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SUPLRIN-FENDENCIA DE INDUSTRIA Y COMERCIO

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FORMULARIO UNICO DE OPOSICION I2
0 OPOSICION A:
Patente de tnvenclon, 0 Marca Cotectiva.
0 Patente de Modelo de Utüidad. 0 Marca de Certlficacton.
0 Diseflo Industilal 0 Lerna Comercial,
0 Esquema de Trazado para Circultos Integrados.
Marcas de Productos o

Numero del expediente: "6-021164 Soilcitante: WA1N1R I A\fRRRT Cfl!4PANY H
SOLICITUD

PUBIJCADA Apoderado: CARLOS REINALDO O1AiTh GARCIA

Tittdo tie la nueva creaciOn o denominaciOn del signo: "IoRMAs CRISTALINAS DE ACfD [R(R*,
HJPIANQ1CO", Gaceta:

LI

Seæora Jefe,
DIVISION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio
D.

Referencia

: Expediente N° 06021164
Asunto : Oposición a la solicitud de patente de Invención
titulada "FORMAS CRISTALINAS DE ACIDO FR-
(R*, R*)12(4FLUOROFENIL).?,?DIHIDROXI5.(1-METILETIL)-3-FENIU4-[(FENILAMINO)- CARBONIL}-1H-PIRROk1-HEPTANOICO."
Solicitante : WARNER LAMBERT COMPANY LLC..
Opositora : Gynopharm S.A.

Publicada en la Gaceta de La Propiedad Industrial
N° 583 del 18 de diciembre de 2007

Yo, ELIANA ISAURA MORENO BOHORQUEZ, abogada

V
en ejercicio,
identificada como aparece al pie de su firma, conjeta profesional No. 83823 del Consejo Superior de la Judicat a, en mi condición de apoderada de La sociedad Gynopharm S.A. conformada bajo las leyes de La Repiihlica de Colombia y domiciliada en la ciudad de Barranquilla,

Carrera 13 N 119-95, Oficina 104. Tel. (571) 2 1312 13 - Fax. (571)6 12 19 79 E-mail: negoclos@optimurn-co.com - wWw.optllflUfli-co.COfl) Bogota Colombia

4-

Colombia, atentamente manifiesto que estando dentro del tØrmino de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de InvenciOn titulada ’FORMAS CRISTALINAS DE ACIDO [Ro(R*, R*)]2(4.FLUOROFENIL)?,?. DIHIDROXI-5-(1-METILETIL)-3-FENIL-4-[(FENILAM1NO)- CARBONIL]-1H-PIRROL-1-HEPTANOICO", cuyo titular es WARNER LAMBERT COMPANY LLC., y pido a Usted deciarar fundada esta oposición y en consecuencia negar ci registro de la patente solicitada.

1. INTERES PARA ACTUAR

Conforme a lo dispuesto en el artIculo 42 de la Decision 486 de 2000 de la CAN, estando dentro del tØrmino estipulado por la Icy, manifiesto el legitimo interØs de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se anaiizarÆ mÆs adelante y de ser concedida afectarIa dircctamentc la cornercializaciOn de aigunos productos dc mi representada, que contienen, en particularstatin-or lo tanto, solicito rcspetuosamentc a ese Despacho se sirva tcncr en cucnta la prcsentc oposición dentro del trÆmite administrativo que se surte en esta Superintendencia.

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BogotA Colombia

2. FUNDAMENTOS DE HECHOS

2,1. La solicitud objeto de la presente fue presentada el 3 de marzo de 2006, reivindicando prioridad bajo la solicitud US20030503592P del 2003-09-17; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial No 583 del 18 de diciembre de 2007, cuya pubiicación internacional corresponde a la W02005026116 del 2005-03-24.
2.2. La solicitud colombiana 06021164 objeto de la presente oposiciOn, se refiere a un Æcido libre atorvastatinacristalino Forma A o uno de sus hidratos que tiene un patron de difracciOn de rayos X en polvo que contiene los valores 2? siguientes medidos utilizando radiaciOn CuKa: 8,9, 20,6, 22,5, 0 25,9; donde ci Æcido libre atorvastatina cristalino Forma A o uno de sus hidratos tiene un patron de difracciOn de rayos X en polvo que contiene los valores 2? siguientes medidos utilizando radiaciOn CuKa: 4,7, 6,0, 8,9, 9,1, 9,4, 13,2, 14,1, 17,8, 18,1, 18,9, 19,9, 20,2, 20,6, 21,8, 22,1, 22,5, 23,7, 25,9 y 26,7; donde ci acido libre atorvastatina cristalino Forma A hidrato de Østa tiene un patron de difracción de rayos X en polvo que contiene los valores 2 siguientes medidos utilizando radiación CUKa: 8,9, 20,6, 22,5, 0 25,9; donde ci Æcido libre atorvastatina cristalino Forma A hidrato de Østa tiene un

patrOn de difracción de rayos X en polvo que contiene los valores 2 siguientes medidos utilizando radiaciOn CuKa: 4,7, 6,0, 8,9, 9,1, 9,4, 13,2, 14,1, 17,8, 18,1, 18,9, 19,9,20,2, 20,6, 21,8, 22,1, 22,5, 23,7,

