CO., Inc
II-5 Dirección 126 East Lincoln Avenue
Rahway, NJ 07065-0907
Estados Unidos de América

II-6 Estado de Nacionalidad US
II-7 Estado de residencia US
II-8 No. Teléfono 732-594-3809
II-9 No. Fax. 732-594-4720

III-1 Solicitud y/o inventor

III-1-1 Esta persona es: solicitante e inventor
III-1-2 Solicitante para: Solamente los Estados Unidos
III-1-4 Nombre(Apellido, Nombre: Tylllyer, Richard, D.
III-1-5 Dirección 126 East Lincoln Avenue
Rahway, NJ 07065-0907
Estados Unidos de América
III-1-6 Estado de Nacionalidad Reino Unido
III-1-7 Estado de residencia US

III-2 Solicitud y/o inventor

III-2-1 Esta persona es: solicitante e inventor

Edw. de la Cruz
SECRETARY
MAR 11 1988
FEDERAL BUREAU OF INVESTIGATION
U.S. DEPARTMENT OF JUSTICE

248
211

Estados Unidos de América

III-4-6 Estado de Nacionalidad China

III-4-7 Estado de residencia US

III-5 Solicitud y/o inventor

III-5-1 Esta persona es: solicitante e inventor

III-5-2 Solicitante para: Solamente los Estados Unidos

III-5-4 Nombre(Apellido,
Nombre): VEGA, José, M.

III-5-5 Dirección 126 East Lincoln Avenue
Rahway, NJ 07065-0907
Estados Unidos de América

III-5-6 Estado de Nacionalidad US

III-5-7 Estado de residencia US

IV-1 Agente o representante común;
o dirección de correspondencia

La persona identificada anteriormente se ha nombrado
para que actúe a favor del solicitante (es) ante las Autoridades
Internacionales Competentes como:

IV-1-1 Nombre Merck & Co., Inc

IV-1-2 Dirección 126 Esat Lincoln Avenue
Rahway, NJ 07065-0907
Estados Unidos de América

IV-1-3 No. Teléfono 723-594-3809

IV-1-4 No. Fax: 723-594-4720

Edwards Calado

245
212

V Designación de Estados

V-1 Patente Regional

(otros tipos de protección o
tratamiento, en el caso que existan,
son especificadas entre parentesis
después de la designación
(es) relacionada)

AP: GH GM KE LS MW SD
SL SZ TZ UG ZW y cualquier
otro Estado que sea un Estado
Contratante del Protocolo de
Harare y del PCT.

EA: AM AZ BY KG KZ MD
RU TJ TM y cualquier otro
Estado que sea un Estado
Contratante de la Convención
de Patentes de Eurasia y de la
PCT.

EP: AT BE CH&LI CY DE
DK ES FI FR GR GR IE IT
LU MC NL PT SE y cualquier
otro Estado contratante de la
Convención de Patentes
Europeas y de la PCT.

OA: BF BJ CF CG CI CM
GA GN GW ML MR NE SN
TD TG y cualquier otro
Estado que sea Estado

Edoardo Calado
"Estado No Adherido"
"COLECTOR OFICIAL"
"CANCILLER-POLES"
"SEPTO DE 19 6"

246
213

miembro del OAPI y un
Estado Contratante de PCT.

V-2 Patente Nacional

(otros tipos de protección o
tratamiento, en el caso que existan,
son especificadas entre paréntesis
después de la designación
(es) relacionada)

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

V -5 Designación de declaración preventiva.

además de las designaciones realizadas
bajo los ítems V-1, V-2 y V-3, el
solicitante puede también realizar
bajo la regulación 4.9(b)
todas las designaciones que pueden
ser permitidas bajo la PCT a excepción
de cualquier designación (es) de los estado (s)
indicados bajo el ítem V-6 anteriormente
mencionado. El solicitante declara que
esas designaciones adicionales son sujetas
a confirmación y que cualquier designación

Eduardo Salado
"FOR OFFICIAL USE"
INGLES-ESPAÑOL-INGLES
Rev. 541 Febrero de 19.6

247
214

que no sea previamente confirmada antes
de la fecha de vencimiento a los 15 meses
desde la fecha de prioridad será considerado
como retirado por el solicitante en esa fecha
límite de vencimiento.

V-6 Exclusión (es) de las designaciones preventivas NINGUNA

**VI-1 Reivindicación de prioridad sobre
solicitud nacional anterior**

VI-1-1 Fecha de registro Marzo 08 1999 (08.03.1999)

VI-1-2 Número 60/123, 227

VI-1-3 País US

**VI-1-2 Reivindicación de prioridad sobre
solicitud nacional anterior**

VI-2-1 Fecha de registro Marzo 09, 1999 (09.03. 1999)

VI-2-2 Número 09/264,744

VI-2-3 País US

VI- 3 Documento de Petición de prioridad

Edoardo Caludo
SECRETARÍA DE ECONOMÍA
DIRECCIÓN GENERAL DE REGISTRO Y MARCAS
ESTADO DE GUATEMALA
19 de marzo de 1999

~~218~~
215

VII-1 Autoridad Internacional
escogida para la Oficina de patentes Europeas (EPO)
la Investigación (ISA/EP)

VIII-1	Peticiones	5	-
VIII-2	Descripción	40	-
VIII-3	reivindicaciones	8	-
VIII-4	resumen	1	20416v resumen para barbara cozzi. txt

ítems acompañantes documentos adjuntos registros
electrónicos adjuntos

VIII-9 poder firmado
separadamente /

Edwards Cabedo
 Cabedo Vagner
 CABO OFFICIAL
 CABO-INOLES
 19.6

249
216

VIII-10	copia de Poder general	/	-
VIII-16	PCT EASY -diskette	-	diskette
VIII-18	Diseño de gráfica que debe acompañar el resumen	1	
VIII-19	Idioma de registro de la solicitud Internacional	Inglés	
IX-1 Quagliato)	firma del solicitante o agente (hay firma de Carol S.		
IX-1-1	Nombre	Merck & Co., Inc	
IX--1-2	Nombre del firmante	Carol S, Quagliato	
IX-1-3	Cargo	Abogado	
10-1	Fecha de recibo de la solicitud internacional que se gestiona.	Registro de 520 PCT/PTO Febrero 02/2000	
10-2	Graficas		
10-2-1	Recibidas		
10-2-2	No recibidas		
10-3	Fecha corregida de consignación con fecha de vencimiento posterior pero con recibo de documentación a tiempo o gráficas que complementan la solicitud internacional que se gestiona.		

Edurne de Calabro
SECRETARÍA DE ECONOMÍA
OFICINA DE ASesorÍA
SAN ANTONIO
Febrero de 1996

~~250~~
217

- | | | |
|------|--|--------|
| 10-4 | Fecha de recibo a tiempo, de las correcciones requeridas bajo el Artículo de PCT 11(2). | |
| 10-5 | Autoridad Internacional investigadora | ISA/EP |
| 10-6 | Trámite de investigación de copia postergada hasta que se paguen honorarios correspondientes a la investigación. | |

SOLO PARA USO INTERNACIONAL

- 11-1 Fecha de recibo de copia de registro
de la oficina internacional.

Edwards Caludo

251
218

PCT

PODER

(para uso de solicitud internacional registrado bajo el Tratado de Cooperacion para Patentes)

(PCT regla 90.4

El abajo solicitante (s) suscrito (Nombres deben ser indicados tal como aparecen en la petición):

TILLYER, Richard D., REIDER, Paul J., GRABOWSKI,
Edward J.J., XU, Feng

Yo por medio de la presente nombro a
la siguiente persona como:

☒ representante

Nombre y Dirección

(Apellido seguido por el nombre: para una entidad legal, designación oficial total. La dirección debe incluir código postal y nombre del país.)

MERCK & CO., INC
126 East Lincoln Avenue

Eduardo Palacios
R. 11/11/11

Rahway, New Jersey 07065-0907

Estados Unidos de América

252
219

para que represente el abajo firmante ☒ todas las autoridades competentes

relacionadas con la solicitud internacional identificada a continuación:

Título de la invención: SALES Y ÁCIDOS ABIERTOS DE
DIHIDROXI INHIBIDORES DE
REDUCTASE HMG-CO

Referencia de solicitante o agente : PCT 20416Y

Número de solicitud Internacional (si está disponible):

registrada con la siguiente oficina **Oficina de Los Estados Unidos Receptora** como la Oficina que recibe y que recibe y realiza pagos por parte del abajo firmante.

Firma del solicitante (s) (en la cual se encuentran varios solicitantes, cada uno de ellos debe firmar; al lado de cada firma, se debe indicar el nombre de la persona que firma y el cargo para el cual firma, si dicho cargo no es evidente al leer la petición o este poder):

Fecha: Feb. 1, 2000

Richard D. Tillyer

Edwards Calado
Edwards Calado
OFICIAL
13

Fecha: Feb. 1, 2000

Paul J. Reider

Fecha: Feb. 1, 2000

Edward J. J. Grabowski

Fecha: Feb. 1, 2000

Feng, Xu

Formulario PCT/ejemplo de poder (para una solicitud Internacional) (Julio 1992)

Edw. J. J. Grabowski

*253
220*

254
221

PCT

PODER

(para uso de solicitud internacional registrado bajo el Tratado de
Cooperación para Patentes)

(PCT regla 90.4

El abajo solicitante (s) suscrito (Nombres deben ser indicados tal
como aparecen en la petición):

TILLYER, Richard D., REIDER, Paul J., GRABOWSKI,
Edward J.J., XU, Feng

Yo por medio de la presente nombro a
la siguiente persona como:

☒ representante

Nombre y Dirección

(Apellido seguido por el nombre: para una entidad legal, designación
oficial total. La dirección debe incluir código postal y nombre del país.)

MERCK & CO., INC
126 East Lincoln Avenue

Edward Caludo
EDWARD CALUDO
126 EAST LINCOLN AVENUE
PO BOX 1000
KENNETH CITY, MD 21115

Rahway, New Jersey 07065-0907

Estados Unidos de América

para que represente el abajo firmante [x] todas las autoridades competentes relacionadas con la solicitud internacional identificada a continuación:

Título de la invención: SALES Y ÁCIDOS ABIERTOS DE DIHIDROXI INHIBIDORES DE REDUCTASE HMG-CO

Referencia de solicitante o agente : PCT 20416Y

Número de solicitud Internacional (si está disponible):

registrada con la siguiente oficina **Oficina de Los Estados Unidos Receptora** como la Oficina que recibe y que recibe y realiza pagos por parte del abajo firmante.

Firma del solicitante (s) (en la cual se encuentran varios solicitantes, cada uno de ellos debe firmar; al lado de cada firma, se debe indicar el nombre de la persona que firma y el cargo para el cual firma, si dicho cargo no es evidente al leer la petición o este poder):

Fecha: Feb. 1, 2000

José M. Vega

Formulario PCT/ejemplo de poder (para una solicitud Internacional) Julio 1992)

Edw. Paludo
DIRECTOR OFICIAL
SOLICITANTES
JULIO 1992

ASUNTOS DE PATENTES

Resuelto, que cualquiera de las personas mencionadas a continuación:

Raymond V. Gilmartin - Presidente de la Junta, Presidente y
Director Ejecutivo

Kenneth C. Frazier- Vicepresidente Superior y Abogado General

Joseph F. DiPrima- Vicepresidente y Abogado Asistente General

Paul D. Matukaitis- Vicepresidente y Abogado Asistente General

Edward Murray- Abogado, Litigio

Charles M. Caruso-Abogado Internacional

W. Gwyn Cole - Abogado de Patentes Europeas

Mark R. Daniel- Abogado, Patentes

David L. Rose - Abogado, Patentes

Jack L. Tribble - Abogado, Patentes

Melvin Winokur - Abogado, Patentes

Donna L. Pollock- Administrador, Patentes

se autorizo ejecutar y revocar a beneficio de Merck & Co., In. y sus
afiliados (incluyendo subsidiarios) los siguientes documentos
relacionados con asuntos de patentes.

Poder total de acuerdo a la ley de acuerdo a como sea necesario
y apropiado relacionado con la adquisición, registro, mantenimiento
y coacción de patentes y solicitudes para patentes, incluyendo poderes

Edward P. Ladd
EDWARD P. LADD
CLERK OFFICIAL
NOV 23 1999
16

relacionados con la demanda o defensa de los derechos de patentes
antes las cortes de leyes u otros tribunales gubernamentales, agencias
o departamentos; declaración juramentada y declaraciones; y
cualquier otro documento que sea necesario y apropiado para la
adquisición, registro, mantenimiento, litigio y protección de patentes.

257
224

Eduardo Calado K.
Eduardo Noguera
COR. OFICIAL
ALICANTE

258
225

CERTIFICACIÓN

Yo, DEBRA A. BOLLWAGE, como secretaria encargada de Merck & Co., Inc Una empresa debidamente organizada y existente bajo las leyes del estado de Nueva Jersey, por la presente certifico que el anexo, de la presente es una copia fiel y verdadera de la Resolución Empresarial General #5, Asuntos de Patentes, tal como fue enmendada en noviembre 23, 1999, efectiva en diciembre 1, 1999 por el Presidente de la Junta de dicha entidad, en la junta debidamente convocada y llevada a cabo en noviembre 23, 1999 en la cual hubo quórum presente.

EN TESTIMONIO DE QUE, he firmado y fijado el sello de la Empresa al día 9 de Diciembre del año de 1999.

Firma: Debra A. Bollwage
Secretaria Encargada

Eduardo Calado
Eduardo Calado Noguera
SECRETARIO OFICIAL
1999 12 09 6

259
226

TRATADO DE COOPERACIÓN DE PATENTES

Nombramiento General de Agente o Representantes

Los abajo firmantes solicitante(s) por la presente designan:

Sylvia A. Ayler	Shu Muk Lee
Richard C. Billups	James L. McGinnis
Valerie J. Camara	David A. Muthard
Anna L. Cocuzzo	Curtis C. Panzer
Joseph A. Coppola	Richard S. Parr
Mark R. Daniel	Dianne Pecoraro
Joseph F. DiPrima	Carol S. Quagliato
Phillippe L. Durette	David L. Rose
Catherine D. Fitch	Anthony D. Sabatelli
J. Antonio Garcia -Rivas	J. Eric Thies
Joanne M. Giesser	Jack L. Tribble
J. Mark Hand	Nicole M. Wallinger
Sheldon O. Heber	Kenneth R. Walton
James M. Hunter, Jr	Melvin Winokur
Elliot Korsen	Mollie M. Yang
	Michael D. Yablonsky

todos de la empresa Merck & Co., Inc., 126 East Lincoln Avenue,
Rahway, New Jersey 07065

Eduardo Calabrese
Eduardo Calabrese
"POR OFICIAL"
TRADUCCIONES
Febrero de 1966

~~260~~
227

Fecha Enero 4, 2000

Edwards Caludo R

261
228

0 **Recibo y uso de Oficina solamente**

0-1 Solicitud Internacional No. PCT/US 00/02626

0-2 Fecha de Registro Internacional 02 Febrero 2000

0-4 Formulario - petición PCT/RO/101 PCT
(Anexo) Cálculo de Honorarios

PCT Versión EASY 2.90

0-4-1 Preparado para uso (actualizado el 15.12.1999)

0-9 **Referencia de registro de solicitante
o agente**

PCT 20416Y

2 **Solicitante**

MERCK & CO., INC. , et al.

12 Cálculo de honorarios prescritos Cantidad honorarios/multiplicador Cantidad Total
en \$ US

12-1 honorarios trámite T	-	240	240
12-2 honorarios Investigación S	-	990	990
12-3 honorarios internacionales honorarios básicos			
Primeras 30 páginas b1	427		427
12-4 Páginas restantes	28		
12-5 cantidad adicional (x)	10		
12-6 Cantidad total adicional b2	280		280
12-7 b1 + b2= B	707		707

Eduardo Calado
Notario Público
Notario de la Oficina de Patentes
del Departamento de Comercio
y Relaciones Exteriores
del Estado de México

262
229

12-8	Honorarios designados			
	Número de designaciones existentes			
	en solicitud internacional	82		
12--9	Número de designaciones de			
	honorarios pagaderos			
	(máximo 8)	8		
12-10	suma de honorarios			
	designados (x)	92		
12-11	Total de honorarios			
	designados D	736		736
12-12	reducción de honorarios			
	PCT EASY R	-132		-132
12-13	Total honorarios			
	internacionales (B+D-R) 1	-	1,311	1,311
12-14	honorarios para documentos			
	de prioridad requeridos	2		
12-15	honorarios por cada			
	documento (x)	15		
12-16	Total de honorarios de			
	prioridad (P)	-	30	30
12-17	TOTAL DE HONORARIOS			
	PAGADEROS (T+S+I+P)	-	2,571	
12-19	Forma de pago	Autorización para cobrar a la cuenta corriente		
12-20	instrucciones para depositar			
	en cuenta corriente			

Eduardo Calandino

Oficina recibidora

Oficina de Marcas y Patente de Los Estados
Unidos (USPTO) (RO/US)

263
230

12-20-1 Por la presente se autoriza a cobrar
los honorarios totales indicados anteriormente
a mi cuenta corriente /

12-20-2 por la presente se autoriza para cobrar
cualquier pago adicional o crédito de sobre pago
sobre los honorarios totales indicados
anteriormente a mi cuenta corriente /

12-20-3 Por la presente se autoriza cobrar los
honorarios para la preparación y trámite de
los documentos de prioridad a la Oficina
Internacional de WIPO a mi cuenta corriente /

12-21 No. de Cuenta Corriente 13-2755

12-22 Fecha 02 Febrero 2000 (02.02.2000)

12-23 Nombre y Firma Carol S. Quagliato

VALIDACIÓN DE APUNTES Y SUGERENCIAS

13-2-2 Mensajes de Estados de Validación

Green?

Existe la posibilidad de que se
hagan validaciones
adicionales.

Eduardo Calvado

~~264~~
231

Los siguientes Estados no han
sido designados

13-2-6 Contenido en Mensajes de Validación

Green ?

Referencia de número anexos
a la copia del poder general no
indicadas.

13-2-8 Pagos en Mensajes de Validación

Green?

Favor verificar que la cuenta
corriente se encuentre vigente
con la Oficina de recibo
seleccionada.

Eduardo Calado

265
232

REIVINDICACIONES

1. Una composición farmacéutica la cual consiste de una cantidad terapéuticamente eficaz de un compuesto seleccionada de una estatina de ácido abierto de dihidroxi y una sal farmacéuticamente aceptable o ésteres del mismo y un portador farmacéuticamente aceptable, formulado como una forma de dosis de acción retardada en el cual la liberación substancial del compuesto de la forma de dosis después de un suministro oral al paciente se demora hasta que la forma de dosis pase por el estómago.
2. La composición farmacéutica de acuerdo a la reivindicación 1, en el cual como máximo se libera un 10% del peso de la estatina hacia el estómago del paciente después de su suministro.
3. La composición farmacéutica de acuerdo a la reivindicación 2, en la cual se libera una máxima cantidad un 5% del peso de la estatina en el estomago del paciente después de sus suministro.

Edwardo Caludo
Edwardo Caludo Noguera
ABogado
BOGOTÁ, D.C. - COLOMBIA
TEL: 312 200 1111
CEL: 312 200 1111
CORREO: eduardo.caludo@bucabogados.com

286
233

4. La composición farmacéutica de acuerdo a la reivindicación 3 en el cual se libera una máxima cantidad un 1% del peso de la estatina en el estomago del paciente después de sus suministroo.

5. La composición farmacéutica de acuerdo a la reivindicación 1 en la cual la composición se encuentra totalmente revestida.

6. La composición farmacéutica de acuerdo a la reivindicación 5 en el cual la forma de dosis es entéricamente revestida.

7. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la forma de dosis consta de gránulos entericamente revestidos de estatina de ácido abierto de dihidroxi o una sal farmacéuticamente aceptable de ésteres del mismo.

8. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la forma de dosis consta de gránulos entericamente revestidos de simvastatina de ácido abierto de dihidroxi o una sal farmacéuticamente aceptable de ésteres del mismo.

9. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la forma de dosis consta de gránulos entericamente

Edmundo Calvo
"REGISTRO OFICIAL"
MARCA-INGLES
Enero de 19.6

revestidos de estática de ácido abierto de dihidroxi o una sal farmacéuticamente aceptable de ésteres del mismo, siempre y cuando que la forma de dosis no conste de gránulos de aspirina.

~~267~~
234

10. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la composición es formulada de una forma de dosis entericamente revestida y de rápida liberación farmacéutica.

11. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la composición es formulada de una forma de dosis farmacéutica entericamente revestida y de liberación de tiempo controlado.

12. La composición farmacéutica de acuerdo a la reivindicación 1, en la cual la composición es formulada de un dispositivo de liberación de droga que consta de:

- (A) Un núcleo comprimido de una mezcla que consiste de:
- (i) una cantidad terapéuticamente eficaz del compuesto; y

Edwardo Calado
Edwardo Viguera
COR OFICIAL
SOL-INGLES
10 de 10 6

268
235

(ii) un polímero el cual cuando se somete a hidratación forma unas partículas gelatinosas microscópicas; y

(B) un revestimiento polimerico impermeable insoluble en agua e impermeable al agua el cual consiste de un polímero y plastificados, el cual cubre y se adhiere al núcleo, el revestimiento tiene un pluralidad de aperturas conformadas expuestas entre aproximadamente 1 y alrededor de 75% del la superficie del núcleo;

en el cual el promedio de liberación del compuesto del dispositivo es la función del número y tamaño de las aperturas.

13. La composición farmacéutica de acuerdo a la reivindicación 12, en la cual el dispositivo de liberación de la droga consta adicionalmente de un revestimiento enterico externo al revestimiento polimérico insoluble en agua e impermeable al agua.

14. La composición farmacéutica de acuerdo a la reivindicación 1, en la cual la estatina es seleccionada en formas de ácido abierto de dihidroxi de lovastatina, simvastatina, atorvastatina, cerivastatina,

Eduardo Palacios
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nivastatina y ZD-4522 y sales farmacéuticamente aceptables y ésteres del mismo.

15. La composición farmacéutica de acuerdo a la reivindicación 1, en la cual la estatina es seleccionada en formas de ácido abierto de dihidroxi de lovastatina, simvastatina y sales farmacéuticamente aceptables y ésteres del mismo.

16. La composición farmacéutica de acuerdo a la reivindicación 1, en la cual la estatina es seleccionada en formas de ácido abierto de dihidroxi de simvastatina y sales farmacéuticamente aceptables y ésteres del mismo.

17. La composición farmacéutica de acuerdo a la reivindicación 1, en la cual la estatina es una sal farmacéuticamente aceptable de la simvastatina de ácido abierto de dihidroxi.

18. La composición farmacéutica de acuerdo a la reivindicación 1, en la cual la estatina es una sal de calcio de la simvastatina de ácido abierto de dihidroxi.

Eduardo Calvo
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19. La composición farmacéutica de acuerdo a la reivindicación 1, en la cual la estatina es una sal de amonio de la simvastatina de ácido abierto de dihidroxi.

20. La composición farmacéutica de acuerdo a la reivindicación 1, en la cual la estatina es una sal de calcio de la simvastatina de ácido abierto de dihidroxi la cual tiene un patrón de difracción de polvos de rayos x obtenida utilizando la radiación CuKa la cual se caracteriza mediante las reflexiones de los espacios - d de 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 y 3.28A.

21. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la estatina es seleccionada en formas de ácido abierto de dihidroxi de lovastatina, simvastatina, atorvastatina, cerivastatina, nivastatina y ZD-4522 y sales farmacéuticamente aceptables y ésteres del mismo.

22. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la estatina es seleccionada en formas de ácido abierto de dihidroxi de lovastatina, simvastatina y sales farmacéuticamente aceptables y ésteres del mismo.

EdUARDO CALABO
SECRETARIO
DE LA ASAMBLEA
DE LA CIUDAD DE
BOGOTÁ

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23. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la estatina es seleccionada en formas de ácido abierto de dihidroxi de simvastatina y sales farmacéuticamente aceptables y ésteres del mismo.

24. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la estatina es una sal farmacéuticamente aceptable de simvastatina de ácido abierto de dihidroxi.

25. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la estatina es una sal de calcio de la simvastatina de ácido abierto de dihidroxi.

26. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la estatina es una sal de amonio de la simvastatina de ácido abierto de dihidroxi.

27. La composición farmacéutica de acuerdo a la reivindicación 5, en la cual la estatina es una sal de calcio de la simvastatina de ácido abierto de dihidroxi la cual tiene un patrón de difracción de polvos de rayos x obtenida utilizando la radiación CuK α la cual se

Edwardo Calado

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caracteriza mediante las reflexiones de los espacios - d de 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 y 3.28A.

28. La composición de acuerdo a la reivindicación 27 la cual a continuación consta de BHA.

29. La composición de acuerdo a la reivindicación 27 la cual a continuación consta de propilo de galato.

30. La composición de acuerdo a la reivindicación 27 la cual a continuación consta de BHA y propilo de galato.

31. Una composición oral farmacéutica la cual se fabrica al mezclar una cantidad que se revuelve de un compuesto seleccionado de una estatina de ácido abierto de dihidroxi y una sal farmacéuticamente aceptable o ésteres del mismo con un portador farmacéuticamente aceptable en una forma de dosis de liberación retardada.

32. Un proceso para la preparación de una composición oral farmacéutica la cual se fabrica al mezclar una cantidad que se

Edwin Salas
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revuelve de un compuesto seleccionado de una estatina de ácido abierto de dihidroxi y una sal farmacéuticamente aceptable o ésteres del mismo con un portador farmacéuticamente aceptable en una forma de dosis de liberación retardada.

33. El uso de estatina de ácido abierto de dihidroxi y una sal farmacéuticamente aceptable o ésteres del mismo para la preparación de un medicamento de suministro oral adaptado para una liberación de acción retardada en el cual la liberación substancial de la estatina después del suministro oral no sucede hasta que el medicamento pase a través del estomago.

34. El uso de acuerdo a la reivindicación 33 en el cual por lo menos un 10% del peso de la estatina se libera en el estomago del paciente después de su suministro.

35. El uso de acuerdo a la reivindicación 33 en el cual por lo menos un 5% del peso de la estatina se libera en el estomago del paciente después de su suministro.

Eduardo Chaves

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36. El uso de acuerdo a la reivindicación 33 en el cual por lo menos un 1% del peso de la estatina se libera en el estomago del paciente después de su suministro.

37. El uso de simvastatina de ácido abierto de dihidroxi o una sal farmacéuticamente aceptable o ésteres del mismo para la preparación del medicamento de la reivindicación 33.

38. El uso de estatina de ácido abierto de dihidroxi y una sal farmacéuticamente aceptable o ésteres del mismo para la preparación de un medicamento de suministro oral adaptado para una liberación de acción retardada útil para la para la liberación de un 90% del peso de la estatina en su forma de ácido abierto de dihidroxi a la mucosa intestinal de un paciente después del suministro oral.

39. El uso de acuerdo a la reivindicación en el cual por lo menos un 95% del peso de la estatina liberada en su forma de ácido abierto de dihidroxi a la mucosa intestinal en un paciente después del suministro oral.

40. El uso de acuerdo a la reivindicación en el cual por lo menos un 99% del peso de la estatina liberada en su forma de ácido abierto

Edwardo Salgado
"Edwardo Salgado Saguera"
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"Edwardo Salgado Saguera"
"Edwardo Salgado Saguera"

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de dihidroxi a la mucosa intestinal en un paciente después del suministro oral.

41. El uso de ácido abierto de dihidroxi de simvastatina o una sal farmacéuticamente aceptable o éster de la misma para preparar el medicamento de la reivindicación 38.

42. El uso de estatina de ácido abierto de dihidroxi o una sal farmacéuticamente aceptable o éster del mismo para la preparación de un medicamento oral adaptado para la liberación tardía útil para la inhibición de reductase HMG-CoA en un paciente que necesita dicho tratamiento en el cual la liberación substancial de la estatina después de su suministro oral se retarda hasta que el medicamento pasa por el estómago.

43. El uso de estatina de ácido abierto de dihidroxi o una sal farmacéuticamente aceptable o éster del mismo para la preparación de un medicamento oral adaptado para la liberación tardía útil para tratar la hipercolesterolemia en un paciente que necesita dicho tratamiento en el cual la liberación substancial de la estatina después de su suministro oral se retarda hasta que el medicamento pasa por el estómago.

Eduardo Calado
Eduardo Calado
Ingeniero en Alimentos
Instituto Tecnológico de México

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44. El uso de estatina de ácido abierto de dihidroxi o una sal farmacéuticamente aceptable o éster del mismo para la preparación de un medicamento oral adaptado para la liberación tardía útil para la prevención o reducción del riesgo del desarrollo de enfermedades arteriosclerosis en un paciente que tenga el riesgo de desarrollar enfermedades arterioscleróticas en el cual la liberación substancial de la estatina después de su suministro oral se retarda hasta que el medicamento pase por el estomago.

45. El uso de la reivindicación 44 en el cual el medicamento es útil para prevenir y reducir el riesgo de desarrollar la enfermedad arterosclerótica seleccionada de un una enfermedad cardiovascular , enfermedad cerebrovascular y enfermedad de un vaso periférico.

46. El uso de la reivindicación 44 en el cual el medicamento es útil para prevenir y reducir el riesgo de desarrollar enfermedades coronarias.

47. El uso de estatina de ácido abierto de dihidroxi o una sal farmacéuticamente aceptable o éster del mismo para la preparación de un medicamento oral adaptado para la liberación tardía útil para

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tratar enfermedades arteriosclerótica en un paciente que necesita dicho tratamiento en el cual la liberación substancial de la estatina después de su suministro oral se retarda hasta que el medicamento pasa por el estómago.

48. El uso de la reivindicación 47 en el cual el medicamento es útil para tratar la enfermedad arteriosclerótica seleccionada de una enfermedad cardiovascular, enfermedad cerebrovascular y enfermedad de un vaso periférico.

49. El uso de acuerdo a la reivindicación 47 en el cual el medicamento es útil para tratar enfermedades coronarias.

50. El uso de estatina de ácido abierto de dihidroxi o una sal farmacéuticamente aceptable o éster del mismo para la preparación de un medicamento oral adaptado para la liberación tardía útil para prevenir o reducir los riesgos de incidencia y recurrencia de enfermedades arterioscleróticas en un paciente que se encuentra en riesgo de contraer enfermedades arterioscleróticas en el cual la liberación substancial de la estatina después de su suministro oral es retardada hasta que el medicamento pasa por el estómago.

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51. El uso de acuerdo a la reivindicación 50 en la cual el medicamento es útil para prevenir y reducir el riesgo de incidentes o recurrencia de enfermedades arterioscleróticas en personas que se encuentran ya con la enfermedad.

52. El uso de acuerdo a la reivindicación 50 en la cual el medicamento es útil para prevenir y reducir el riesgo de incidentes o recurrencia de enfermedades arterioscleróticas en personas que se encuentran en el riesgo de desarrollar la enfermedad.

53. El uso de acuerdo a la reivindicación 50 en la cual el medicamento es útil para prevenir y reducir el riesgo de incidentes o recurrencia en el caso de enfermedades arterioscleróticas seleccionadas en el caso de enfermedades coronarias, en el caso de enfermedades cerebrovascular e intermitente claudicación.

54. El uso de acuerdo a la reivindicación 50 en la cual el medicamento es útil para prevenir y reducir el riesgo de incidentes o recurrencia en el caso de enfermedades coronarias seleccionada por el caso de muerte por enfermedad coronaria, infarto del miocardio o procedimientos de revascularización coronaria.

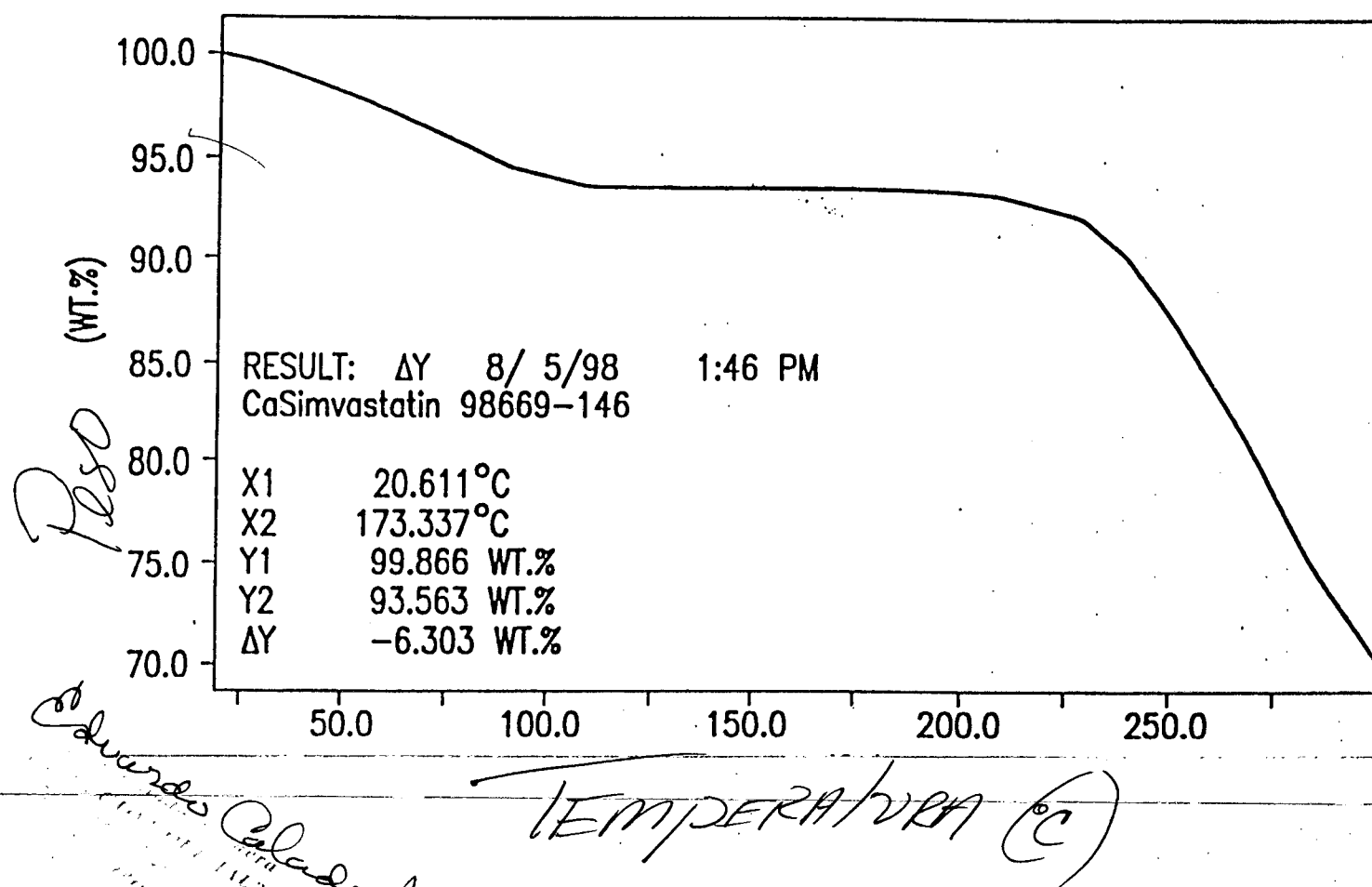
Edwardo Calado
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58. El uso de acuerdo a las Reivindicaciones 42 hasta la 55 en la cual la forma de estatina es una sal farmacéuticamente o simvastatina de ácido abierto de dihidroxi.

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GRÁFICA 1

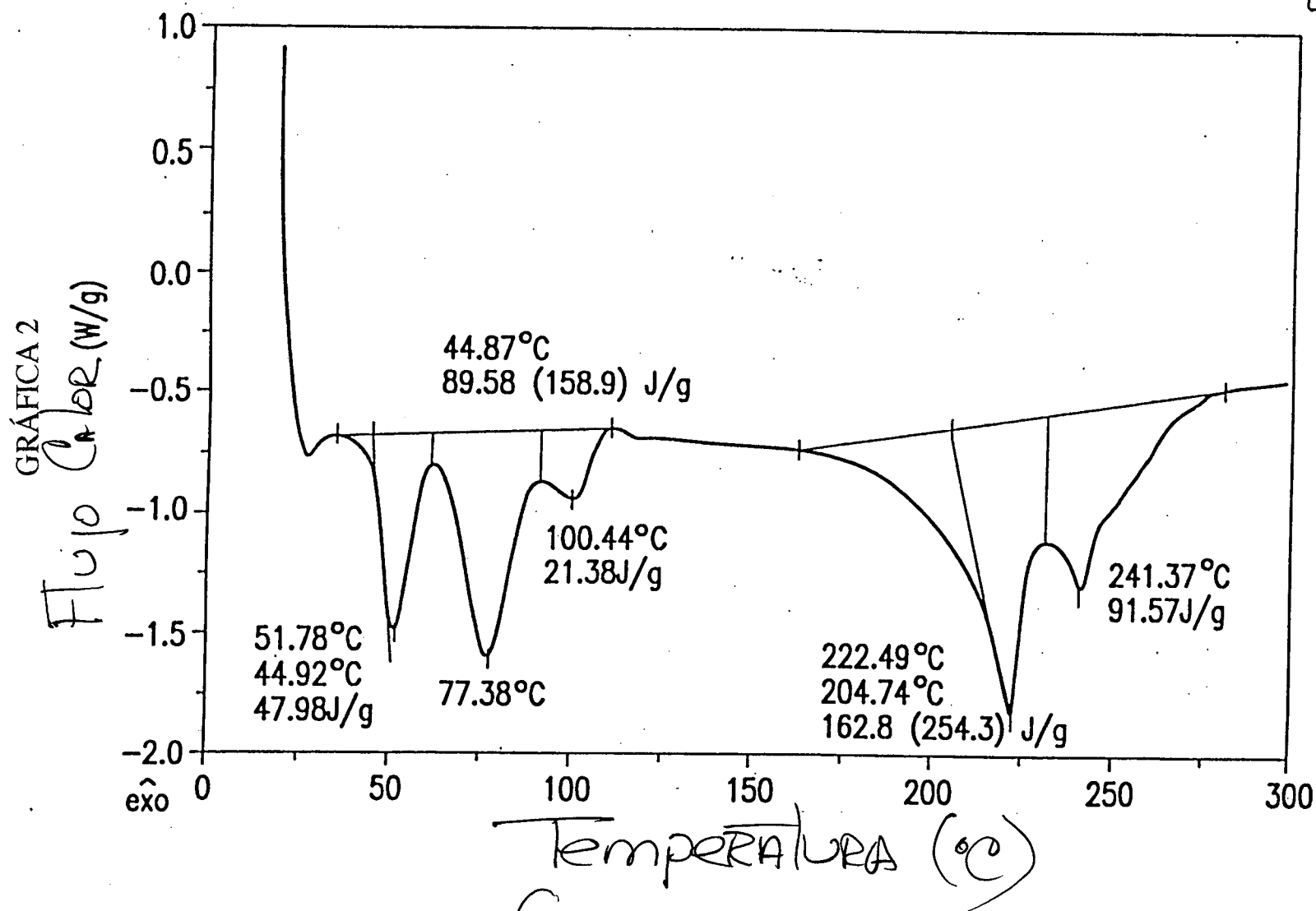
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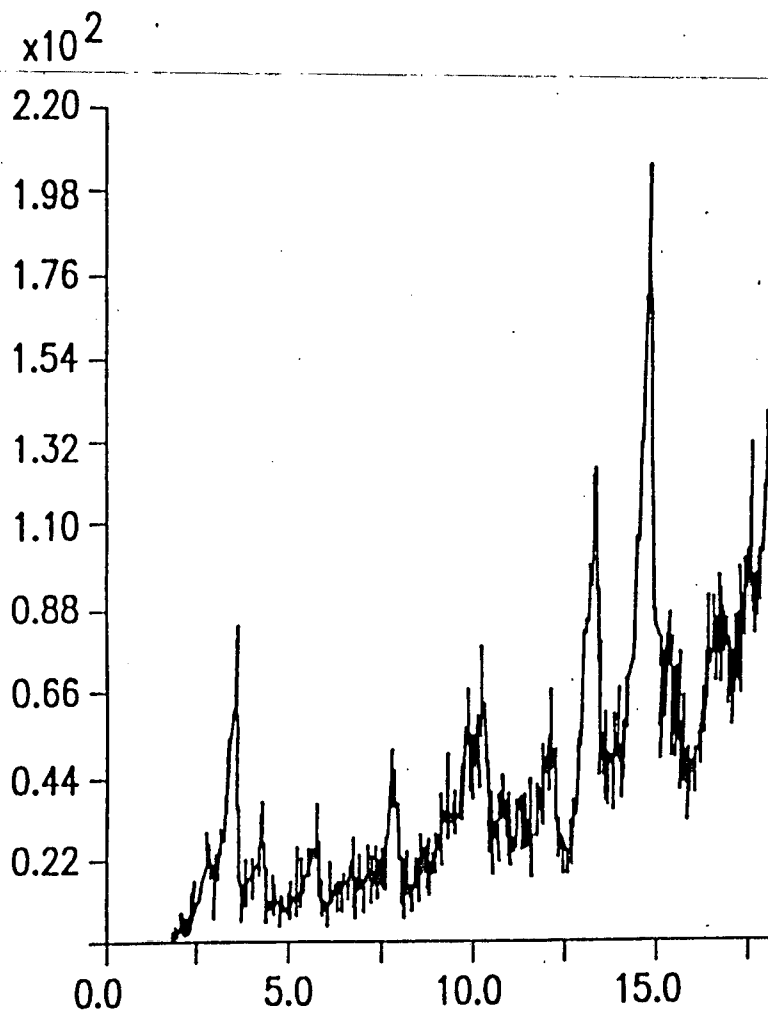
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GRÁFICA 3

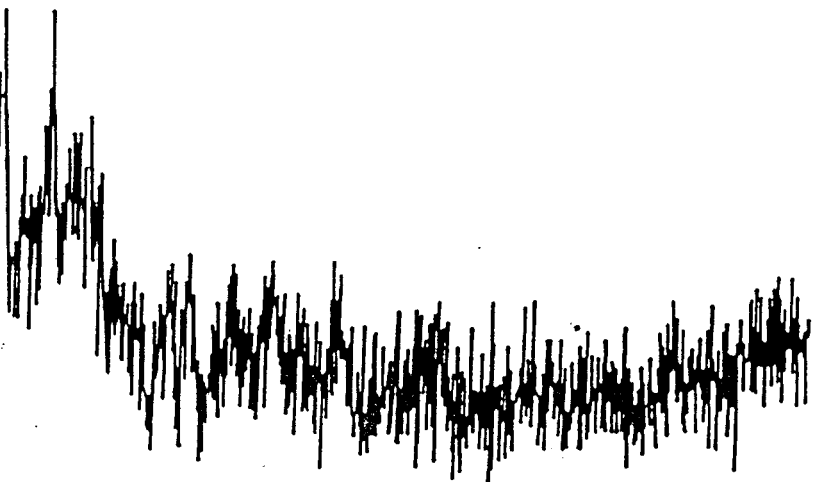


GRÁFICA

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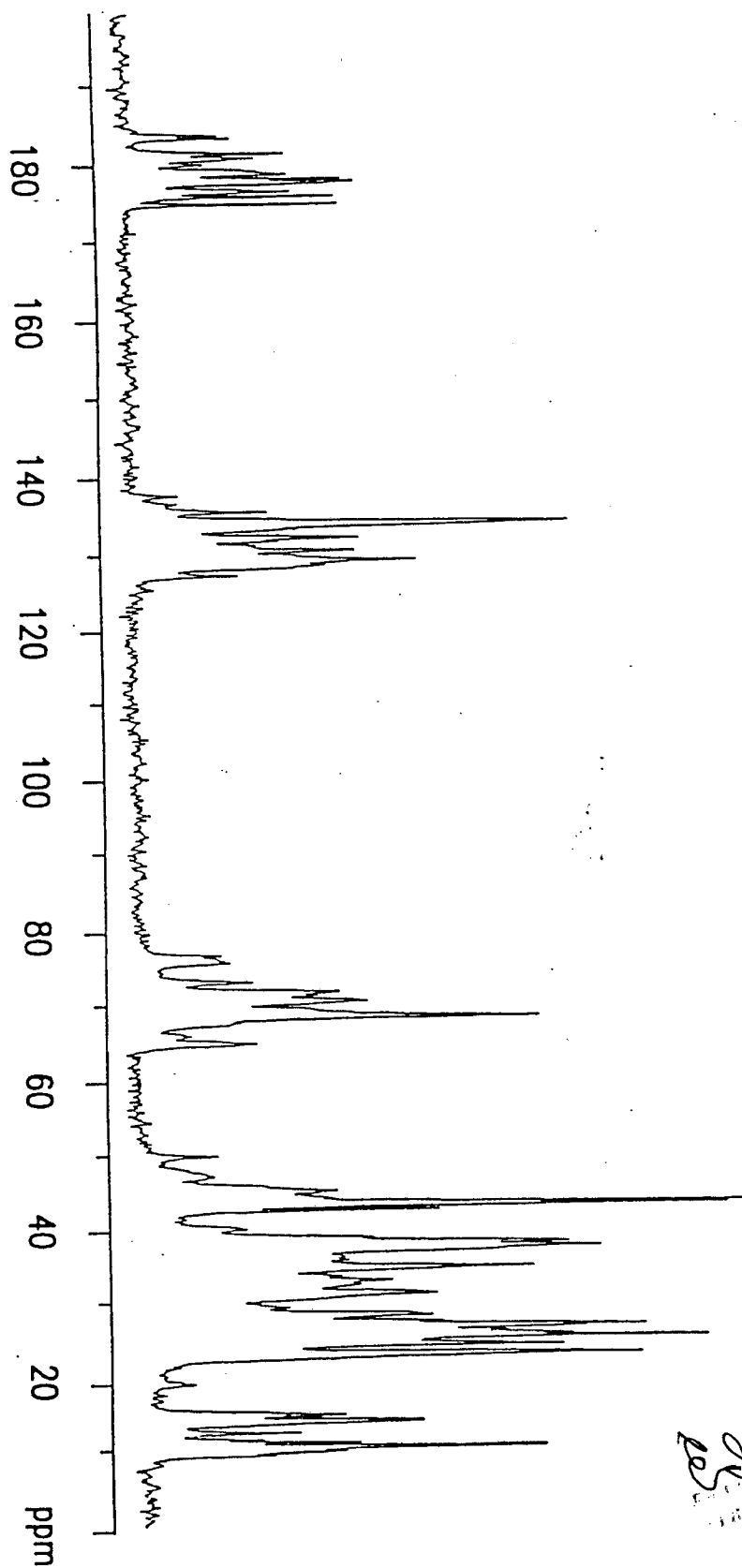
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GRÁFICA 4

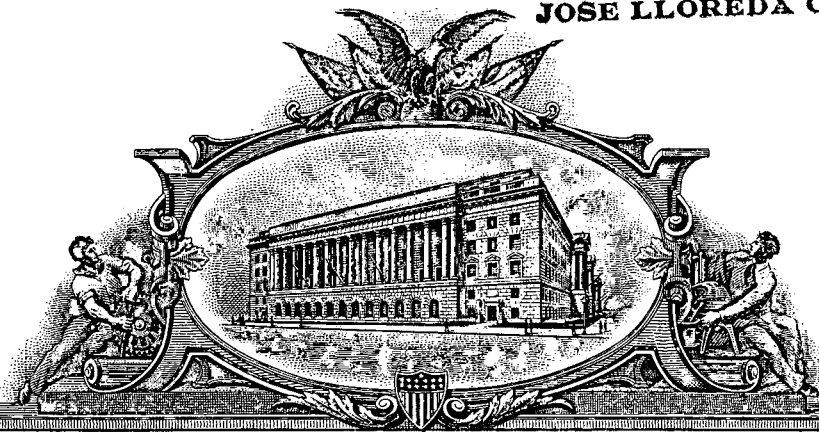


GRÁFICA 4

Escuela Politécnica
de Ingeniería
de la Universidad
de los Andes

JOSE LLOREDA CAMACHO & CO.
HERRERA & CO., INC.
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THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

May 10, 2000

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY OF
THE BELOW IDENTIFIED INTERNATIONAL APPLICATION AS
ORIGINALLY FILED AND ANY CORRECTIONS THERETO FROM THE
RECORDS OF THE UNITED STATES PATENT AND TRADEMARK
OFFICE ACTING AS A RECEIVING OFFICE UNDER THE PATENT
COOPERATION TREATY.**

APPLICATION NUMBER: PCT/US00/02626

FILING DATE: February 2, 2000



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. R. GRANT
Certifying Officer

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PCT 20416Y

PCT REQUEST

Original (for SUBMISSION) - printed on 02.02.2000 11:38:15 AM

0 0-1	For receiving Office use only International Application No.	PCT/US 00/02626
0-2	International Filing Date	02 FEB 2000 (02.02.00)
0-3	Name of receiving Office and "PCT International Application"	PCT INTERNATIONAL APPLICATION RO/US
0-4 0-4-1	Form - PCT/RO/101 PCT Request Prepared using	PCT-EASY Version 2.90 (updated 15.12.1999)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	PCT 20416Y
I	Title of invention	DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE INHIBITORS
II II-1 II-2 II-4 II-5	Applicant This person is: Applicant for Name Address:	applicant only all designated States except US MERCK & CO., INC. 126 East Lincoln Avenue Rahway, NJ 07065-0907 United States of America
II-6 II-7 II-8 II-9	State of nationality State of residence Telephone No. Facsimile No.	US US 732-594-3809 732-594-4720
III-1 III-1-1 III-1-2 III-1-4 III-1-5	Applicant and/or inventor This person is: Applicant for Name (LAST, First) Address:	applicant and inventor US only TILLYER, Richard, D. 126 East Lincoln Avenue Rahway, NJ 07065-0907 United States of America
III-1-6 III-1-7	State of nationality State of residence	GB US

287
254

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PCT 20416Y

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III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	REIDER, Paul, J.
III-2-5	Address:	126 East Lincoln Avenue Rahway, NJ 07065-0907 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	GRABOWSKI, Edward, J., J.
III-3-5	Address:	126 East Lincoln Avenue Rahway, NJ 07065-0907 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	XU, Feng
III-4-5	Address:	126 East Lincoln Avenue Rahway, NJ 07065-0907 United States of America
III-4-6	State of nationality	CN
III-4-7	State of residence	US
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	VEGA, Jose, M.
III-5-5	Address:	126 East Lincoln Avenue Rahway, NJ 07065-0907 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US
IV-1	Agent or common representative; or address for correspondence	
	The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
IV-1-1	Name	MERCK & CO., INC.
IV-1-2	Address:	126 East Lincoln Avenue Rahway, NJ 07065-0907 United States of America
IV-1-3	Telephone No.	732-594-3809
IV-1-4	Facsimile No.	732-594-4720

PCT REQUEST

Original (for SUBMISSION) - printed on 02.02.2000 11:38:15 AM

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AL AM AT AU AZ BA BB BG BR BY CA CH&LI CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	08 March 1999 (08.03.1999)
VI-1-2	Number	60/123,227
VI-1-3	Country	US
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	09 March 1999 (09.03.1999)
VI-2-2	Number	09/264,744
VI-2-3	Country	US

289
256

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PCT 20416Y

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VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Check list	number of sheets	electronic file(s) attached
VIII-1	Request	5	-
VIII-2	Description	40	-
VIII-3	Claims	8	-
VIII-4	Abstract	1	20416y_abstract_for_barbara_cozzi.txt
VIII-5	Drawings	4	-
VIII-7	TOTAL	58	-
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-9	Separate signed power of attorney	✓	-
VIII-10	Copy of general power of attorney	✓	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	Figure of the drawings which should accompany the abstract	1	
VIII-19	Language of filing of the international application	English	
IX-1	Signature of applicant or agent	<i>Carol S. Quagliato</i>	
IX-1-1	Name	MERCK & CO., INC.	
IX-1-2	Name of signatory	Carol S. Quagliato	
IX-1-3	Capacity	Attorney	

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(02.02.00)

10-1	Date of actual receipt of the purported international application	520 Rec'd PCT/PTO 02 FEB 2001
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

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290
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PCT REQUEST

PCT 20416Y

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11-1	Date of receipt of the record copy by the International Bureau	
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291
58

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):
TILLYER, Richard D.; REIDER, Paul J.; GRABOWSKI, Edward J.J.; XU, Feng

hereby appoints (appoint) the following person as:



common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MERCK & CO., INC.
126 East Lincoln Avenue
Rahway, New Jersey 07065-0907
United States of America

to represent the undersigned before



all the competent International Authorities

in connection with the international application identified below:

Title of the invention: DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A
REDUCTASE INHIBITORS

Applicant's or agent's file reference: PCT 20416Y

International application number (if already available):

filed with the following Office United States Receiving Office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):

Date: FEB 1 2000

Richard D. Tillyer

Date: FEB 1, 2000

Paul J. Reider

Date: Feb 1, 2000

Edward J. J. Grabowski

Date: Feb 1, 2000

Feng Xu

292
259**PCT****POWER OF ATTORNEY**

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):
VEGA, Jose M.

hereby appoints (appoint) the following person as:



common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MERCK & CO., INC.
126 East Lincoln Avenue
Rahway, New Jersey 07065-0907
United States of America

to represent the undersigned before



all the competent International Authorities

in connection with the international application identified below:

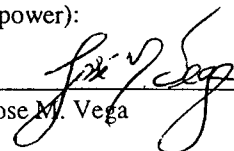
**Title of the invention: DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A
REDUCTASE INHIBITORS**

Applicant's or agent's file reference: PCT 20416Y

International application number (if already available):

filed with the following Office United States Receiving Office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):

Date: JANUARY 5, 2000
Jose M. Vega

Date: _____

Date: _____

Date: _____

293
260**General Corporate Resolution #5****PATENT MATTERS**

RESOLVED, that any of the following:

Raymond V. Gilmartin-Chairman of the Board, President and Chief Executive Officer
Kenneth C. Frazier-Senior Vice President and General Counsel
Joseph F. DiPrima-Vice President and Assistant General Counsel
Paul D. Matukaitis-Vice President and Assistant General Counsel
Edward Murray-Counsel, Litigation
Charles M. Caruso-Counsel, International
W. Gwyn Cole-Counsel-European Patents
Mark R. Daniel-Counsel, Patents
David L. Rose-Counsel, Patents
Jack L. Tribble-Counsel, Patents
Melvin Winokur-Counsel, Patents
Donna L. Pollock-Administrator, Patents

are authorized to execute and to revoke on behalf of Merck & Co., Inc. and its affiliates (including subsidiaries) the following documents relating to patent matters:

Powers of attorney as fully in law as may be necessary and proper in connection with the acquisition, registration, maintenance and enforcement of patents and applications for patents, including powers of attorney relating to the prosecution or defense of patent rights before courts of law or other governmental tribunals, agencies or departments; affidavits and declarations; and any other documents which are necessary and proper for the acquisition, registration, maintenance, litigation and protection of patents.

294
261CERTIFICATION

I, DEBRA A. BOLLWAGE, Assistant Secretary of Merck & Co., Inc., a Corporation duly organized and existing under the laws of the State of New Jersey, do hereby certify that the attached, presently in full force and effect, is a true and correct copy of General Corporate Resolution #5, Patent Matters, as amended on November 23, 1999, effective December 1, 1999, by the Board of Directors of said Corporation at a meeting thereof duly called and held on November 23, 1999 at which a quorum was present.

IN WITNESS WHEREOF, I have hereunto subscribed my signature and affixed the seal of the Corporation this 9th day of December, 1999.

Debra Bollwage
Assistant Secretary

SEAL

295
262

PATENT COOPERATION TREATY
General Appointment of Agent or Common Representative

The undersigned applicant(s) hereby appoints:

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Richard C. Billups
Valerie J. Camara
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All of Merck & Co., Inc., 126 East Lincoln Avenue, Rahway, New Jersey 07065

as agents (attorneys)

to act on his behalf before the competent International Authorities in connection with any and all International Applications filed by him and of which he is the sole applicant and to receive payments on his behalf.

[Place] Rahway, New Jersey

[Date] January 4, 2000

[Signature of Applicant]
MERCK & CO., INC.

Donna L. Pollock
Donna L. Pollock
Administrator, Patents

296
263

PCT (ANNEX - FEE CALCULATION SHEET)

PCT 20416Y

Original (for SUBMISSION) - printed on 02.02.2000 11:38:15 AM

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only			
0-1	International Application No.	PCT/US 00/02626		
0-2	Date stamp of the receiving Office	02 FEB 2000 (02.02.00)		
0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet			
0-4-1	Prepared using	PCT-EASY Version 2.90 (updated 15.12.1999)		
0-9	Applicant's or agent's file reference	PCT 20416Y		
2	Applicant	MERCK & CO., INC., et al.		
12	Calculation of prescribed fees	fee amount/multiplier	total amounts (USD)	
12-1	Transmittal fee T	⇒	240	240
12-2	Search fee S	⇒	990	990
12-3	International fee Basic fee (first 30 sheets) b1	427		427
12-4	Remaining sheets	28		
12-5	Additional amount (X)	10		280
12-6	Total additional amount b2	280		
12-7	b1 + b2 = B	707		707
12-8	Designation fees Number of designations contained in international application	82		
12-9	Number of designation fees payable (maximum 8)	8		
12-10	Amount of designation fee (X)	92		
12-11	Total designation fees D	736		736
12-12	PCT-EASY fee reduction R	-132		-132
12-13	Total International fee (B+D-R) I	⇒	1,311	1,311
12-14	Fee for priority document Number of priority documents requested	2		
12-15	Fee per document (X)	15		
12-16	Total priority document fee P	⇒	30	30
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒	2,571	
12-19	Mode of payment	authorization to charge deposit account		
12-20	Deposit account instructions The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	is hereby authorized to charge the total fees indicated above to my deposit account	✓		
12-20-2	is hereby authorized to charge any deficiency or credit any over-payment in the total fees indicated above to my deposit account	✓		

297
284

PCT (ANNEX - FEE CALCULATION SHEET)

PCT 20416Y

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12-20-3	is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account	✓
12-21	Deposit account No.	13-2755
12-22	Date	02 February 2000 (02.02.2000)
12-23	Name and signature	Carol S. Quagliato <i>Carol S. Quagliato</i>

VALIDATION LOG AND REMARKS

13-2-2	Validation messages States	Green? More designations could be made. The following States have not been designated: KP. Please verify.
13-2-6	Validation messages Contents	Green? Reference number for attached copy of general power of attorney not indicated.
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

298
265

TITLE OF THE INVENTION

DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE
INHIBITORS

5 FIELD OF THE INVENTION

The instant invention relates to the use of dihydroxy open acid statins and salts and esters thereof, which are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, in such a way so as to minimize their in vivo lactonization, and to a particular crystalline hydrated form of the calcium salt of
10 dihydroxy open acid simvastatin referred to herein as compound I.