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25,9 y 26,7; donde el Æcido libre atorvastatinacristalino Forma A o uno de sus hidratos caracterizado por resonancia magnØtica nuclear de 13C en estado sólido que tiene los desplazamientos quimicos siguientes expresados en partes por mil!ón: 18,1, 18,8, 20,5, y 21,2; donde el Æcido libre atorvastatina cristalino FormaA o uno de sus hidratos por resonancia magnØtica nuclear de 1C en estado sólido tiene los desplazamientos quimicos siguientes expresados en partes por millón: 161,5, 163,6, 166,3, 167,1, 174,3, y 180,6; donde el Æcido libre de atorvastatina cristalino Forma A o uno de sus hidratos por resonancia magnØtica nuclear de ’3C en estado sólido tiene los desplazamientos quimicos siguientes expresados en partes por millón: 18,1, 18,8, 20,5, 21,2, 25,0, 25,5, 26,2, 26,8, 37,1, 38,9, 4Q,0, 40,6, 41,8, 42,9, 43,5, 65,3, 68,6, 69,1, 70,0, 71,3, 112,3, 113,7, 115,1, 116,4, 118,4, 119,3, 121,6, 123,3, 125,4, 128,0, 128,8(meseta), 130,0, 132,9, 134,1, 135,2, 137,9, 140,7, 141,8, 161,5, 163,6, 166,3, 167,1, 174,3, y 180,6; y, donde el Æcido libre atorvastatina cristalino Forma A o uno de sus hidratos por resonancia magnetica nuclear de ’9F en estado sólido tiene los desplazamientos quimicos siguientes expresados en partes por millón: -114,1,,112,6, -110,6, -105,6.
2.3. En primera instancia, se debe advertir que la reivindicación 15 se refieren al mØtodo de tratamiento y no solo a la composiciOn farmacologica o a un mØtodo de fahricaciOn mediante la cual se obtenga tin producto tangible y segUn la legislacion, decision 486 de la

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Comunidad Andina de Naciones, Articulo 14.- "Los Palses Miembros otorgardn patentes Para Las invenciones, sean de producto o de procedimiento (...)", los usos no estÆn contempladoscomo patentables; y, Articulo 20.- "No serctn patentables (...) d) Los me’todos terape’uticos o quirürgicos Para el tratamiento h.umano o animal, asI como Los mØtodos de diagnostico aplicados a Los seres h.umanos o a animates". Solo serÆn patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al mØtodo de tratamiento no seria patentable.

2.4. Ahora bien, con base en el artIdulo 14 de la Decision 486 de la CAN consagra lo siguiente: "Los paises miembros otorga’rÆn patentes Para Las invenciones, sean de producto o procedimiento, en todos Los campos de La tecnologIa, sienipre que sean nuevas, tengan niveL inventivo y sean susceptibles de apiicaciOn industrial". AsI las cosas, las invenciones objeto de patente deben set nuevas y tenet five1 inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta La patentabilidad de la presente solicitud:

Dl: US658 3295 publicada el 24 de junio de 2003.
D2: W00243667 publicada el 6 de junio de 2002.
D3: ES2167587, del 24 de mayo de 1998.
D4: ES2 166456, del 24 de mayo de 1998.

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Bogota Colombia

2.5. Es de anotar que con anterioridad a la fecha de prioridad de esta solicitud, la molØcula de la atorvastatina ya era parte del estado de la tØcnica tal y como lo referencia ci mismo solicitante en su texto descriptivo cuando hace referencia al estado del arte anterior.
2.6. Ahora bien, ci documento Dl en la descripción revela derivados y anÆlogos de lovastatina, pravastatina, simvastatina, mevastatina, atorvastatina, conocidos como inhibidores de reductasa HMG-CoA usados como agentes antihipercoleterolØmicos. Particularmente, en el ejemplo 22 (pÆrrafos 87 y 88) de dicho documento Dl, se revela mØtodo de preparación de un Æcido libre de atorvastatina o una sal calcica de atorvastatina (3 g) suspendido en 100 ml agua. En este ejemplo se revela que ci pH de 4 flue es ajustado con Æcido fosfórico y ci cido libre de atorvastatina fue extraido a partir de acetato de etilo (3-100 ml); donde el extracto de acetato de etilo combinado fue secado para obtener 2.7 g de atorvastatina en forma libre. Igualmente, dicho ejemplo 22 revela la preparación de 1 g de sal TBA de 5 atorvastatina. Ahora bien ci documento D2, revela por su parte un proceso para preparar hemicalcio de atorvastatina desde un derivado de ester de atorvastatina con hidróxido de calcio donde ci proceso se incorpora convenientemente en un proceso para preparar hemicalcio de atorvastatina desde un compuesto precursor de Æcido Y, d-dihidroxi heptanoico protegido con ester, protegido con acetonuro mediante un primer paso de hidrOlisis de Æcido seguido por una hidrOlisis de base