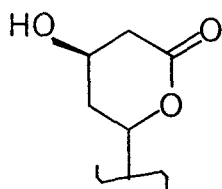
BACKGROUND OF THE INVENTION

It has been clear for several decades that elevated blood cholesterol is a major risk factor for coronary heart disease (CHD), and many studies have shown that
15 the risk of CHD events can be reduced by lipid-lowering therapy. Prior to 1987, the lipid-lowering armamentarium was limited essentially to a low saturated fat and cholesterol diet, the bile acid sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of these treatments have limited efficacy or tolerability, or both. With the introduction of lovastatin
20 (MEVACOR®; see US Patent No. 4,231,938), the first inhibitor of HMG-CoA reductase to become available for prescription in 1987, for the first time physicians were able to obtain comparatively large reductions in plasma cholesterol with very few adverse effects.

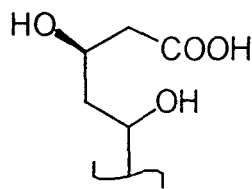
In addition to the natural fermentation products, mevastatin and
25 lovastatin, there are now a variety of semi-synthetic and totally synthetic HMG-CoA reductase inhibitors, including simvastatin (ZOCOR®; see US Patent No. 4,444,784), pravastatin sodium salt (PRAVACHOL®; see US Patent No. 4,346,227), fluvastatin sodium salt (LESCOL®; see US Patent No. 5,354,772), atorvastatin calcium salt (LIPITOR®; see US Patent No. 5,273,995) and cerivastatin sodium salt (also known
30 as rivastatin; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors, are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996). The HMG-CoA reductase inhibitors described above belong to a structural class of compounds which contain a moiety which can exist as either a 3-hydroxy lactone ring
35 or as the corresponding ring opened dihydroxy open-acid, and are often referred to as

289
266

"statins." An illustration of the lactone portion of a statin and its corresponding open-acid form is shown below.

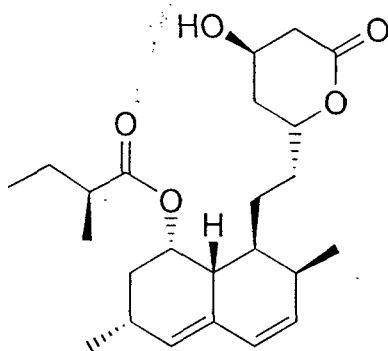


Lactone

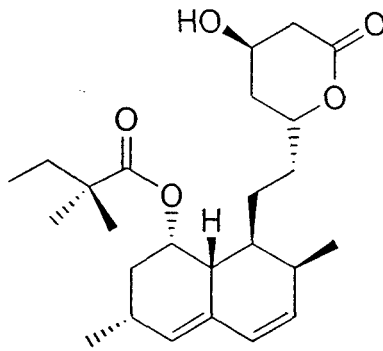


Dihydroxy Open-Acid

- 5 Salts of the dihydroxy open-acid can be prepared, and in fact, as noted above, several of the marketed statins are administered as the dihydroxy open acid salt forms. Lovastatin and simvastatin are marketed worldwide in their lactonized form. Lovastatin is shown as structural formula II, and simvastatin is shown as structural
- 10 formula III, below.



II



III

- The lactonized forms of the statins are not active inhibitors of HMG-CoA reductase, but the dihydroxy open acid forms are. It is known that condensation of the dihydroxy open acid form of statins to the corresponding lactonized form occurs under acidic conditions, that is at about pH 4 or under. Therefore, due to the low gastric pH of the stomach, a statin conventionally administered by oral dosing in its lactone form will remain largely in its lactone form in the stomach. The vast majority of the drug will still be in the lactone form at the time of absorption from the intestine following oral dosing with the lactone. After absorption, the lactone enters the liver and it is in the hepatocytes that the lactone can be metabolized to the active
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300
267

open acid form, a reaction catalyzed by two hepatic esterases or "lactonases," one which is in the cytosolic and the other in the microsomal fraction. Once in the blood there is an additional plasma esterase which can also hydrolyze the lactone to the open acid. There may be some minimal chemical, i.e., non-enzymatic, hydrolysis that
5 occurs in blood or in the liver; however, at the pH in blood and liver, there should not be any lactonization, i.e., conversion of open acid back to the lactone.

A statin conventionally administered by oral dosing in its dihydroxy open acid form or a pharmaceutically acceptable salt or ester thereof will tend to convert to its lactone form in the acidic environment of the stomach, so that a mixture
10 of the open ring and the corresponding closed ring forms will co-exist there. For example, see M.J. Kaufman, International Journal of Pharmaceutics, 1990, 66(Dec 1), p. 97-106, which provides hydrolysis data that are used to simulate the extent of drug degradation that occurs in acidic gastric fluids following oral administration of several structurally related hypocholesterolemic agents, including simvastatin and lovastatin,
15 and also see A.S. Kearney, et al., Pharmaceutical Research, 1993, 10(10), p. 1461-1465, which describes the interconversion kinetics and equilibrium of CI-981 (atorvastatin in its free acid form). Therefore, even after conventional oral dosing with a dihydroxy open acid statin or a salt or ester thereof, a mixture of the open acid and the corresponding lactone form of the drug could exist by the time of absorption
20 from the intestine.

The preparation of the naturally occurring compound lovastatin and the semi-synthetic analog simvastatin leads to a mixture of the lactone and the open-ring dihydroxy acid forms. Several procedures have been published describing ways to make simvastatin from lovastatin, and most proceed through a lactone ring opening
25 step at some point in the process and sometimes formation of a salt at the resulting carboxy acid, and end with a ring-closing step in order to make the final simvastatin product. For example, U.S. Patent No. 4,820,850 describes a process for making simvastatin which involves opening the lactone ring of lovastatin and forming an alkyl-amide at the resulting carboxy acid, followed by protection of the two hydroxy
30 groups and methylation of the 8' acyl sidechain. After the methylation step, the hydroxy protecting groups are removed, the amide is hydrolyzed to the free acid and an ammonium salt of the free acid is formed, followed by a step to re-lactonize the ring. In U.S. Patent No. 4,444,784, the 8'-acyl sidechain of lovastatin is removed and the lactone ring opened in the first step, followed by re-lactonization of the ring and
35 protection of its hydroxy group. Next, the 8' position is acylated to introduce the

307
262

simvastatin sidechain and a deprotection step is performed to obtain the simvastatin final product. In another process disclosed in U.S. Patent No. 4,582,915, the potassium salt of the ring opened form of lovastatin is methylated at the 8' acyl sidechain, the free acid is then re-generated, and the dihydroxy open acid moiety is re-lactonized.

Since becoming available, millions of doses of simvastatin have been administered and these drugs have developed an excellent safety record. However, as noted in the Physician's Desk Reference (PDR), in rare instances myopathy has been associated with the use of all statins, including simvastatin. The mechanism for statin-related myopathy is currently poorly understood. It is also known that many drugs, including certain statins such as simvastatin, are metabolised in the liver and intestine by the cytochrome P450 3A4 (CYP 3A4) enzyme system. As also noted in the PDR, there are adverse drug interaction concerns if a potent inhibitor of CYP3A4, such as itraconazole, and a CYP3A4-metabolized statin are used together, and some cases of myopathy were found to have occurred in patients taking such a drug combination. Simvastatin has been administered to over 20 million patients worldwide in the past 11 years and has been demonstrated to be remarkably safe. However, the very low risk of myopathy is substantially increased when simvastatin is given together with potent inhibitors of CYP3A4. While the overall safety record for simvastatin is exceptional, it would be desirable to further optimize its safety profile by reducing the potential for drug interactions with inhibitors of CYP3A4. It would also be desirable to further reduce the already low rate of occurrence of myopathy associated with the use of all statins. Statins are among the most widely used drugs in the world, and therefore the benefit of any further optimization of their safety profile would be significant.

SUMMARY OF THE INVENTION

One object of this invention is to minimize or eliminate the in vivo lactonization of a dihydroxy open-acid statin. For oral administration, the dihydroxy open-acid statin or a pharmaceutically acceptable salt or ester thereof is to be administered so as to minimize formation of lactonized statin and thereby minimize the amount of lactonized statin that is absorbed from the intestine while maximizing the amount of dihydroxy open-acid statin that is absorbed from the intestine.

Accordingly, this invention involves a method of inhibiting HMG-CoA reductase with an effective inhibitory amount of an orally dosed statin comprising

302
269

delivering at least 90% of the dosed statin in its dihydroxy open acid form to the intestinal mucosa of a patient in need of such treatment.

The instant invention further provides a method for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

One embodiment of the first object is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is a gel extrusion module (GEM) drug delivery device.

Another embodiment of the first object is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is an enterically coated pharmaceutical dosage form. An additional aspect of this embodiment is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is selected from an enterically coated rapid-release pharmaceutical dosage form and an enterically coated time controlled-release pharmaceutical dosage form. Yet another aspect of this embodiment is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is an enterically coated gel extrusion module (GEM) drug delivery device.

The compound used for the above-described object and embodiments may particularly be dihydroxy open acid simvastatin and the pharmaceutically acceptable salts thereof, and more particularly a pharmaceutically acceptable salt thereof.

A second object of the instant invention is to provide novel HMG-CoA reductase inhibitors which are crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, and particularly the compound referred to herein as compound I.

Additional objects are to provide the use of the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, particularly compound I, for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, and also to provide pharmaceutical formulations, including conventional rapid-release, delayed-

303
270

release and time controlled-release formulations, including the GEM drug delivery device and enterically coated dosage forms, that can be used with the compounds. A further object is to provide a process for making compound I. Additional objects will be evident from the following detailed description.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a thermogravimetry (TG) weight loss curve for compound I obtained under a nitrogen flow at a heating rate of 10°C/minute.

Figure 2 is a differential scanning calorimetry (DSC) curve for compound I obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup.

Figure 3 is an x-ray powder diffraction (XRPD) pattern for compound I. The XRPD pattern was obtained using CuK α radiation. The ordinate or Y-axis is x-ray intensity (cpm) and the abscissa or X-axis is the angle two-theta (2 θ) in degrees.

Figure 4 is a solid-state ^{13}C nuclear magnetic resonance spectrum for Compound I.

DETAILED DESCRIPTION OF THE INVENTION

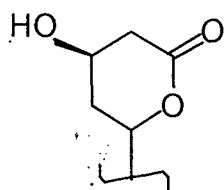
Applicants have now discovered that dihydroxy open acid statins may be less reliant on CYP3A4 metabolism than their closed ring lactonized counterparts. The instant invention involves methods and pharmaceutical compositions for orally administering open-ring dihydroxy open acid statins and salts and esters thereof, which are HMG-CoA reductase inhibitors, in such a way so as to minimize conversion to their lactonized counterparts. This allows for delivery of a dihydroxy open acid statin without its lactone counterpart directly to the absorptive mucosa of the small intestine thus allowing for absorption of the open acid statin into the portal circulation, penetration by active open acid statin into hepatocytes to achieve enhanced efficacy, and systemic exposure consisting of open acid moieties. More particularly, delayed-release of an orally administered dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof, for example dihydroxy open acid simvastatin or a salt thereof, until after passage through the stomach reduces the amount of lactone formed and absorbed in the body. Maintaining the statin in its open acid form in the body thereby reduces the potential for drug interactions between statins whose metabolism is CYP3A4-mediated and other active agents which inhibit the CYP3A4 enzymatic pathway, and also can provide enhanced efficacy. Moreover,

304
271

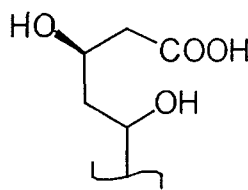
maintaining the statin in its open acid form in the body may have additional clinical benefits for all statins, even for those statins that are not significantly metabolized by the CYP3A4 enzymatic pathway.

5 In addition, a novel crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin has now been discovered to be a pharmaceutically suitable salt form having desirable physical properties for formulation into an anti-hypercholesterolemic drug composition.

10 The term "statin(s)" as used herein is intended to be defined as inhibitors of HMG-CoA reductase which belong to a structural class of compounds that contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open acid, wherein the lactone portion of the statin and its corresponding dihydroxy open-acid form is shown below.



Lactone



Dihydroxy Open-Acid

15 All hydrates, solvates and polymorphic crystalline forms of HMG-CoA reductase inhibitors having the above-described lactone/dihydroxy open acid moiety are included within the scope of the term "statin(s)". Pharmaceutically acceptable salts and esters of the dihydroxy open-acid statins are included within the scope of the term "statin(s)".

20 Statins inhibit HMG-CoA reductase in their dihydroxy open acid form. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33.

25 The term "dihydroxy open acid statin(s)" is intended to be defined as statins which contain the dihydroxy open acid moiety, including pharmaceutically acceptable salts and esters thereof. The phrases "dihydroxy open acid statin(s)" and "dihydroxy open acid statin(s) and the pharmaceutically acceptable salts and esters thereof" are used interchangeably herein and are both intended to encompass the open acid and salt and ester forms of the open acid of the statin, unless otherwise indicated.

305
272

All hydrates, solvates and polymorphic crystalline forms are encompassed within the the scope of the term "dihydroxy open acid statin(s)."

In the broadest embodiment, any dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof may be used with the present invention. Examples of dihydroxy open acid statins that may be used with the present invention include but are not limited to the dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof of: lovastatin (see US Patent No. 4,342,767); simvastatin (see US Patent No. 4,444,784), pravastatin, particularly the sodium salt thereof; fluvastatin particularly the sodium salt thereof; atorvastatin, particularly the calcium salt thereof; cerivastatin, particularly the sodium salt thereof, nisvastatin also referred to as NK-104 (see PCT international publication number WO 97/23200) and ZD-4522 (see US Patent No. 5,260,440, and Drugs of the Future, 1999, 24(5), pp. 511-513).

In a narrower embodiment, any dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof may be used with the present invention, such as those listed above, provided the statin is not pravastatin or fluvastatin. In a class of this embodiment, the open acid statin includes dihydroxy open acid lovastatin, simvastatin, atorvastatin, cerivastatin, nisvastatin and pharmaceutically acceptable salts thereof. Pharmaceutically acceptable salts of dihydroxy open acid simvastatin, particularly the ammonium and calcium salt forms thereof, are preferred for use in the methods and compositions of this invention. More particularly, the calcium salt of dihydroxy open acid simvastatin includes the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, and more particularly the hydrated calcium salt of dihydroxy open acid simvastatin referred to herein as compound I.

Herein, the term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, morpholine, 2,4,4-trimethyl-2-pentamine and tris(hydroxymethyl)aminomethane. Pharmaceutically acceptable

306
273

esters at the carboxylic acid group can be made by treating a dihydroxy open acid statin with an alcohol. Examples of pharmaceutically acceptable esters of dihydroxy open acid statins include, but are not limited to, -C₁₋₄ alkyl and -C₁₋₄ alkyl substituted with phenyl-, dimethylamino-, and acetylamino. "C₁₋₄ alkyl" herein

5 includes straight or branched aliphatic chains containing from 1 to 4 carbon atoms, for example methyl, ethyl, n-propyl, n-butyl, *iso*-propyl, *sec*-butyl and *tert*-butyl.

The instant invention involves methods and pharmaceutical compositions for orally administering open-ring dihydroxy open acid statins and salts and esters thereof, which are HMG-CoA reductase inhibitors, in such a way so as to minimize conversion to their lactonized counterparts. This allows for delivery of a dihydroxy open acid statin without its lactone counterpart directly to the absorptive mucosa of the small intestine thus allowing for absorption of the open acid statin into the portal circulation, penetration by active open acid statin into hepatocytes to achieve enhanced efficacy, and systemic exposure consisting of open acid moieties.

15 More particularly, delayed-release of an orally administered dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof, for example dihydroxy open acid simvastatin or a salt thereof, until after passage through the stomach reduces the amount of lactone formed and absorbed in the body. Maintaining the statin in its open acid form in the body thereby reduces the potential for drug

20 interactions between statins whose metabolism is CYP3A4-mediated and other active agents which inhibit the CYP3A4 enzymatic pathway, and also can provide enhanced efficacy. Administering a statin in its open acid form in such a way so as to minimize conversion to its lactonized counterpart, for example by using an oral delayed release dosage form, should reduce the potential for drug interaction compared to the

25 conventional administration of an open acid statin or its lactonized counterpart, for example by using an oral rapid release dosage form.

An object of this invention is to provide methods for reducing the amount of lactonized statin formed and absorbed in the body after oral administration of a dihydroxy open acid statin in order to achieve enhanced clinical benefits. A way to achieve this is to administer the dihydroxy open acid statin in a delayed-release pharmaceutical dosage form. A delayed-release pharmaceutical dosage form as defined herein is an orally administerable pharmaceutical dosage form or device that does not release a substantial amount of the active compound, i.e., the dihydroxy open-acid statin, until after the dosage form has passed through the stomach.

35 Therefore, substantial release of the active compound would initially occur after entry

307
274

into the duodenum. By "substantial release," it is intended that 90% or more by weight of the active compound in the delayed-release dosage form is released after entry into the duodenum, and that 10% or less by weight of the active compound in the delayed-release dosage form is released in the stomach, i.e., the geometric mean ratio of the plasma AUC (area under the curve) of active vs. total HMG-CoA reductase inhibitory activity will be greater than or equal to 90%. Particularly, the amount of active compound released in the stomach before entry into the duodenum is 5% or less by weight, i.e., the geometric mean ratio of the plasma AUC of active vs. total HMG-CoA reductase inhibitory activity will be greater than or equal to 95%, and more particularly the amount of active compound released in the stomach before entry into the duodenum is 1% or less by weight, i.e., the geometric mean ratio of the plasma AUC of active vs. total HMG-CoA reductase inhibitory activity will be greater than or equal to 99%.

It is to be understood that metabolism of the dihydroxy open acid statins will occur, primarily in the liver, after orally dosing in a delayed-release dosage form. However, since lactonization of the dihydroxy open acid statin would have been substantially avoided by use of a delayed release dosage form, the active and inactive metabolites that are formed will also be in the dihydroxy open acid form. In essence, if the dihydroxy open acid statin is administered in a delayed release dosage form, the internal exposure to lactonized parent compound and also to lactonized active and inactive metabolites will be minimized.

One example of a suitable delayed-release dosage form is a pH-dependent enterically coated dosage form. The enteric coating will not dissolve in the acidic gastric environment, but will dissolve in the higher pH environment of the duodenum. An enterically coated dosage form will therefore not permit release of any significant amount of the active compound from the dosage form in the stomach, but once the enteric coating dissolves in the duodenum, the active compound will be released. Suitable compositions for enteric coatings that can be used with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see L. Lachman, *The Theory and Practice of Industrial Pharmacy*, 3rd Ed., H. Liebermann and J. Kanig contributors (Lea & Febiger, 1986). An example of a suitable enteric coating includes but is not limited to SURETERIC WHITE sold by Colorcon which is composed of polyvinyl acetate phthalate, titanium dioxide, talc, colloidal silicon dioxide, triethyl acetate, polyethylene glycol, sodium bicarbonate, purified stearic acid, and sodium alginate. Many other suitable enteric coating

308
275

materials are commercially available and are known in the art. Additional coatings employed in the preparation of the dosage form, such as those used to provide an elegant, aesthetically pleasing final product or for other purposes, may be applied before or after, or before and after, application of the enteric coating.

5 Suitable enterically coated pharmaceutical dosage forms for use with this invention include enterically coated conventional rapid-release (also referred to as immediate-release) pharmaceutical dosage forms wherein the drug is relatively rapidly released once the enteric coating is breached, and enterically coated time-controlled release dosage forms such as but not limited to an enterically coated GEM
10 delivery device, described below. Time controlled-release dosage forms are also well known in the pharmaceutical art, and are designed so as to slowly release the active compound in the body over a period of time, for example over a period of from about 6 to 24 hours. Use of an enteric coated time controlled-release dosage form is preferred with more potent dosage amounts of a dihydroxy open acid statin so as to
15 lower the systemic exposure to the active statin. Whether the dosage form is an enterically coated rapid-release or time-controlled release dosage form, the enteric coating will prevent release of any substantial amount of the active compound from the dosage form in the stomach.