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con hidroxido de calcio donde el proceso posterior se puede realizar como un proceso de un recipiente. Particularmente en el ejemplo 1 de D2, define ci mØtodo de preparaciOn de derivados de ester de atorvastatina desde dioxano 2.

2.7. Por su parte, las solicitudes D3 y D4, se refieren a formas cristalinas de atorvastatina conocida con el nombre de hemisal de calcio de Æcido

[R(R*,R*)12o(4ofluorofenil) beta, delta -dihidroxi-5-(1 -metiletil)-3-fenil-4-[(fenilamino)carbonil]- 1 H-p irrol- 1 -heptanoico designado como una Forma I, Forma 11 y Forma IV en ci D3 y la Forma III en ci D4, caracterizados por tener un patron de difracción de rayos X en poivo y/o en estado sólido, asI como los mØtodos para la preparación y la composiciOn farmacØutica del mismo, que es Util como agentes para tratar la hiperlipidemia y la hipercolesterolemia. Como se puede apreciar a simple vista, el arte anterior descrito en estas solicitudes D3 y D4, ya revelaba un compuesto farmacØutico que comprendia unas formas cristalinas de atorvastatina. Adicionalmente y como es de conocimiento general en la tØcnica, una forma cristalina representa un ordenamiento en ci espacio o red cristalina de una estructura qulmica (fenOmeno denominado "Poliformismo"), de tal suerte, que solo se requiere conjugar apropiadamente las condiciones de cristalizaciOn de un compuesto conocido para obtener un polimorfo derivado. Por lo tanto, aün alterando la forma de la molØcula de atorvastatina, los componentes de dicha molØcula se mantienen iguales, alterÆndose

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ü nicamente algunas propiedades fisicoquimicas del producto. El poliformismo es una tØcnica conocida desde 1788 (Martin Kiaproth) para hacer pasar la molØcula de una forma a otra. Ahora bien, si combinamos el conocimiento indicado en estas solicitudes D3 y D4, y ci conocimiento revelado en los documentos Dl y D2 ademÆs del conocimiento general que dicta que las modificaciones polimorficas de un compuesto, en general pueden alterar algunas propiedades de las molØculas tales como su forma cristalina, velocidad de disoluciOn, punto de fusiÆn,densidad verdadera, dureza y/o fragilidad cristalina, el espectro de absorciOn infrarrojo o ci difractograma de rayos X entre otros, indudablemente es posible derivar un Æcido libre atorvastatina cristalino Forma A o uno de sus hidratos que tiene un patron de difracciOn de rayos X en poivo que contiene los valores 2 siguientes medidos utilizando radiación CuKa: 8,9, 20,6, 22,5, 2 5,9.
2,8. Por to tanto, este documento objeto de oposición a la luz de los documentos D3 y D4 y el conocimiento revelado en los documentos Dl y D2, carece evidentemente de ALTURA INVENTIVA.
2.9. En consecuencia y de acuerdo a to descrito anteriormente, se deriva que la solicitud colombiana 06-021164 no puede pretender un monopolio por patente toda vez que to que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.10.1. CARENCIA DE ALTURA INVENTIVA. Segün la Decision 486 de la Comunidad Andina de Naciones, ArtIculo 18.- "Se considerarÆ que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en La n-iateria te’cnica correspondiente, esa invenciOn no Iiubiese resultado obvia ni se hubiese derivado de manera evidente del estado de La te’cnica.". A la fecha de prioridad, 17 de septiembre de 2003, a partir de los documentos D3 y D4 y el conocimiento revelado en los documentos Dl y D2, cualquier persona versada en la materia, puede liegar de manera ohvia y evidente a La conformación de un Æcido libre atorvastatina cristalino Forma A o uno de sus hidratos que tiene tin patrOn determinado de difracción de rayos X en poivo sobre el cual husca protección en ci capitulo reivindicatorio.
2.10.2. CARENCIA DE APLICACION INDUSTRIAL La Decision 486 de la CAN consagra en su artIculo 14 lo siguiente: "Los palses miembros otorgarÆn patentes para Las invenciones, sean de producto o procedimiento, en todos los campos de la tecnologIa, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".
La presente solicitud carece de aplicación Industrial ya que como se demostrO anteriormente, algunas clÆusulas reclaman ci mØtodo

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terapØutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, ci objeto
de la presente invenciOn referido a los usos y mØtodos terapØuticos,
no dumplen con el requisito de la aplicación industrial.

2.11. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la DecisiOn 486 de la Comunidad Andina de Naciones, ArtIculo 14.- "Los Palses Miernbros otorgardn patentes para Las invenciones, sean de producto o de procedimiento, en todos Los campos de La tecnologIa, siempre que sean nuevas, tengan nivel inventivo y sean su.sceptibles de aplicación industrial.". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.12. Por todo lo anterior, atentamente solicito a usted que se sirva deciarar fundada la presente oposición y negar ci registro Patente de invención denominada ’FORMAS CRISTALINAS DE ACIDO IR-

(R*, 1-METILETIL)-3-FENIL-4-[(FENILAMINO)-CARBONIL]-1H-P1RROL 1-HEPTANOICO", cuyo titular es WARNER LAMBERT COMPANY LLC., solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial No 583 del 18 de diciembre de 2007.

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Bogota Colombia

3. PRUEBAS

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

Dl: US6583295 publicada el 24 de junio de 2003.
D2: W00243667 publicada el 6 de junio de 2002.
D3: ES2 167587, del 24 de mayo de 1998.
D4: ES2 166456, del 24 de mayo de 1998.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del articulo 586 del Codigo de Comercio.

4.2. Articulo 42 de la Decision 486 de la ComisiOn del Acuerdo de
Cartagena.

4.3. En las demÆs normasconcordantes.

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5. ANEXOS

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

1. Poder para actuar en el presente.
2. Documento que acredita at representante legal de Gynopharm S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
Dl: US6583295 publicada ci 24 de junio de 2003.
D2: W00243667 publicada ci 6 de junio de 2002.
D3: ES2 167587, del 24 de mayo de 1998.
D4: ES2 166456, del 24 de mayo de 1998.

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6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artIculo 90 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretarla de su Despacho o en mis oficinas situadas en la Carrera 13 No 119-95, Of. 104 de esta ciudad de Bogota.

Seæor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51’975.664 de Bogota
T.P.A. 83823 del C.S. de la J.

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PODE/SPECIAL

Yo, LUIS PALACIOS A4AGON, mayor de edad y vecino de la ciudad de Barranquilla (Colombia)Jdentificado como aparece al pie de mi firma, quien en el presente documento aath en calidad de Representante Legal de la sociedad GYNOPHARM S.A. sociedad legalmente constituiday dopiiciliada en la ciudad de Barranquilla (Colombia), por el presente docume6 otorgo a la doctora ELIANA ISAURA MORENO BOHORQUEZ, abogada en ejercicio, identificada como aparece al pie de su firma, con taijeta profçsional No. 83823 del C.S. de la j., poder especial, amplio y suficiente, para foular oposiciones u observaciones a la solicitud de patente No. 06,021,164, titulada "FORMAS
CRISTALINAS DE ACIDO [R(R*, *)]..(44jjJOROFENIL)..?,?..
DIHLDROXI-5(1-METILETIL)-3-FENIL-4-[(FENILAMINO)- CARBONIL]-iH-PIRROL-i HEPTANOICO", cuyo titular es WARNER
LAMBERT COMPANY LLC, publicada en la gaceta No. 583 del 18 de
Diciembre de 2007.

Nuestro apoderado queda facultado, de manera expresa, para realizar toclo tipo de actos necesarios para Ilevar a cabo el trÆmitede la oposiciôn, incluyendo, sin limitación, preparar y presentar solicitudes, bacer deciaraciones, pagar tasas, contribuciones e impuestos, recabar los tItulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que lucre resuelto en el expediente a que se bace expresa referencia en el presente poder, con todas las facultades generales y especIficas que fuera requerido para ella.

De la misma manera, ademÆs delas facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir ci presente poder, incoar acciones, interponer recursos y demÆsfacultades conferidas porla Icy.