 Enterically coated pharmaceutical dosage forms also include but are
20 not limited to those wherein the dosage form or unit is comprised of the dihydroxy open acid statin in a tablet, capsule or the like that is surrounded by an enteric overcoating, and those wherein the dosage form or unit is a tablet, capsule or the like comprised of enterically coated granules of the dihydroxy open acid statin. Where the dosage form is surrounded by an enteric overcoat, the enteric coating may be the
25 outer-most external coating on the dosage form, or there may be one or more additional finish coatings applied over the enteric coat. In a more limited embodiment, when the delayed-release dosage unit contains enterically coated granules of the drug, the drug is selected from the dihydroxy open-acid form of lovastatin and simvastatin and the pharmaceutically acceptable salt and ester forms
30 thereof, and is more preferably a salt of dihydroxy open acid simvastatin, and most preferably the calcium or ammonium salt thereof. In an alternative embodiment, any dihydroxy open acid statin or pharmaceutically acceptable salt or ester thereof may be used with the present invention, such as those described herein, provided that the statin is not dosed in a single pharmaceutical dosage form or unit comprised of enteric

coated granules of the statin and enteric coated or non-enteric coated granules of aspirin.

An example of a delayed-release dosage form that also functions as a time controlled-release dosage form is described in U.S. Patent No. 5,366,738, herein incorporated by reference in its entirety. The controlled-release drug delivery device described in U.S. Patent No. 5,366,738 is known as a gel extrusion module (GEM) delivery device. The GEM device is a drug delivery device for the controlled in situ production and release of a dispersion containing a beneficial agent such as a pharmaceutical drug comprising:

- 10 (A) a compressed core prepared from an admixture comprising:
- (i) a therapeutically effective amount of the beneficial agent; and
- (ii) a polymer which upon hydration forms gelatinous microscopic particles; and
- (B) a water insoluble, water impermeable polymeric coating comprising a
- 15 polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;
- and wherein the release rate of the beneficial agent from the device is a function of the number and size of the apertures.

In the GEM device, the polymer inside the compressed core is preferably selected from sodium polyacrylate, carboxypolymethylenes and the pharmaceutically acceptable salts thereof such as a sodium salt, wherein the carboxypolymethylenes are prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and more preferably it is selected from carboxypolymethylenes prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and the pharmaceutically acceptable salts thereof. Most preferably, CARBOPOL® 974P and pharmaceutically acceptable salts thereof, particularly the sodium salt, is used as the polymer inside the compressed core. In addition, the compressed core may also contain one or more polymer hydration modulating agents, anti-oxidants, lubricants, fillers and excipients. An optional subcoating may be applied to the compressed core prior to application of the water insoluble coating as an aid in the manufacturing process. The subcoating may be comprised of, for example, hydroxypropyl cellulose and hydroxypropylmethylcellulose. Additional coatings may be applied for aesthetic or functional purposes.

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277

The water insoluble, water impermeable polymeric coating is preferably comprised of (1) a polymer selected from polyvinyl chloride, cellulose acetate, cellulose acetate butyrate, ethylcellulose and combinations of these polymers; and (2) a plasticizer selected from diethylphthalate, dibutylsebacate and triethylcitrate.

5 More preferably, the polymeric coating is comprised of cellulose acetate butyrate and triethyl citrate. The GEM device does not function as an osmotic drug delivery device, hence the release function of the device depends on passage of fluids from the external environment of the body to the internal environment of the compressed core through the formed apertures. It is intended that the terms "water insoluble, water

10 impermeable" used to describe the polymeric coating define a coating which is essentially water insoluble and water impermeable, meaning that the polymeric coating allows minimal to no passage of water through the coating from the external environment of the body to the internal environment of the compressed core, except for the fluid passage that occurs through the drilled apertures, during the period of

15 time the drug is being released from the GEM device in the body. Any minimal amount of water that does pass through the water insoluble, water impermeable polymeric coating is insubstantial and does not significantly contribute to the function of the GEM device, i.e. the release rate of the drug through the apertures. Rather the release rate of the drug from the GEM device is primarily a function of the number

20 and size of the apertures on the device.

For an elegant, aesthetically pleasing final product, an outer finish coat may finally be applied to the GEM delivery device containing colorants, waxes, and the like. The GEM device can also be enterically coated, either before or after the application of additional finish coatings. Even without enteric coating, extrusion of

25 the polymer which carries the drug out from inside the compressed core of the GEM device does not occur to a substantial extent in the acidic pH of the stomach, therefore substantial release of the drug should not occur in the stomach. Further details and examples of the GEM delivery device are described in US Patent No. 5,366,738. The compound employed with the GEM device may particularly be a pharmaceutically

30 acceptable salt of dihydroxy open acid simvastatin, and more particularly the ammonium salt of dihydroxy open acid simvastatin.

The term "patient" includes mammals, especially humans, who use the instant active agents for the prevention or treatment of a medical condition. Administering of the drug to the patient includes both self-administration and

35 administration to the patient by another person. The patient may be in need of

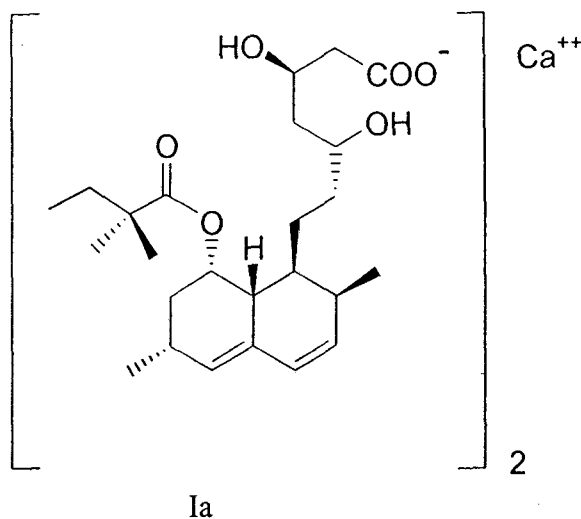
24/279

treatment for an existing disease or medical condition, or may desire prophylactic treatment to prevent or reduce the risk for diseases and medical conditions affected by inhibition of HMG-CoA reductase.

The term "therapeutically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term "prophylactically effective amount" is intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician. Particularly, the dosage a patient receives can be selected so as to achieve the amount of LDL (low density lipoprotein) cholesterol lowering desired; the dosage a patient receives may also be titrated over time in order to reach a target LDL level. The dosage regimen utilizing a dihydroxy open acid statin is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the potency of the compound chosen to be administered; the route of administration; and the renal and hepatic function of the patient. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition.

The novel compounds of this invention are the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin. A particular crystalline hydrated calcium salt of dihydroxy open acid simvastatin is the one having an x-ray powder diffraction (XRPD) pattern obtained using CuK α radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å. For convenience, the crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin having the above-defined XRPD pattern will also be referred to herein as compound I.

Compound I can be represented two-dimensionally as a hydrated form of the following structural formula Ia:

3/2
279

In addition to the XRPD pattern described above, compound I of the instant invention is further characterized by the thermogravimetry (TG) curve shown in Figure I. The TG curve for compound I was obtained under a nitrogen flow at a heating rate of 10°C/minute and is characterized by a 6.3% weight loss from ambient room temperature to a stable weight loss plateau at about 175°C. Additional weight losses due to the onset of decomposition of the compound are observed above about 190°C.

Compound I is still further characterized by the differential scanning calorimetry (DSC) curve shown in Figure 2. The DSC curve for compound I was obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup, and is characterized by three lower temperature endotherms with peak temperatures of 52, 77 and 100°C and associated heats of 48, 90 and 21 J/g, respectively, and two higher temperature endotherms due to decomposition with peak temperatures of 222 and 241°C and associated heats of 163 and 92 J/g.

Compound I of the instant invention is still further characterized by the ¹H nuclear magnetic resonance (NMR) spectral data, ¹³C NMR and mass spectral (MS) data as given in Example 1 herein.

Compound I is also characterized by the solid-state ¹³C nuclear magnetic resonance spectrum shown in Figure 4, which was completed using a Bruker DSX 400WB NMR system operating at 100.6 MHz for ¹³C and 400.1 MHz for ¹H using a Bruker MAS 400WB BL7 double-resonance probe with a spinning module

3/3
280

housing a 7 mm zirconia rotor with Kel-f end caps. The solid-state ^{13}C nuclear magnetic resonance (NMR) spectrum was acquired using cross polarization (CP), magic-angle spinning (MAS), and high-power (~ 59 kHz) decoupling with variable-amplitude cross-polarization and total sideband suppression. Proton and carbon 90° pulse widths were 4.25 μsec with a contact time of 2.0 msec. The sample was spun at 7.0 kHz and a total of 1024 scans were collected for the spectrum with a recycle delay of 3.0 seconds. A line broadening of 10 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported on the TMS scale using the carbonyl carbon of glycine (176.03 ppm) as a secondary reference.

10 In the methods of treatment and prophylaxis described herein, as well as the pharmaceutical compositions and medicaments, a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof is employed. Preferably the compound employed is a pharmaceutically acceptable salt of a dihydroxy open acid statin, more preferably it is a pharmaceutically acceptable salt of dihydroxy open acid
15 simvastatin such as an ammonium salt or calcium salt, and particularly a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin such as compound I. All hydrates, solvates and polymorphic crystalline forms of the above-described compounds and their use are encompassed within scope of the instant invention.

20 The instant invention provides methods for inhibiting HMG-CoA reductase, and for treating lipid disorders including hypercholesterolemia, hypertriglyceridemia and combined hyperlipidemia, comprising administering a therapeutically effective amount of a dihydroxy open acid statin to a person in need of such treatment. Further provided are methods for preventing or reducing the risk of
25 developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a prophylactically or therapeutically effective amount, as appropriate, of a dihydroxy open acid statin to a mammal who is at risk of developing atherosclerosis or who already has atherosclerotic disease.

30 Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease including restenosis following revascularization procedures, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease including multi-infarct

314
281

dementia, and peripheral vessel disease including erectile dysfunction are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease."

5 A dihydroxy open acid statin may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular
10 accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom
15 the potential for recurrence of such an event exists.

Accordingly, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of a prophylactically effective amount of a dihydroxy open acid statin to a patient at risk for such an event.
20 The patient may or may not have atherosclerotic disease at the time of administration, or may be at risk for developing it.

The instant invention also provides a method for preventing and/or treating inflammatory diseases or disorders alone or in conjunction with the treatment of conditions described above, comprising the administration of a dihydroxy open-
25 acid statin to a patient in need of such treatment. This includes, for example, the treatment of inflammatory conditions susceptible to treatment with a non-steroidal anti-inflammatory agent, arthritis including rheumatoid arthritis, and degenerative joint diseases (osteoarthritis), dementia, Alzheimer's disease, multiple sclerosis, inflammatory bowel disease, asthma, psoriasis, systemic lupus erythematosus, vasculitis, gout, adrenoleukodystrophy, diabetic retinopathy, nephropathy and diabetes
30 mellitus type II.

Persons to be treated with the instant therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician
35 practicing in the relevant fields of medicine. Such known risk factors include but are

315
282

not limited to hypertension, smoking, diabetes, low levels of high density lipoprotein (HDL) cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: National Cholesterol Education Program, Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), National Institute of Health, National Heart Lung and Blood Institute, NIH Publication No. 93-3095, September 1993; abbreviated version: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Summary of the second report of the national cholesterol education program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), JAMA, 1993, 269, pp. 3015-23. People who are identified as having one or more of the above-noted risk factors are intended to be included in the group of people considered at risk for developing atherosclerotic disease. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within the group of people considered to be at risk for having an atherosclerotic disease event.

The oral dosage amount of the dihydroxy open acid statin, particularly a salt of a dihydroxy open acid statin such as simvastatin, and more particularly the ammonium salt or a crystalline form of the calcium salt of dihydroxy open acid simvastatin such as compound I, is from about 1 to 200 mg/day, and more preferably from about 5 to 160 mg/day. However, dosage amounts will vary depending on factors as noted above, including the potency of the particular compound. Although the active drug of the present invention may be administered in divided doses, for example from one to four times daily, a single daily dose of the active drug is preferred. As examples, the daily dosage amount may be selected from, but not limited to, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 40 mg, 50 mg, 75 mg, 80 mg, 100 mg, 150 mg and 160 mg.

The active drug employed in the instant therapy can be administered in such oral forms as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Oral formulations are preferred.

For the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, for example compound I, administration of the active drug can be via any pharmaceutically acceptable route and in any pharmaceutically acceptable dosage form. This includes the use of oral conventional rapid-release, time

316
283

controlled-release and delayed-release (such as described above) pharmaceutical dosage forms. An oral delayed-release dosage formulation of the instant drug is preferred, and particularly an enteric overcoat surrounding a rapid-release dosage unit, or the GEM controlled-release drug delivery device with an enteric overcoat

5 surrounding the dosage unit, and most particularly an enteric overcoat surrounding a rapid-release dosage unit. Additional suitable pharmaceutical compositions for use with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

10 In the methods of the present invention, the active drug is typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

15 For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with a non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, modified sugars, modified starches, methyl cellulose and its derivatives, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and other reducing and non-reducing sugars, magnesium
20 stearate, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring and flavoring agents can also be
25 incorporated into the mixture. Stabilizing agents such as antioxidants, for example butylated hydroxyanisole (BHA), 2,6-di-tert-butyl-4-methylphenol (BHT), propyl gallate, sodium ascorbate, citric acid, calcium metabisulphite, hydroquinone, and 7-hydroxycoumarin, particularly BHA, propyl gallate and combinations thereof, can also be added to stabilize the dosage forms; the use of at least one stabilizing agent is
30 preferred with the instant composition. Preferably an antioxidant is employed with dihydroxy open acid simvastatin or a salt thereof, and particularly compound I. Other suitable components include gelatin, sweeteners, natural and synthetic gums such as acacia, tragacanth or alginates, carboxymethylcellulose, polyethylene glycol, waxes and the like.

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The active drug can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

5 Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or
10 polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans,
15 polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The instant invention also encompasses a process for preparing a pharmaceutical composition comprising combining a dihydroxy open acid statin with a pharmaceutically acceptable carrier. Also encompassed is the pharmaceutical composition which is made by combining a dihydroxy open acid statin with a
20 pharmaceutically acceptable carrier.

In a broad embodiment, any suitable additional active agent or agents may be used in combination with the dihydroxy open acid statin in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration of the active agents. One or
25 more additional active agents may be administered with a dihydroxy open acid statin. The additional active agent or agents can be lipid lowering compounds or agents having other pharmaceutical activities, or agents that have both lipid-lowering effects and other pharmaceutical activities. Examples of additional active agents which may be employed include but are not limited to HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1 or ACAT-2 as well as dual inhibitors of ACAT-1 and
30 -2; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; cholesterol absorption inhibitors such as SCH-58235, which is described in U.S. Patent No.'s 5,767,115 and 5,846,966; bile acid sequestrants; LDL (low density
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318
285

lipoprotein) receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPAR γ) agonists including the compounds commonly referred to as glitazones for example troglitazone, pioglitazone and
5 rosiglitazone and, including those compounds included within the structural class known as thiazolidinediones as well as those PPAR γ agonists outside the thiazolidinedione structural class; PPAR α agonists such as clofibrate, fenofibrate including micronized fenofibrate, and gemfibrozil; PPAR dual α/γ agonists; vitamin B₆ (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such
10 as the HCl salt; vitamin B₁₂ (also known as cyanocobalamin); folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; anti-oxidant vitamins such as vitamin C and E and beta carotene; beta-blockers; angiotensin II antagonists such as losartan; angiotensin converting enzyme inhibitors such as enalapril and captopril; calcium channel
15 blockers such as nifedipine and diltiazam; endothelial antagonists; agents that enhance ABC1 gene expression; FXR and LXR ligands including both inhibitors and agonists; bisphosphonate compounds such as alendronate sodium; and cyclooxygenase-2 inhibitors such as rofecoxib and celecoxib. Additionally, the dihydroxy open acid statins of this invention, for example compound I, may be used
20 in combination with anti-retroviral therapy in AIDS infected patients to treat lipid abnormalities associated with such treatment, for example but not limited to their use in combination with HIV protease inhibitors such as indinavir, nelfinavir, ritonavir and saquinavir.

A therapeutically or prophylactically effective amount, as appropriate,
25 of a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin, for example compound I, can be used for the preparation of a medicament useful for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, such as treating lipid disorders, preventing or reducing the risk of developing atherosclerotic
30 disease, halting or slowing the progression of atherosclerotic disease once it has become clinically manifest, and preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event. For example, the medicament may be comprised of about 1 mg to 200 mg of a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin, or more particularly
35 about 5 mg to 160 mg.

319
206

A therapeutically or prophylactically effective amount, as appropriate, of a dihydroxy open acid statin can be used for the preparation of an oral medicament adapted for delayed-release, wherein substantial release of the statin after oral administration does not occur until after passage of the medicament through the stomach, or alternately wherein at least 90% of the statin is delivered in its dihydroxy open acid form to the intestinal mucosa of a patient after oral administration. Said oral medicaments are also useful for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, as described above.

The medicament comprised of a dihydroxy open acid statin, for example compound I, may also be prepared with one or more additional active agents, such as those described supra.

Simvastatin is a semi-synthetic product which can be made from the natural product lovastatin. Processes for preparing lovastatin and simvastatin are well documented in the published literature. For example, U.S. Patent No. 4,231,938, herein incorporated by reference, describes a fermentation and isolation process for obtaining lovastatin using the microorganism *Aspergillus terreus*. U.S. Patent No.'s 4,444,784, 4,820,850, 4,916,239 and 4,582,915, herein all incorporated by reference, describe methods for making dihydroxy open-acid and lactonized forms of simvastatin.

Compound I of the instant invention can generally be prepared as follows. Simvastatin and its dihydroxy open acid counterpart, including compound I, tend to form oxidative by-products; therefore, to minimize the formation of such by-products, it is preferred that the procedures used to make compound I are performed under an inert atmosphere such as nitrogen. Although compound I can be obtained without using an inert atmosphere, the purity of the desired product will not be optimized.

Hydrolysis of the lactone ring of simvastatin can be accomplished by treating simvastatin with at least one equivalent, and preferably a slight excess of one equivalent, of an aqueous base. If more than a slight excess of base is used, the excess base is preferably neutralized before proceeding to the salt-formation step in order to prevent formation of insoluble calcium hydroxide or calcium carbonate by-product. The base employed for the hydrolysis can be an aqueous solution of a metal hydroxide or metal carbonate, for example but not limited to sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate and potassium carbonate.

320
207

Sodium hydroxide is preferred. The hydrolysis can be performed in water, an aqueous-protic organic solvent mixture, or an aqueous-aprotic organic solvent mixture. Suitable protic organic solvents include but are not limited to methanol (MeOH), ethanol (EtOH), isopropyl alcohol, n-propyl alcohol (propanol). Examples of suitable aprotic organic solvents include but are not limited to acetonitrile, dimethyl sulfoxide (DMF), N,N-dimethylformamide (DMSO), tetrahydrofuran (THF), *tert*-butyl methyl ether (MTBE) and toluene. Particularly, an aqueous ethanol or n-propyl alcohol solvent mixture may be used, and more particularly an aqueous n-propyl alcohol solvent mixture.

After the hydrolysis reaction is complete, the pH of the reaction mixture is adjusted to about 6 to 11, particularly 6 to 9, and more particularly 7 to 8.5, by addition of an acid. In this pH range, the dihydroxy open acid simvastatin will exist as a metal salt, for example as the sodium salt if the base used in the hydrolysis step is sodium hydroxide or sodium carbonate. Any acid that is capable of forming a soluble calcium salt such as calcium chloride or calcium citrate, is suitable. A soluble calcium salt is intended to be a salt that is soluble in the solvent system employed in the instant process. Preferably an acid such as acetic acid (HOAc) or a mineral acid is employed, particularly HCl.