Dado y Firmado en Barranquilla (Colombia) a los 12 dias del mes de Marzo de
2008. /

GYNOPHARM

CØdula de ExUJ4Iª: Io. 319788.
NIT: 8oz.00& /

Acepto:

FaAat-?- (R

ELIANA ISAURA MORENO BOHORQUEZ C.C. 511975.664 do Bogota
T.P.A. 83823 dot C.S. do la J.

gQMOCIENTO DE DOC1JENT0 PR1’JD

AGUSTIN FIJERTES

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CERTIFICADO NACIONAL

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CA1’1ARA DE COMERCIO DE BARRANQUILLA CANt
DE COMERCIO IJEBOGOTA Fecha 20080312 Hora Certificaclo 18:25:01

\ Operacion: 02CP20312099 PAGINA No. 1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL 0 DE INSCRIPCION DE DOCUMENTOS.
EN JUN10 DE ESTE A?O SE ELEGIR? JUNTA DIRECTIVA DE LA C?MARA DE
COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERà
QUINCENA DE MAYO. PARA INFORMACI?N DETALLADA DIRIGIRSE A LA SEDE
PRINCIPAL 0 COMUNICARSE AL SIGUIENTE TELEFONO: 3303911.

EL SUSCRITO SECRETARIO DE LA CA14ARA DE COMERCIO DE BARRANQUILLA, CON
FUNDAIVIENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que par Escritura P?blica No. 3,551 del 17 de Dic/bre de 1997,
otorgada en la Notaria 3a. de Barpnqui11a, inscrito(as) en esta
C?mara de Camercio, el 18 de Dic/b$ de 1997 bajo el No. 72,965 del
libro respectivo, fue constituida ly’sociedad-------------------------
ananima denominada GYNOPHARM S.A.

CERTIFICA

C E R T I F I C A

. 463.982, actuando como Presidente y represen-tante legal de la saci
edad GYNOPHARM S.A., otorga Poder Especial, Amplia y Suficienta a KA
REN JENNIFER FIGUEROA GARCIA C.C. Na. 32.-732.070, para que en nombr
e y representacion de la sociedad suscriba todas las declaraciones C
ambiarias a que esta obligada GYNOPHARS.A., en el giro normal de sus
negocios y aperacianes sociales.---

C E R T I F I C A

Que dicha sociedad ha sido reformada par las siguientes escrituras
y/o documentos privadas:
Numera aaaa/mm/dd Nataria Na. Insc a Reg aaaa/mm/dd
532 1999/03/25 Nataria 3a. de Barranquilla 80,373 1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad
se rige par las siguientes disposiciones:
DENOMINACION 0 RAZON SOCIAL:
GYNOPHARMS.A. --

DOMICILIO PRINCIPAL: Barranquilla.
NIT Na: 802.006.279-4.
MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha: 20080312 Hora Certificado 18:25:01

Operacion 02CP20312099 PAGINA No. 2

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Direccion para notificaciones judiciales:
CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DtJRACION: El t?rmino de duraci?n de la sociedad se fij? hasta el
16 de Dic/bre de 2047.

CE R IF I CA

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos simi-
lares a partir de materiales tales como gelatinas u otros de distin-
ta naturaleza, que puedan ser utilizados como envases o recipientes
de productos y sustancias quimicas, farmaceuticas y cosmeticas, para
uso y consumo humano y veterinario. b) La investigacion, desarrollo
y fabricacion de toda clase de productos y sustancias quimicas, far-
maceuticas y cosmeticas para uso y consumo humano, animal y vegetal.
C) La compra y yenta de meterias primas, insumos y productos inter -
medics necesarios para los procesos de fabricacion de sustancias
quimicas, farmaceuticas y cosmeticas, asi como la comercializacion
interna y externa de los productos terminados. d) La compra, yenta,
importacion, exportacion y distribucion de toda clase de elementos
instrumentales y equipos, medicos, quirurgicos, odontologicos y hos-
pitalarios para la salud humana y animal. e) Actuar como represen-
tante o agente de personas naturales y juridicas nacionales y ex-
tranjeras en la realizacion de operaciones o transacciones relacio-
nadas con la industria farmaceutica y en especial con cualesquiera
de las actividades descritas en los literales a), b), c) y d) antes
transcritos. f) Prestar los servicios de asesoria y consultoria en
las areas administrativa, de mercadeo, analisis clinico, asistencia
tecnica, investigacion, costos y produccion exportaciones, importa-
ciones, ventas, relacionadas con iguales o similares actividades a
las que constituyen el objeto de GYNOPHARM S.A., asi como los de pu-
blicidad y promocion de productos quimicos, cosmeticos y farmaceuti-
cos para uso humano, animal o industrial. g) Adquirir, operar, admi-
nistrar y explotar, a cualquier titulo,empresas o establecimientos
dedicados a la investigacion, desarrollo, fabricacion o comerciali-
zacion de productos quimicos, farmaceuticos, hospitalarios o cosme-
ticos. En desarrollo de su objeto principal, la sociedad podra to-
mar interes social como accionista, socio o fundador de empresas que
tengan igual o similar objeto; comprar, vender, importar y exportar
maquinarias, insumos y repuestos requeridos para el desarrollo de
sus actividades; tomar dinero en prestamo,financiar y garantizar las
operaciones comerciales que celebre con terceros relativas a su ob-
jeto; celebrar y ejecutar todo tipo de actos y contratos necesarios
para desarrollar sus operacioes; girar, aceptar, otorgar y protestar
todo tipo de titulos valores e instrumentos negociables; comprar,

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) C :

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

\ CAMARA
1)ECOMERCIODEBOGOTA / Fecha: 20080312 Hora Certificado 18:25:01

)m --’(Operacion: 02CP20312099 PAGINA No. 3

vender y constituir gravamenes sobre bienes muebles e inmuebles; de-
signar representantes o apoderados en el pais y en el exterior y, en
general, realizar cualquier acto o negocio que sea necesario o con-
veniente para el desarrollo de su objeto social y para la mejor pro-
teccion de sus intereses corporativos o lo de sus socios. -----------

CAPITAL
Autorizado

$**********4, 000, 000, 000
Suscrito

$****** ** **2, 672, 646, 000
Pagado

$*** ***** **2, 672, 646, 000

CERTIFICA

Nro Acciones Valor Acci?n

*************4,000,000 *****************1,000

*************2,572,646 *****************1,000

*************2,672,646 *****************1,000

C E R T IF I CA

ADMINISTRACION: Seran funciones de la junta directiva, entre otras:
Autorizar cualquier acto o contrato cuya cuantia sea superior al
equivalente en pesos Colombianos a cincuenta mil dolares de los Es-
tados Unidos de America (US$50.000.00), liquidados a la tasa de cam-
bio representativa del mercado vigente el dia en que se surta la
aprobacion y para enajenar o gravar bienes inmuebles y demas activos
fijos de la sociØdad, cualquiera que sea la cuantia de la transac-
cion. Las demas que le sean propias y no esten atribuidas a otro or-
gano social y las que le correspondan en virtud de la ley. la socie-
dad tendra un Gerente General, quien ejercera la administracion y
representacion legal de la sociedad y tendra las siguientes atribu-
ciones, entre otras: Ejercer la representacion legal de la sociedad
en todos los actos y contratos que se requieran para el desarrollo
del objeto social, de conformidad con lo previsto en las leyes y en
los presentes estatutos. Aprobar y celebrar en nombre de la sociedad
todo acto o contrato cuya cuantia sea igual o inferior al equivalen-
te en pesos Colombianos a cincuenta mil dolares de los Estados Uni-
dos de America (US$50.000.00), liquidados a la tasa de cambio repre-
sentativa del mercado vigente el dia en que se surta la aprobacion o
celebracion del acto. Para enajenar, a cualquier titulo, bienes in-
muebles de la sociedad o constituir gravamenes sobre los mismos, de-
bera obtener la aprobacion de la junta directiva, cualquiera que sea
la cuantia de la transaccion; o las demas funciones que le corres-
pondan como representante legal por disposicion de la ley, de estos
estatutos o de la junta directiva. El Gerente General tendra un su-
plente, designado por la junta directiva, quien lo reemplazara con
identicas facultades en sus faltas temporales, absolutas o meramente
acciedentales, sin que sea necesario para ello acreditar la ausencia
del principal.

*** CONTINUA ***

CERTIFICADO NACIONAL

CAIVIARA DE COMERCIO DE BARRANQUILLA

Fecha: 20080312 Hora Certificado 18:25:01

Operacion: 02CP20312099 PAGINA No. 4

C E R T I F I C A

Que seg?n Acta No. 15 del 18 de Febrero de 2008 correspondiente a
la Asamblea de Accionistas en Bogota, de la sociedad:
GYNOPHARMS.A. --

cuya parte pertinente se inscribi? en esta C?mara de Comercio, el
25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron
hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales
1. Liobet Poal Manuel CC.******14,670,196
2. Zanatta Reherman Leonardo Andres CC.*******2,760,271
3. Munoz Marroquin Diego CC.*******7,688,292
4. Montealegre Gonzalez Andres Leonardo CC.******79,950,262

Suplentes
1. Agudelo Pelaez Luis Hernando CC.******14,238,997
2. Aroca Almanza Arleth Ayelina CC.******36,718,415
3. Penaranda Urbina Adriana Paola CC.******53,120,683
4. tovar Vasquez Ruth CC.******52,175,756