The resulting pH-adjusted reaction mixture containing the metal salt of dihydroxy open acid simvastatin is next combined with a solution of about 0.50 to 0.55 equivalents of calcium acetate hydrate $[\text{Ca}(\text{OAc})_2 \cdot x\text{H}_2\text{O}]$ in water or an aqueous-organic solvent mixture, such as aqueous EtOH, MeOH, i-PrOH, n-PrOH, acetonitrile, DMF, DMSO, THF, and particularly aqueous EtOH or aqueous n-propyl alcohol. The pH-adjusted reaction mixture can be added to the calcium acetate hydrate solution, or the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture. The addition can occur all at once, or optionally it can be performed in portions over time with periods of aging. For example, a small portion, e.g., about one-quarter, of the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture over a short period of time, for example over about 30 minutes, and then the resulting mixture can be allowed to age for an additional short period of time at room temperature, optionally followed by a further period of aging at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, more particularly from about 30 to 40°C, and most particularly from about 30 to 35°C, after which the remaining calcium acetate hydrate solution can be added in portions over several hours at a

321
288

temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 40°C, and most particularly from about 30 to 35°C. Optionally, the reaction mixture can be seeded with crystalline Compound I.

5 Whether the pH-adjusted reaction mixture and the calcium acetate hydrate solution are combined at once or in portions, the resulting slurry must be aged until turnover of the resulting amorphous calcium salt of dihydroxy open acid simvastatin to the crystalline product is complete, usually for at least several hours. Complete turnover to the crystalline product can be assessed by standard techniques in
10 the art, for example, by examining a sample of the product under a microscope. This aging step can be performed at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 40°C, and most particularly from about 30 to 35°C. During the aging period or periods, the use of lower temperatures will lead to
15 crystallized product; however, it has been found that as the temperature drops, the rate of crystal turnover becomes slower, making the procedure less time-efficient.

 If necessary, the slurry is then allowed to cool to room temperature and is collected by suction filtration. The recovered solid is suction dried under a moist atmosphere (about 30 to 70% relative humidity, particularly 40 to 70%), preferably a
20 moist inert atmosphere such as nitrogen, and particularly at a temperature from about 10 to 40°C, and more particularly 25 to 35°C. The final step of suction filtration in the recovery of compound I should be done under a moist atmosphere, and preferably a moist inert atmosphere in order to minimize oxidative by-products. If an additional step of adding an antioxidant to compound I is performed, as described below, then
25 the final suction filtration is the one performed after combining the antioxidant with compound I.

 As noted above, compound I has a tendency to oxidize upon contact with air, and one way to minimize oxidation is to perform the reaction sequence under an inert atmosphere. Additionally, one or more anti-oxidants such as BHA, BHT,
30 propyl gallate, ascorbic acid, calcium metabisulphite, hydroquinone, nordihydroguaiaracetic acid (NDGA) or 7-hydroxycoumarin can be combined with compound I. This is done by agitating a slurry of compound I with one or more of the antioxidants and recovering the resulting solid by suction filtration.

 Alternatively, the ammonium salt of dihydroxy open acid simvastatin
35 can be used as the starting material to be combined with the calcium acetate hydrate,

322
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thus avoiding the hydrolysis and pH adjustment steps needed when starting with lactonized simvastatin. The other reaction conditions described above, such as solvents, temperatures, etc., can otherwise be employed.

Abbreviations which may appear herein are as follows: MeOH is methanol; EtOH is ethanol; PrOH is propanol; HOAc is acetic acid; MeCN is acetonitrile; DMF is dimethyl sulfoxide; DMSO is N,N-dimethylformamide; Ca(OAc)₂ is calcium acetate; HPLC is high performance liquid chromatography; min. is minutes; h is hour(s); D.I. is de-ionized; NMR is nuclear magnetic resonance; EI MS is electron impact mass spectrum; HR-EI MS is high resolution electron impact mass spectrum; RH is relative humidity. The "seed" used in the examples is Compound I.

EXAMPLE 1

15 Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I)

A 22 L four-necked round bottom flask was equipped with a temperature probe, a N₂ inlet, an addition funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H₂O was added and the solution was purged with N₂ for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry was purged with N₂ for 5 min. Then 5N NaOH (198 mL) was added at room temperature. After about 1 hour, the hydrolysis reaction was complete as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (approx. 65 mL). A solution of Ca(OAc)₂·H₂O (116.6 g, 0.662 mol) in 4.0 L of 60% EtOH-H₂O was purged with nitrogen for 5 min. A 1.0 L portion of this solution was added to solution of the sodium salt over 30 min. The resulting slurry was aged at room temperature for 30 min, and then at 30 to 35° C for 1-2 h.

The rest of Ca(OAc)₂ in EtOH-water was added over approx. 30 min at 30 to 35° C. The slurry was aged at 30 to 35° C for 5 hours under atmosphere of N₂. The slurry was cooled to room temperature and was collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H₂O, 4 L 20% EtOH-H₂O, followed by 6 L x 3 of D.I. water. The solid was suction dried under an atmosphere of moist N₂ (40 to 70% relative humidity) at room temperature for 4 days. Crystalline

322
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hydrated calcium salt of dihydroxy open acid simvastatin was obtained as a white powder.

The calcium salt was delumped with a single pass through a cleaned QUADRO™ COMIL® (Model 197S).

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HPLC CONDITIONS

Column: YMC Basic 4.6 mm x 25 cm

Detector: ABS 757 1AU/volt output

10 Sample solvent: EtOH/CH₃CN/H₂O (1:1:1)

Column temp: 25 °C (Anal. Dept. runs samples at 5 °C to prevent formation of simvastatin on column).

Flow rate: 1.5 mL / min.

Wavelength: 238 and 210 nm

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Gradient: %H₂O (10 mM 2HPO₄-

Time (min.) %CH₃CN KH₂PO₄, pH = 6.5)

0.00 30 70

20.00 45 55

20 34.00 70 30

39.00 70 30

39.50 30 70

43.00 30 70

25 Retention time of simvastatin open acid: 17.07 min.

Retention time of simvastatin: 32.90 min.

SPECTRAL DATA

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¹H NMR (400 MHz, CD₃OD), δ 5.97 (d, J = 9.6 Hz, 1 H), 5.77 (dd, J = 9.6, 5.2 Hz, 1 H), 5.49 (m, 1 H), 5.33 (m, 1 H), 4.17 (m, 1 H), 3.70 (m, 1 H), 2.44 - 2.35 (m, 2 H), 2.42 (dd, J = 15.7, 3.6 Hz, 1 H), 2.31 - 2.27 (m, 1 H), 2.29 (dd, J = 15.7, 8.4 Hz, 1 H), 2.00 (ddd, J = 15.7, 7.6, 2.4 Hz, 1 H), 1.93 (m, 1 H), 1.68 (m, 1 H), 1.61 - 1.55 (m, 2

324
291

H), 1.55 (m, 2 H), 1.42 (m, 1 H), 1.32 (m, 1 H), 1.19(m, 1 H), 1.12 (s, 6 H), 1.08 (d, J = 7.2 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 3 H), 0.84 (t, J = 7.6 Hz, 3 H) ppm.

^{13}C NMR (100.55 MHz, CD_3OD), δ 182.3, 179.3, 134.1, 133.2, 130.3, 129.6, 72.5, 69.8, 45.1, 44.4, 44.1, 38.8, 38.3, 36.4, 34.3, 33.9, 32.0, 28.6, 25.9, 25.37, 25.36, 23.7, 14.3, 9.9 ppm

EI MS: m/e: 437 (M+H), 419(M+H-H₂O), 303.

10 HR-EI MS: Calcd. for $\text{C}_{25}\text{H}_{38}\text{O}_5$ 418.2719; Found: 418.2712.

EXAMPLE 2

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) with BHA

15 A 22 L three-necked round bottom flask was equipped with a temperature probe, a N_2 inlet, an additional funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H₂O was added and purged with N_2 for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry purged with N_2 for 5 min. 198 mL of 5N NaOH (0.993 mol, 1.05 equiv.) was then added at room temperature. The hydrolysis reaction
20 is usually complete in 1 h. as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (about 65 mL).

A solution of $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (91.7 g, 0.520 mol, 0.55 equiv.) in 4.0 L of 60% EtOH- H₂O was purged with nitrogen for 5 min. 1.0 L of this solution was added to reaction solution over 30 min. The slurry was aged at room temperature for
25 30 min, and then at 30 to 35 °C for 1-2 h. The rest of the $\text{Ca}(\text{OAc})_2$ in EtOH-water was added in portions over 3h hours at 30-35°C. The slurry was allowed to age at 30 to 35 °C for 5 h under an atmosphere of N_2 . The slurry was allowed to cool to room temperature and was collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H₂O, 4 L 20% EtOH-H₂O, followed by 6 L x 3 of D.I. water. The solid
30 was suction dried under atmosphere of moist N_2 (40 to 70% RH) at room temperature to give 1.7 Kg of wet cake.

The above wet cake was placed in a clean 20 L three necked flask under atmosphere of nitrogen. A solution of BHA (2.603 g, 0.2 wt % equiv) in degassed 15% EtOH H₂O (8.5 L) was added, followed by addition of degassed water

375
292

(2.55 L), and the slurry was agitated at room temperature for 1 to 2 h. The solid was collected by suction filtration under atmosphere of moist N₂ with no washing to give 1.49 Kg wet cake. The solid was suction dried under atmosphere of moist N₂ (40 to 70% RH) at room temperature for 4 days. The calcium salt title product was obtained as a white powder (94% yield. 99.4%A at 238 nm, 0.2wt% BHA, KF = 7.3 %wt).

EXAMPLE 3

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) in aqueous nPrOH: Conventional addition mode

Step 1: Hydrolysis

A 72 L three-necked round bottom flask was equipped with a temperature probe, a N₂ inlet, an additional funnel, and an overhead stirrer. 28.5 L of D.I. H₂O was added and purged with N₂ for 10 min. 1.5 Kg simvastatin was added, followed by 788mL of 5N NaOH in one portion at room temperature. The hydrolysis reaction is usually complete in 2 h. as analyzed by HPLC (> 99.9% conversion). 1.5L of nPrOH was added and the pH of the reaction solution was adjusted to 9.5 to 11.0 by adding 2 N HOAc (about 170 mL).

Step 2: Salt Formation

150 g of seed (Compound I) was added to the above solution and the resulting slurry was allowed to warm up to 35 to 40 °C. A solution of Ca(OAc)₂•H₂O (347 g) in 15 L of 20% nPrOH was purged with nitrogen for 5min. and added to slurry over 3 h. The resulting slurry was aged at 35 to 40 °C for 5 h. under an atmosphere of N₂ and then cooled to room temperature. The solid was collected by filtration and was washed with 10% nPrOH-H₂O (15 L x 3).

Step 3: BHA loading

The above wet cake (9.1 kg) was transferred into a clean 72 L three necked flask under an atmosphere of nitrogen. A solution of BHA (7.6 g) in degassed 10% nPrOH (45 L) was added and the slurry was agitated at room temperature for 1 h. and filtered under atmosphere of N₂, and then suction dried under atmosphere of moist N₂ (30 to 70% RH) at room temperature for 7 days. 1.78 Kg of Ca salt title

326
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product was obtained as a white powder (94% yield, 99.4%A at 238 nm, 0.2wt% BHA, KF = 6.6 %wt).

EXAMPLE 4

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Preparation of hydrated crystalline calcium salt of dihydroxy open acid simvastatin in aqueous PrOH: Simultaneous addition mode

The process described in this example allows for keeping half of the batch in the vessel at all times as seed in a semi-continuous process.

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100 g of simvastatin was hydrolyzed in 1.9 L water as described in Example 3. Then, 100 ml nPrOH was added and the solution pH was adjusted to 9 to 11 with 1 N HOAc. The resulting solution and a solution of $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (23.2 g) in 1.0 L of 20% nPrOH were added separately but simultaneously to a suspension of 10-50 wt% Ca salt in 10% nPrOH (30 volume 10% PrOH relative to the amount of the seed) at 30 to 40 °C over 3 h. After 5 h age at 30 to 40 °C, the slurry was cooled to room temperature, filtered, and loaded with anti-oxidant and dried as described in conventional addition mode process. 95% yield.

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EXAMPLE 5

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Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) in aqueous PrOH: Loading BHA through co-crystallization

Method A: 100 g of simvastatin was hydrolyzed in 1.9 L water as described in Example 3. Then, 100 ml nPrOH was added and the solution pH was adjusted to 9 to 11 with 1 N HOAc. 10wt% seed was added and the slurry was allowed to warm up to 35 to 40 °C. A solution of $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (23.2 g) and BHA (540 mg) in 1.0 L of 20% nPrOH were added to the slurry at 35 to 40 °C over 3 h. After 5 h age at 30 to 40 °C, the slurry was cooled to room temperature, filtered and washed with a solution of BHA (0.1g/L) in 10% nPrOH (1L x 3). The wet cake was dried under moist N_2 as described in conventional addition mode process. The final dried Ca salt title product contained 0.2wt% BHA. 95% yield.

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Method B: The procedure of Method A was employed with the following change. Instead of adding BHA to a $\text{Ca}(\text{OAc})_2$ solution, the same amount of BHA was added into the pH adjusted solution of hydrolyzed simvastatin at room temperature. The solution was warmed to 35 to 40 °C to dissolve BHA. Then, 10wt%

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seed was introduced. The rest of the steps were as described in Method A. The final dried Ca salt title product contained 0.2wt% BHA. 95% yield.

EXAMPLE 6

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Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin
(Compound I) in aqueous PrOH: Loading BHA/propyl gallate

Starting with 2.0 Kg of simvastatin, the calcium salt of dihydroxy open acid simvastatin was crystallized, isolated, and washed as described in Example 3.

10 The first wet cake was transferred to a clean 100L vessel under atmosphere of N₂. A solution of BHA (9.2g) and propyl gallate (11.2 g) in 50 L 10% nPrOH was added to above vessel. The slurry was aged at room temperature for 1h. The slurry was filtered with no wash. The wet cake was dried under moist N₂. 95% yield. The dried salt was loaded with 0.07wt% propyl gallate and 0.2 wt% BHA.

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EXAMPLE 7

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin
(Compound I) in aqueous PrOH: Loading propyl gallate

20 Starting with 2.0 Kg of simvastatin, the calcium salt of dihydroxy open acid simvastatin was crystallized, isolated, and washed as described in Example 3. Then, the wet cake was washed with 10L of a solution of propyl gallate in 10% nPrOH (propyl gallate concentration = 0.224 g/L). Then, 20 L of propyl gallate solution in 10% nPrOH (propyl gallate concentration = 0.224 g/L) was added and the
25 wet cake was mixed in the filtration pot before filtration. The wet cake was dried under moist N₂. 95% yield. The dried salt was loaded with 0.07wt% propyl gallate.

EXAMPLE 8

30 Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin
(Compound I) Loading BHA, BHA/Vitamin E, and Vitamin E in heptane

100 g of simvastatin was hydrolyzed in 1.9 L water as described in Example 3. Then, 100 ml nPrOH was added and the solution pH was adjusted to 9 to
35 11 with 1 N HOAc. 10wt% seed was added and the slurry was allowed to warm up to

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35 to 40 °C. A solution of $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (23.2 g) in 1.0 L of 20% nPrOH was added to a slurry at 35 to 40 °C over 3 h. After 5 h age at 30 to 40 °C, the slurry was cooled to room temperature. The calcium salt slurry was filtered and washed with 10% nPrOH (500 mL x 1), followed by water (1L x 3). The wet cake (KF = 75 to 80 wt% water) was then washed with 1 L of heptane, to displace most of the water. This wet cake was washed with a solution of BHA or Vitamin E or BHA/Vitamin E (conc. = 1.38 g/ L, 800 mL) and dried under moist N_2 .

EXAMPLE 9

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Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) in aqueous MeCN

A 7.2 L three-necked round bottom flask was equipped with a temperature probe, a N_2 inlet, an additional funnel, and an overhead stirrer. 2.1 L of D.I. H_2O was added and purged with N_2 for 10 min. 150 g simvastatin was added, followed by 78.8mL of 5N NaOH in one portion at room temperature. The hydrolysis reaction is usually complete in 2 h. as analyzed by HPLC (> 99.9% conversion). 900 mL of MeCN was added and the pH of the reaction solution was adjusted to 9.5 to 11.0 by adding 2 N HOAc (about 17 mL).

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30.0 g crystalline seed was added to above solution and the resulting slurry was allowed to warm up to 30 to 35 °C. A solution of $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (34.7 g) in 1.5 L of 30% MeCN was purged with nitrogen for 5 min. and added to reaction slurry over 3 h. The slurry was at 35 to 40 °C for 5 h. under atmosphere of N_2 . The slurry was allowed to cool to room temperature and the solid was collected by filtration. The wet cake was washed with 30% MeCN (1.5 L) and 10% MeCN (1.0 L), and rinsed/washed with a solution of BHA (0.9 g/L) in degassed 10% MeCN (1.0 L x 2). The solid was suction dried under atmosphere of moist N_2 (30 to 70% RH) at room temperature for 5 days. 1.67 Kg of the title compound was obtained as a white powder (88% yield. 99.4%A at 238 nm, 0.2wt% BHA, KF = 6.6 %wt).

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EXAMPLE 10

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) in aqueous MeOH

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50 g simvastatin was hydrolyzed in 850 mL water as described in Example 3. Then, 150 ml MeOH was added and the solution pH was adjusted to 7 to 11 with 1N HOAc. 10wt% seed was added and the slurry was allowed to warm up to 30-35 °C. A solution of $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (11.6 g) in 500 mL of 30% MeOH was added to the slurry at 30-35 °C over 3 h. After 5 h age at 30-35 °C, the slurry was cooled to room temperature. The dihydroxy open acid simvastatin calcium salt slurry was filtered and washed with 20% MeOH (200 ml) and water (500 ml x 3). The wet cake was dried under moist N_2 . The final dried Ca salt title product was isolated in 96% yield.

EXAMPLE 11

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) in aqueous i-PrOH, DMF, DMSO

50 g simvastatin was hydrolyzed in 850 mL water as described in Example 3. Then, 150 ml i-PrOH was added and the solution pH was adjusted to 7 to 11 with 1 N HOAc. 10wt% seed was added and the slurry was allowed to warm up to 30-35 °C. A solution of $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (11.6 g) in 500 mL of 30% i-PrOH was added to the slurry at 30-35 °C over 3 h. After 5 h age at 30-35 °C, the slurry was cooled to room temperature. Ca salt slurry was filtered and washed with 20% ml i-PrOH (200 ml) and with water (500 ml x 3). The wet cake was dried under moist N_2 . The final dried Ca salt title product was isolated in 96% yield.

The same procedure could be applied to prepare Compound I in DMF, DMSO, and similar solvents.

EXAMPLE 12

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) in water

50 g of simvastatin was hydrolyzed in 1.0 L water as described in Example 3. Then, the solution pH was adjusted to 11 with 1 N HOAc. 10wt% seed was added and the slurry was allowed to warm up to 35-40 °C. A solution of $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (11.6 g) in 500 mL of water was added to the slurry at 35-40 °C over 5 h. After 10 h age at 35-40 °C, the slurry was cooled to room temperature. Ca salt

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slurry was filtered and washed with water (500 ml x 3). The wet cake was dried under moist N₂. The final dried Ca salt title product was isolated in 96% yield.

EXAMPLE 13

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Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin
(Compound I) from dihydroxy open acid simvastatin ammonium salt

Method A: 50 g of dihydroxy open acid simvastatin ammonium salt was dissolved into 800 ml of 25% nPrOH which was then added dropwise to a
10 solution of Ca(OAc)₂•H₂O (10.7 g) in 75 ml of water at room temperature over 2h. The resulting slurry was aged at 30 to 35 °C 5 h. After cooling to room temperature, the slurry was isolated by filtration. The wet cake was washed with 10% nPrOH (500 ml x 3). The wet cake was loaded with antioxidants and dried under moist N₂ as described above to give the title product.

15 Method B: 50 g of dihydroxy open acid simvastatin ammonium salt was added into a solution of Ca(OAc)₂•H₂O (10.7 g) in 1.5 L of 10% nPrOH in one portion at room temperature. The resulting slurry was aged at 30 to 35 °C 5 h. After cooling to room temperature, the slurry was isolated by filtration. The wet cake was washed with 10% nPrOH (500 ml x 3). The wet cake was loaded with antioxidants
20 and dried under moist N₂ as described above to give the title product.

By using both Methods A and B described as above, the title product could also prepared from ammonium salt in the following aqueous solvents: acetone, MeOH, EtOH, iPrOH, , MeCN, neat water, DMF, DMSO, and similar solvents.

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EXAMPLE 14

Recrystallization Procedure Using nPrOH-H₂O

Dried Compound I (21 g) was dissolved in 150ml of 40% nPrOH at 35°C and line filtered. This solution was added dropwise to a slurry of 10 wt% seed in
30 480 ml of 4% PrOH at 35 to 40°C over 3 to 5 h. After aging overnight at 35 to 40°C, the slurry was allowed to cool to room temperature. The solid was filtered and washed with 10% nPrOH (200ml x 2). The wet cake was dried under moist N₂. 95% yield.

EXAMPLE 15

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299Recrystallization Process Using EtOH-H₂O

Method A: 25 g of Compound I was dissolved into 425ml of 95% EtOH at 40 °C and line filtered. The filtered solution was added dropwise to 825ml of water in the presence of 10% wt seed at 30 to 35 °C over 3 to 5 h. The slurry was aged overnight and cooled to 0 to 5 °C before filtration. The wet cake was washed with 250 ml of 30% EtOH and dried under moist N₂ at room temperature. 92% yield.

Method B: 25 g of Compound I was dissolved into 625ml of 95% EtOH at 30 to 40 °C and line filtered. 525 ml of water was added at 30 to 40 °C. After adding 10wt% seed, 825-ml of water was added dropwise at 30 to 40 °C over 3 h. The slurry was aged overnight and cooled to 0 to 5 °C before filtration. The wet cake was washed with 250 ml of 30% EtOH and dried under moist N₂ at room temperature. 92% yield.

EXAMPLE 16

An open, randomized, four-period, crossover study to compare the effect of itraconazole on the single-dose pharmacokinetics of intraduodenally administered dihydroxy open acid simvastatin versus orally administered simvastatin in healthy male subjects

Objectives: (1) To determine the effect of itraconazole, a potent CYP3A inhibitor, on the plasma AUC of active and of total HMG-CoA reductase inhibitory activity following a single intraduodenal dose of a solution containing 5 mg dihydroxy open acid simvastatin; (2) to determine and compare the dose-adjusted plasma AUC of active HMG-CoA reductase inhibitory activity following a single intraduodenal dose of a solution containing 5 mg dihydroxy open acid simvastatin versus a single oral administration of simvastatin 20-mg film coated tablet (FCT); (3) to determine the effect of itraconazole on the plasma AUC's of dihydroxy open acid simvastatin and of simvastatin lactone concentration following a single intraduodenal dose of a solution containing 5 mg dihydroxy open acid simvastatin.

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- Study Design: This study was designed in an open, four-period crossover randomized fashion. Twelve healthy male subjects received four treatments (A, B, C and D). In Treatment A, subjects received itraconazole 200 mg (2 x 100-mg capsule) for 4 days followed by a single dose of 5-mg dihydroxy open acid simvastatin solution administered intraduodenally on day 4, 1 hour after the fourth daily dose of itraconazole. In Treatment B, subjects were given a single dose of 5-mg dihydroxy open acid simvastatin solution administered intraduodenally on day 1. Intraduodenal administration was accomplished via a nasoduodenal tube placed under fluoroscopic guidance by an experienced gastroenterologist just prior to dosing and removed following the 1-hr postdose measurements. Treatments C and D were similar to those of Treatments A and B, except that orally dosed simvastatin 20-mg conventional film coated tablet was used. The wash out between treatment periods was at least 7-days following a treatment containing itraconazole or at least 3 days following a treatment without itraconazole. Plasma samples were collected at appropriate time intervals for up to 24 hours following simvastatin or dihydroxy open acid simvastatin administration, for analysis of total and active HMG-CoA reductase inhibitory activities as well as for simvastatin and dihydroxy open acid simvastatin concentrations.
- 20 Analytical Methodology: Plasma concentrations of simvastatin and dihydroxy open acid simvastatin acid were determined simultaneously by an improved liquid chromatography/tandem mass spectrometry (LC/MS/MS) method using lovastatin and dihydroxy open acid lovastatin acid as internal standards. An enzymatic assay method was used to determine plasma concentrations of active and total (active plus potentially active) HMG-CoA reductase inhibitory activity.

- Pharmacokinetics: The area under the plasma concentration-time profile from time zero to the last sampling time (AUC_{0-last}) was calculated using linear trapezoidal rule. The apparent elimination rate constant (k) of simvastatin and dihydroxy open acid simvastatin was estimated by least-squares regression analysis of the log-linear portion of the simvastatin and dihydroxy open acid simvastatin concentration-time data, and the apparent elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = 0.693/k$. All calculations were based on designated sampling times or actual sampling times when they differed from the designated times by more than 10 minutes.

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Discussion of Results: This was an open, randomized, four-period crossover study in twelve healthy male subjects. The results showed that intraduodenal administration of dihydroxy open acid simvastatin 5-mg solution yielded higher (~4-fold) dose-adjusted plasma AUC of the active HMG-CoA reductase inhibitory activity than oral administration of simvastatin 20-mg tablet (Table 1). Following dihydroxy open acid simvastatin administration, the unchanged dihydroxy open acid simvastatin was the major component (~60%), while simvastatin was a minor component (<10%) contributing to plasma HMG-CoA reductase inhibitory activity. As evident by comparable AUC values for both the total and active inhibitors (see Table 1) as well as low plasma levels of simvastatin in plasma (AUC <10% of dihydroxy open acid simvastatin AUC) (see Table 3), lactonization of either dihydroxy open acid simvastatin or its active metabolites occurred minimally following intraduodenal administration of dihydroxy open acid simvastatin. Pretreatment with itraconazole caused minimal changes (1.3-1.5-fold) in the systemic exposure as measured by AUC and C_{max} of HMG-CoA reductase inhibitory activity (total or active) following administration of dihydroxy open acid simvastatin 5-mg intraduodenally, as compared to that observed following oral administration of simvastatin 20-mg tablet (1.3-3.8-fold) (see Table 2). When measured as the unchanged drug, the effect of itraconazole observed following dihydroxy open acid simvastatin administration was also minimal (1.5-fold) and was much less than the corresponding measure obtained following simvastatin administration (19-fold) (see Table 3). A moderate effect (3-4-fold increase) was noted for the AUC and C_{max} of simvastatin following treatment with itraconazole prior to dihydroxy open acid simvastatin administration (see Table 3). However, apparent t_{1/2} values for dihydroxy open acid simvastatin or simvastatin were essentially unchanged by itraconazole (see Table 3). Overall, these results indicate that the pharmacokinetics of dihydroxy open acid simvastatin is less prone to alteration by itraconazole, a potent CYP3A inhibitor, than that of simvastatin in humans. From these results it appears that dihydroxy open acid simvastatin, although a substrate for CYP3A, is metabolized with a much lower intrinsic clearance than that of simvastatin in human liver microsomes.

334
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TABLE 1

Pharmacokinetic parameters for total and active HMG-CoA reductase inhibitors following administration of 5-mg dihydroxy open acid simvastatin (SVA) intraduodenally or 20-mg simvastatin (SV) tablet orally to 12 healthy male volunteers. Results are means from 12 subjects. Values in parentheses are SD.

	Drug Administered	5 mg SVA (ID)	20 mg SV (ECT)
	N	12	12
AUC (ng eq. hr/ml)	Total	56.0 (28.6)	180.7 (57.2)
	Active	54.1 (28.5)	59.7 (18.1)
	SV	1.02 (0.5)	16.9 (10.5)
	SVA	33.9 (16.7)	7.7 (4.9)
Cmax (ng eq./ml)	Total	6.2 (3.6)	67.1 (27.2)
	Active	5.7 (3.0)	16.1 (4.4)
	SV	0.13 (0.05)	6.84 (4.6)
	SVA	3.78 (1.93)	0.92 (0.58)
Tmax (hr)	Total	3.3 (2.3)	1.2 (0.5)
	Active	3.6 (2.5)	1.4 (0.5)
	SV	4.9 (2.0)	1.1 (0.5)
	SVA	4.1 (2.1)	3.7 (2.1)
t1/2 (hr)	SV	6.7 (1.7) n=8	4.2 (1.9)
	SVA	2.3 (0.5)	3.5 (1.0)

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TABLE 2

Pharmacokinetic parameters for total HMG-CoA reductase inhibitor following administration of 5-mg dihydroxy open acid simvastatin (SVA) intraduodenally or 20-mg simvastatin (SV) tablet orally with or without pretreatment with itraconazole (2x100-mg capsule, qd) for 4 days to 12 healthy male volunteers. Results are means from 12 subjects. Values in parentheses are SD.

Treatment	AUC (ng eq.hr/mL)	Cmax (ng eq/mL)	Tmax (hr)
Total Inhibitors			
Single 5-mg SVA (ID) + 4 Days of Daily 200-mg Itraconazole	86.1 ± 47	8.2 ± 4.0	4.3 ± 2.2
Single 5-mg SVA (ID)	56.0 ± 28.6	6.2 ± 3.6	3.3 ± 2.3
Geometric Mean Ratio	1.5	1.3	
Single 20-mg SV (CT) + 4 Days of Daily 200-mg Itraconazole	683 ± 232	126 ± 54.8	1.9 ± 0.9
Single 20-mg SV (CT)	180.7 ± 57.2	67.1 ± 27.2	1.2 ± 0.5
Geometric Mean Ratio	3.8	1.9	
Active Inhibitors			
Single 5-mg SVA (ID) + 4 Days of Daily 200-mg Itraconazole	75.0 ± 39.6	7.4 ± 3.9	5.5 ± 1.7
Single 5-mg SVA (ID)	54.1 ± 28.5	5.7 ± 3.0	3.6 ± 2.5
Geometric Mean Ratio	1.3	1.3	
Single 20-mg SV (CT) + 4 Days of Daily 200-mg Itraconazole	195 ± 104	23.0 ± 13.6	3.1 ± 0.9
Single 20-mg SV (CT)	59.7 ± 18.1	16.1 ± 4.4	1.4 ± 0.5
Geometric Mean Ratio	3.1	1.3	

336
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TABLE 3

Pharmacokinetic parameters for simvastatin or dihydroxy open acid simvastatin following administration of 5-mg dihydroxy open acid simvastatin (SVA) intraduodenally or 20-mg simvastatin (SV) tablet orally with or without pretreatment with itraconazole (2x100-mg capsule, qd) for 4 days to 12 healthy male volunteers. Results are means from 12 subjects. Values in parentheses are SD.

Treatment	AUC (ng eq.hr/mL)	Cmax (ng eq/mL)	t1/2 (hr)	Tmax (hr)
Simvastatin				
Single 5-mg SVA (ID) + 4 Days of Daily 200-mg Itraconazole	5.18 ± 3.15	0.43 ± 0.2	6.7 ± 2.5 (n=11)	5.3 ± 1.9
Single 5-mg SVA (ID)	1.02 ± 0.5	0.13 ± 0.05	6.7 ± 1.7 (n=8)	4.9 ± 2.0
Geometric Mean Ratio	4.4	3.2	1.0	
Single 20-mg SV (CT) + 4 Days of Daily 200-mg Itraconazole	316 ± 142	77.2 ± 50.7	5.2 ± 1.5	1.8 ± 1.1
Single 20-mg SV (CT)	16.9 ± 10.5	6.84 ± 4.6	4.2 ± 1.9	1.1 ± 0.5
Geometric Mean Ratio	19.4	11.4	1.3	
Simvastatin Acid				
Single 5-mg SVA (ID) + 4 Days of Daily 200-mg Itraconazole	56.8 ± 33.5	5.78 ± 3.27	2.8 ± 1.1	4.7 ± 2.4
Single 5-mg SVA (ID)	33.9 ± 16.7	3.78 ± 1.93	2.3 ± 0.5	4.1 ± 2.1
Geometric Mean Ratio	1.5	1.5	1.1	
Single 20-mg SV (CT) + 4 Days of Daily 200-mg Itraconazole	86.2 ± 65.6	9.76 ± 7.38	4.5 ± 1.3	4.0 ± 1.4
Single 20-mg SV (CT)	7.70 ± 4.9	0.92 ± 0.58	3.5 ± 1.0	3.7 ± 2.1
Geometric Mean Ratio	11.0	10.7	1.3	

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

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WHAT IS CLAIMED IS:

1. An oral pharmaceutical composition comprising a therapeutically effective amount of a compound selected from a dihydroxy open acid
5 statin and a pharmaceutically acceptable salt or ester thereof and a pharmaceutically acceptable carrier, formulated as a delayed-release dosage form wherein substantial release of the compound from the dosage form after oral administration to a patient is delayed until after passage of the dosage form through the stomach.
- 10 2. The pharmaceutical composition of Claim 1 wherein at most 10% by weight of the statin is released into the stomach of a patient after administration.
- 15 3. The pharmaceutical composition of Claim 2 wherein at most 5% by weight of the statin is released into the stomach of a patient after administration.
- 20 4. The pharmaceutical composition of Claim 3 wherein at most 1% by weight of the statin is released into the stomach of a patient after administration.
5. The pharmaceutical composition of Claim 1 wherein the composition is enterically coated.
- 25 6. The pharmaceutical composition of Claim 5 wherein the dosage form is surrounded by an enteric coating.
- 30 7. The pharmaceutical composition of Claim 5 wherein the dosage form comprises enterically coated granules of the dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof.
8. The pharmaceutical composition of Claim 5 wherein the dosage form comprises enterically coated granules of dihydroxy open acid simvastatin or a pharmaceutically acceptable salt or ester thereof.

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9. The pharmaceutical composition of Claim 5 wherein the dosage form comprises enterically coated granules of the dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof, provided that the dosage form does not contain granules of aspirin.

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10. The pharmaceutical composition of Claim 5 wherein the composition is formulated in an enterically coated rapid-release pharmaceutical dosage form.

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11. The pharmaceutical composition of Claim 5 wherein the composition is formulated in an enterically coated time controlled-release pharmaceutical dosage form.

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12. The pharmaceutical composition of Claim 1 wherein the composition is formulated in a drug delivery device comprised of:

(A) a compressed core prepared from an admixture comprising:

- (i) a therapeutically effective amount of the compound; and
- (ii) a polymer which upon hydration forms gelatinous microscopic particles; and

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(B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

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and wherein the release rate of the compound from the device is a function of the number and size of the apertures.

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13. The pharmaceutical composition of Claim 12 wherein the drug delivery device is additionally comprised of an enteric overcoat exterior to the water insoluble, water impermeable polymeric coating.

14. The composition of Claim 1 wherein the statin is selected from the dihydroxy open acid forms of lovastatin, simvastatin, atorvastatin, cerivastatin, nisvastatin and ZD-4522 and the pharmaceutically acceptable salts and esters thereof.

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15. The composition of Claim 1 wherein the statin is selected from the dihydroxy open acid form of lovastatin, simvastatin and the pharmaceutically acceptable salts and esters thereof.

5 16. The composition of Claim 1 wherein the statin is selected from the dihydroxy open acid form of simvastatin and the pharmaceutically acceptable salts and esters thereof.

10 17. The composition of Claim 1 wherein the statin is a pharmaceutically acceptable salt of dihydroxy open acid simvastatin.

18. The composition of Claim 1 wherein the statin is a calcium salt of dihydroxy open acid simvastatin.

15 19. The composition of claim 1 wherein the statin is an ammonium salt of dihydroxy open acid simvastatin.

20 20. The composition of Claim 1 wherein the statin is a crystalline hydrated calcium salt of dihydroxy open acid simvastatin having an x-ray powder diffraction pattern obtained using CuK α radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å.

25 21. The composition of Claim 5 wherein the statin is selected from the dihydroxy open acid form of lovastatin, simvastatin, atorvastatin, cerivastatin, nisvastatin and ZD-4522 and the pharmaceutically acceptable salts and esters thereof.

30 22. The composition of Claim 5 wherein the statin is selected from the dihydroxy open acid form of lovastatin, simvastatin and the pharmaceutically acceptable salts and esters thereof.

35 23. The composition of Claim 5 wherein the statin is selected from the dihydroxy open acid form of simvastatin and the pharmaceutically acceptable salts and esters thereof.

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24. The composition of Claim 5 wherein the statin is a pharmaceutically acceptable salt of simvastatin.

5 25. The composition of Claim 5 wherein the statin is a calcium salt of dihydroxy open acid simvastatin.

26. The composition of Claim 5 wherein the statin is an ammonium salt of dihydroxy open acid simvastatin.

10 27. The composition of Claim 5 wherein the statin is a crystalline hydrated calcium salt of dihydroxy open acid simvastatin having an x-ray powder diffraction pattern obtained using CuK α radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å.

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28. The composition of claim 27 further comprising BHA.

29. The composition of claim 27 further comprising propyl gallate.

20 30. The composition of claim 27 further comprising BHA and propyl gallate.

31. An oral pharmaceutical composition made by combining a therapeutically effective amount of a compound selected from a dihydroxy open acid
25 statin and a pharmaceutically acceptable salt or ester thereof with a pharmaceutically acceptable carrier in a delayed-release dosage form.

32. A process for preparing an oral pharmaceutical composition comprising combining a compound selected from a dihydroxy open acid statin and a
30 pharmaceutically acceptable salt or ester thereof with a pharmaceutically acceptable carrier in a delayed-release dosage form.

33. The use of a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof for the preparation of an oral medicament adapted for

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delayed-release wherein substantial release of the statin after oral administration does not occur until after passage of the medicament through the stomach.

5 34. The use of Claim 33 wherein at most 10% by weight of the statin is released into the stomach of a patient after administration.

 35. The use of Claim 33 wherein at most 5% by weight of the statin is released into the stomach of a patient after administration.

10 36. The use of Claim 33 wherein at most 1% by weight of the statin is released into the stomach of a patient after administration.

 37. The use of dihydroxy open acid simvastatin or a pharmaceutically acceptable salt or ester thereof to prepare the medicament of claim
15 33.

 38. The use of a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof for the preparation of an oral medicament adapted for delayed-release useful for delivering at least 90% by weight of the statin in its
20 dihydroxy open acid form to the intestinal mucosa of a patient after oral administration.

 39. The use of Claim 38 wherein at least 95% by weight of the statin is delivered in its dihydroxy open acid form to the intestinal mucosa of a patient
25 after oral administration.

 40. The use of Claim 38 wherein at least 99% by weight of the statin is delivered in its dihydroxy open acid form to the intestinal mucosa of a patient
after oral administration.

30 41. The use of dihydroxy open acid simvastatin or a pharmaceutically acceptable salt or ester thereof to prepare the medicament of claim
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42. The use of a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof for the preparation of an oral medicament adapted for delayed-release useful for inhibiting HMG-CoA reductase in a patient in need of such treatment wherein substantial release of the statin after oral administration is delayed
5 until after passage of the medicament through the stomach.

43. The use of a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof for the preparation of an oral medicament adapted for delayed-release useful for treating hypercholesterolemia in a patient in need of such
10 treatment wherein substantial release of the statin after oral administration is delayed until after passage of the medicament through the stomach.