C E R T I F I C A

Que seg?n Acta No. 18 del 30 de OctiIbre de 2003 correspondiente a
la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A.
cuya parte pertinente se inscribi? en esta C?mara de Comercio, el
06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo,
fueron hechos los siguientes nombramients:
Cargo/Nombre 7 Identificaci?n
Gerente General. /
Palacios Aragon Luis Alberto ’ CE.*********319,788

C E R T I F I C A

Que seg?n Acta No. 49 del 03 de Marzo de 2008 correspondiente a la
Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A.
cuya parte pertinente se inscribi? en esta C?mara de Comercio, el
11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo,
fueron hechos los siguientes nombramientos:
Cargo/Nombre Identificaci?n Suplente del Gerente.
Mollajoli Centurion Andres Fernando CE.*********351,283

C E R T I F I C A

Que seg?n Acta No. 2 del 13 de Enero de 1998 correspondiente a la

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CERTIFICADO NACIONAL /

CANARA DE COMERCIO DE BARRANQUILLA

’\ CAMARA / DECOMERCIODEBOGOTA Fecha: 20080312 Hora Certificado 18:25:01
Operacion: 02CP20312099 PAGINA No. 5

Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM
S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio,
el 20 de Enero de 1998 bajo el No. 73,393 del libro respectivo,
fueron hechos los siguientes nombramientos:
Cargo/Nombre Identificaci?n
Revisor Fiscal Ppal.
Barros Cera William Alberto CC.*******8,715,941
Suplente del Revisor Fiscal.
Duarte Diaz David CC.******73,115,965

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, ins
crito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo
el No. 1.872 del libro repectivo, consta que el senor RUBEN MINSKI
GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y represen-
tante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial,
Amplio y Suficienta a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-
732.070, para que en nombre y representacion de la sociedad suscri-
ba todas las declaraciones cambiarias a que esta obligada GYNOPHARM
S.A., en el giro normal de sus negocios y operaciones sociales. -----

C E R T IF I CA

Que segun Documento Privado de fecha 10 de Octubre del 2.000, ins-
crito en esta Camara de Comercio el 12 de junio del 2.002, bajo el
2.164 del libro respectivo,consta que el senor JORGE CASTELLANOS
MARTINEZ,identificado con C.C.No.19.460.089,actuando como represen-
tante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Am-
plio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la ce-
dula de ciudadania No.32.732.070 de Barranquilla, mediante docu-
mento privado de octubre 10/2000, inscrito en la Camara de Corner -
do de Barranquilla bajo el No.1.872 del libro respectivo, para
que en representacion de GYNOFARM S.A, suscriba las declaracio-
nes cambiarias a los que esta obligada GYNOFARM S.A. en el giro
ordinario de sus negocios y operaciones sociales. ------------------

C E R T IF I CA

. 463.982, actuando como Presidente y represen-tante legal de la sod
edad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficienta a KA
REN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombr
e y representacion de la sociedad suscriba todas las declaraciones c
ambiarias a que esta obligada GYNOPHARS.A., en el giro normal de sus
negocios y operaciones sociales--------------------------------------

C E R T I F I C A

- - - .CERTIFICA

*** CONTINUA **

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLIA

Fecha: 20080312 Hora Certificado 18:25:01

Operacion: 02CP20312099 PAGINA No. 6

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Que en esta C?mara de Comercio no aparecen inscripciones posteriores
de documentos referentes a reforma, disoluci?n, liquidaci?n o
nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su?ltima Renovaci?n fue el: 23 de Marzo de 2007.

La informaci?n sobre embargos de establecimiento se suministra en
Certificados de Matr?cula, la de contratos sujetos a registro, en
I Certificados Especiales.

C E R T I F I C A

Que los actos de registro aqu? certificados quedan en firme cinco d?as h?biles despues de la correspondiente inscripci?n, siempre
que, dentro de dicho t?rmino, no Sean objeto de los recursos de
reposici?n ante esta entidad, y/o de apelaci?n para ante la
Superintendencia de Inthistria y Comercio.

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CERTIFICADO NACIONAL

\ CANARA DE COMERCIO DE BARRANQUILLA

CAMAFA DECOMEWO DE BOGOTA/ Fecha: 20080312 Hora Certificado 18:25:01
Operacion 02CP20312099 PAGINA No. 1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL 0 DE INSCRIPCION DE
DOCUMENTOS.
EN JUN10 DE ESTE A?0 SE ELEGIR? JUNTA DIRECTIVA DE LA C?MARA DE
COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA
QUINCENA DE MAYO. PAPA INFORMACI?N DETALLADA DIRIGIRSE A LA SEDE
PRINCIPAL 0 COMUNICARSE AL SIGUIENTE TELEFONO: 3303911.