44. The use of a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof for the preparation of an oral medicament adapted for
15 delayed-release useful for preventing or reducing the risk of developing atherosclerotic disease in a patient at risk of developing atherosclerotic disease wherein substantial release of the statin after oral administration is delayed until after passage of the medicament through the stomach.

20 45. The use of Claim 44 wherein the medicament is useful for preventing or reducing the risk of developing atherosclerotic disease selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

25 46. The use of Claim 44 wherein the medicament is useful for preventing or reducing the risk of developing coronary heart disease.

30 47. The use of a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof for the preparation of an oral medicament adapted for delayed-release useful for treating atherosclerotic disease in a patient in need of such treatment wherein substantial release of the statin after oral administration is delayed until after passage of the medicament through the stomach.

35 48. The use of Claim 47 wherein the medicament is useful for treating atherosclerotic disease selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

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49. The use of Claim 47 wherein the medicament is useful for treating coronary heart disease.

5 50. The use of a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof for the preparation of an oral medicament adapted for delayed-release useful preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event in a person at risk of having an atherosclerotic disease event wherein substantial release of the statin after oral administration is delayed until
10 after passage of the medicament through the stomach.

51. The use of Claim 50 wherein the medicament is useful for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event in a person who has atherosclerotic disease.

15 52. The use of Claim 50 wherein the medicament is useful for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event in a person who is at risk of developing atherosclerotic disease.

20 53. The use of Claim 50 wherein the medicament is useful for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event selected from a coronary heart disease event, a cerebrovascular event and intermittent claudication.

25 54. The use of Claim 50 wherein the medicament is useful for preventing or reducing the risk of occurrence or recurrence of a coronary heart disease event selected from coronary heart disease death, myocardial infarction and coronary revascularization procedures.

30 55. The use of Claim 50 wherein the medicament is useful for preventing or reducing the risk of occurrence or recurrence of a cerebrovascular event selected from a cerebrovascular accident and a transient ischemic attack.

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56. The use of any of Claims 42 to 55 wherein the statin is selected from the dihydroxy open acid forms of lovastatin and simvastatin and the pharmaceutically acceptable salts and esters thereof.

5 57. The use of any of Claims 42 to 55 wherein the statin is selected from dihydroxy open acid simvastatin and the pharmaceutically acceptable salts and esters thereof.

10 58. The use of any of Claims 42 to 55 wherein the statin is a pharmaceutically acceptable salt of dihydroxy open acid simvastatin.

59. The use of any of Claims 42 to 55 wherein the statin is a calcium salt of dihydroxy open acid simvastatin.

15 60. The use of any of Claims 42 to 55 wherein the statin is an ammonium salt of dihydroxy open acid simvastatin.

20 61. The use of any of Claims 42 to 55 wherein the statin is a crystalline hydrated calcium salt of dihydroxy open acid simvastatin having an x-ray powder diffraction pattern obtained using $\text{CuK}\alpha$ radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å.

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TITLE OF THE INVENTION

DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE
INHIBITORS

5 ABSTRACT OF THE DISCLOSURE

The instant invention provides methods and pharmaceutical compositions for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, comprising orally administering a therapeutically effective amount of a
10 compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

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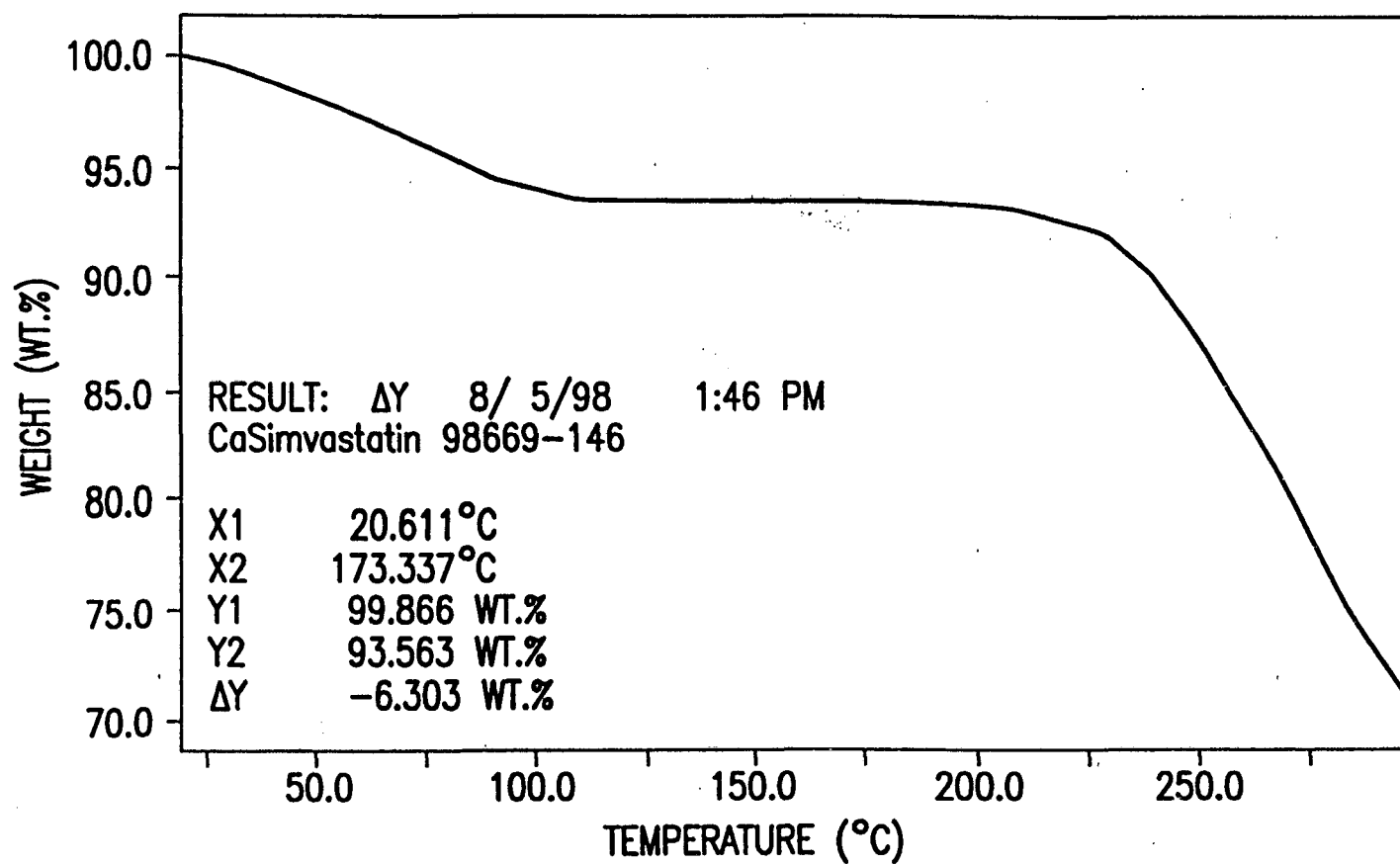


FIG.1

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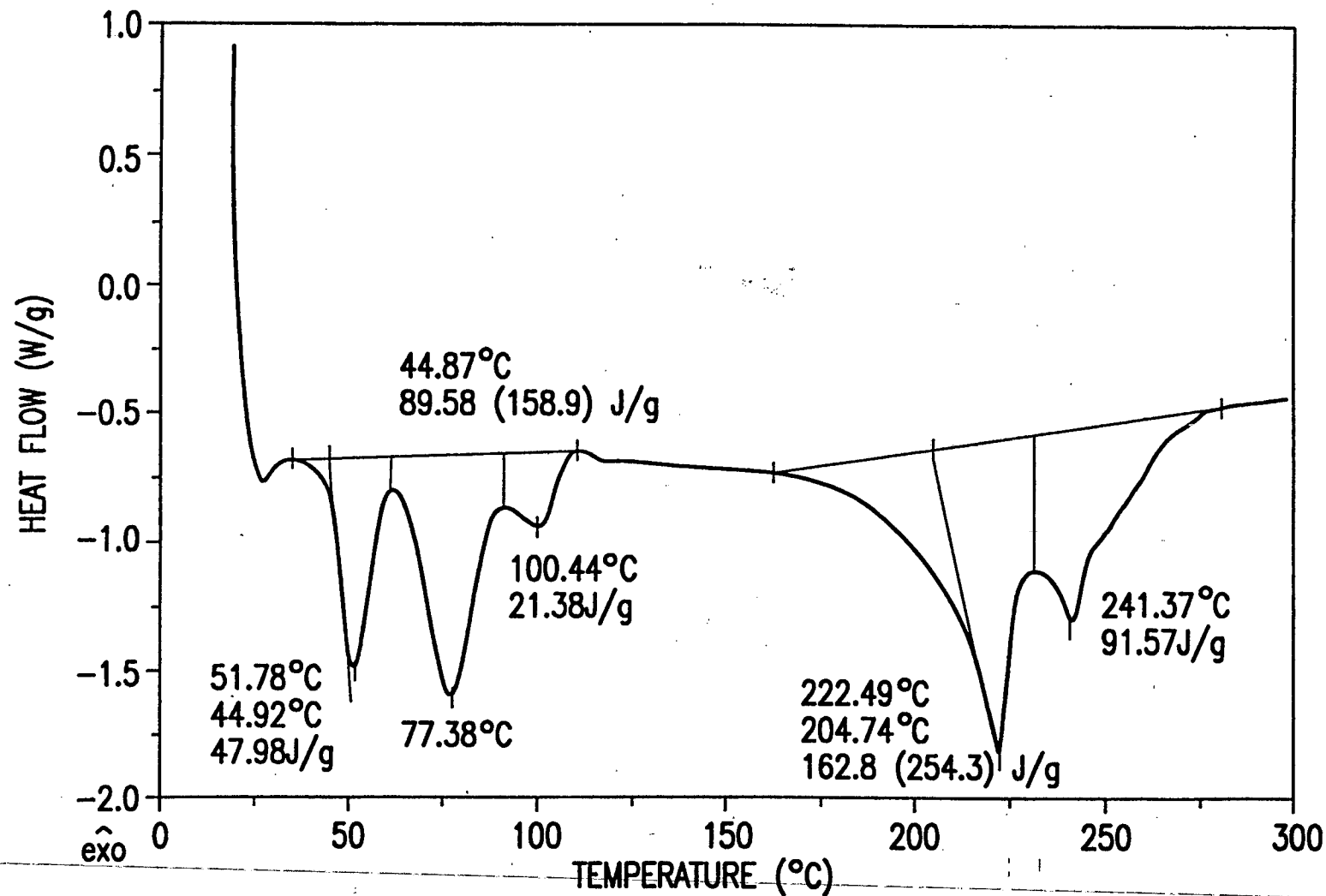


FIG.2

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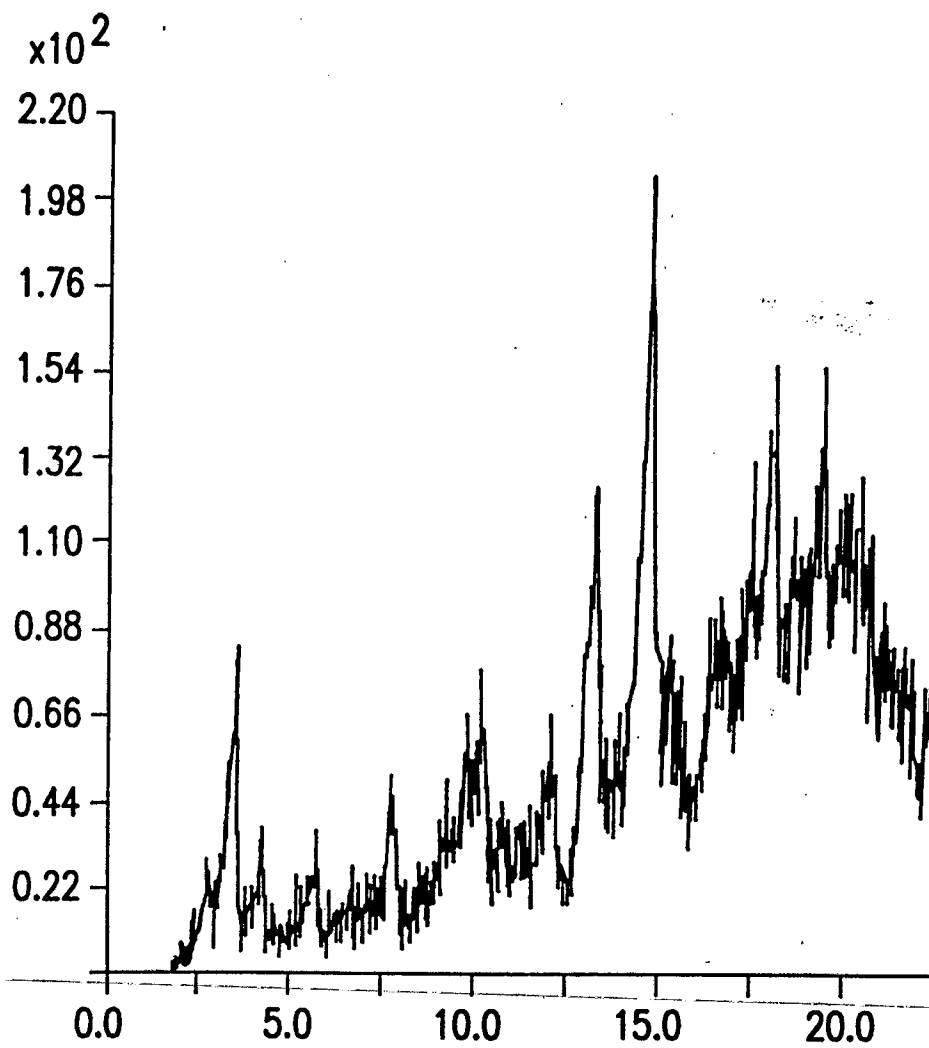


FIG.3

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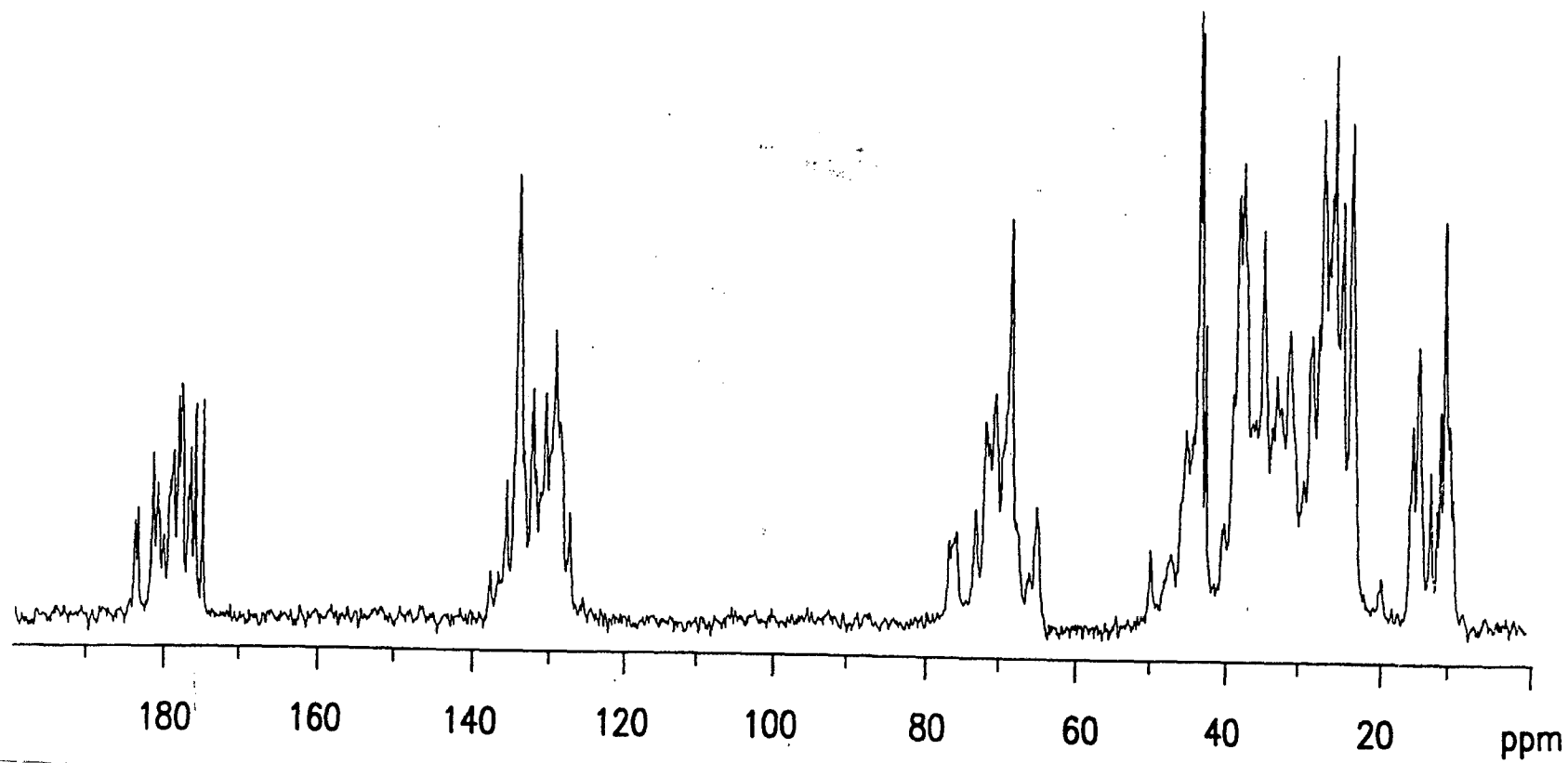


FIG. 4

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2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 353

Radicación no 00-16008

Concepto Técnico no 273

Clasificación Internacional de Patentes A61K 31/185 // 31/015

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de Patente de Invención:

- SI ☒ NO ☐ Contiene un resumen de la invención (Art.26-e).
- SI ☒ NO ☐ Contiene el título o nombre de la invención (Art.27-d).
- SI ☒ NO ☐ Contiene la descripción de la invención (Art.26-b).
- SI ☒ NO ☐ NO ES APLICABLE ☐ Contiene los dibujos necesarios para comprender la invención (Art.26-d)
- SI ☒ NO ☐ Contiene una o más reivindicaciones. (Art.26-c).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-I).
- SI ☐ NO ☒ La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
- SI ☒ NO ☐ La prioridad coincide con la materia reivindicada.
- SI ☒ NO ☐ **CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI ☒ NO ☐ ver hoja(s) anexa(s)

1. Se hace la modificación del título folio 91.
2. Se anexa nuevo resumen, objeto y finalidad de la Invención, que reemplaza el originalmente presentado. folios 107.
3. Se anexa nuevas páginas de la descripción y de las reivindicaciones (8-18 y 62-64), folios 108-111, que reemplazan las originalmente presentadas.
4. Se anexa arte final 6x6 cm y 12x12 cm. folio 105 y Nuevo extracto de publicación folio 106.
5. Se anexan nuevas tarjetas de Archivo Temático y de Proprietarios folios 103 y 104.

EXAMINADOR TÉCNICO
202038

Bogotá D. C., febrero 28/02

Folio 354

2002-04-29
416

2020
Bogotá, D.C.

Doctor(a)
JOSE ANTONIO LLOREDA
Apoderado(a)

REFERENCIA:	Radicación No.	00-16008
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	407
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la comunidad andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase

Dado en Bogotá, D.C., a los

08 MAR. 2002

ALIX CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Bogotá, D.C., Sept-2002 El extracto de esta solicitud fue publicado en el número 515 de la Gaceta de Propiedad Industrial, de fecha 29-04-2002. El término hábil señalado por la ley expiró el 29-07-02 y SI ☒ NO ☐ se presentaron oposiciones por parte de terceros.

AR

202038

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