EL SUSCRITO SECRETARIO DE LA CAIvIARA DE COMERCIO DE BARRANQUILLA, CON
FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura P?blica No. 3,551 del 17 de Dic/bre de 1997,
otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta
C?mara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del
libro respectivo, fue constituida la sociedad-------------------------
anonima denominada GYNOPHARM S.A.

CERTIFICA

C E R T I F I C A

. 463.982, actuando como Presidente y represen-tante legal de la soci
edad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficienta a KA
REN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombr
e y representacion de la sociedad suscriba todas las declaraciones C
ambiarias a que esta obligada GYNOPHARS.A., en el giro normal de sus
negociosy operaciones sociales.---

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras
y/o documentos privados:
Numero aaaa/mm/dd Notaria No. Insc 0 Reg aaaa/mm/dd
532 1999/03/25 Notaria 3a. de Barranquilla 80,373 1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad
se rige por las siguientes disposiciones:
DENOMINACION 0 RAZON SOCIAL:
GYNOPHARMS.A. --

DOMICILIO PRINCIPAL: Barranquilla.
NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T IF I CA

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha: 20080312 Hora Certificado 18:25:01

Operacion: 02CP20312099 PAGINA No. 2

Direccion para notificaciones judiciales:
CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El t?rmino de duraci?n de la sociedad se tij? hasta el
16 de Dic/bre de 2047.

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos simi-
lares a partir de materiales tales como gelatinas u otros de distin-
ta naturaleza, que puedan ser utilizados como envases o recipientes
de productos y sustancias quimicas, farmaceuticas y cosmeticas, para
uso y consumo humano y veterinario. b) La investigacion, desarrollo
y fabricacion de toda clase de productos y sustancias quimicas, far-
maceuticas y cosmeticas para uso y consumo humano, animal y vegetal.
c) La compra y yenta de meterias primas, insumos y productos inter-
medios necesarios para los procesos de fabricacion de sustancias
quimicas, farmaceuticas y cosmeticas, asi como la comercializacion
interna y externa de los productos terminados. d) La compra, yenta,
importacion, exportacion y distribucion de toda clase de elementos
instrumentales y equipos, medicos, quirurgicos, odontologicos y hos-
pitalarios para la salud humana y animal. e) Actuar como represen-
tante o agente de personas naturales y juridicas nacionales y ex-
tranj eras en la realizacion de operaciones o transacciones relacio-
nadas con la industria farmaceutica y en especial con cualesquiera
de las actividades descritas en los literales a), b), c) y d) antes
transcritos. f) Prestar los servicios de asesoria y consultoria en
las areas administrativa, de mercadeo, analisis clinico, asistencia
tecnica, investigacion, costos y produccion exportaciones, importa-
ciones, ventas, relacionadas con iguales o similares actividades a
las que constituyen el objeto de GYNOPHARM S.A., asi como los de pu-
blicidad y promocion de productos quimicos, cosmeticos y farmaceuti-
cos para uso humano, animal o industrial. g) Adquirir, operar, admi-
nistrar y explotar, a cualquier titulo,empresas o establecimientos
dedicados a la investigacion, desarrollo, fabricacion o comerciali-
zacion de productos quimicos, farmaceuticos, hospitalarios o cosme-
ticos. En desarrollo de su objeto principal, la sociedad podra to -
mar interes social como accionista, socio o fundador de empresas que
tengan igual a similar objeto; comprar, vender, importar y exportar
maquinarias, insumos y repuestos requeridos para el desarrollo de
sus actividades; tomar dinero en prestamo,financiar y garantizar las
operaciones comerciales que celebre con terceros relativas a su ob-
jeto; celebrar y ejecutar todo tipo de actos y contratos necesarios
para desarrollar sus operacioes; girar, aceptar, otorgar y protestar
todo tipo de titulos valores e instrumentos negociables; comprar,

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coCERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILIJA

\ CAMARA A(DECOMERCIODEBOGOTA / Fecha: 20080312 Hora Certificado 18:25:01
z

Operacion: 02CP20312099 PAGINA No. 3

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rjehdr y d6æ1tui gravamenes sobre bienes muebles e inmuebles; de-
signar representantes o apoderados en el pais y en el exterior y, en
general, realizar cualquier acto a negocio que sea necesario o con-
veniente para el desarrollo de su objeto social y para la rnejor pro-
teccion de sus intereses corporativos o lo de sus socios. -----------

CAPITAL
Autorizado

$**********4, 000, 000, 000
Suscrito

$**** ******2, 672, 646, 000
Pagado
$**********2, 672, 646, 000

C E R T I F I C A

Nro Acciones Valor Acci?n

*************4,000,000 *****************1,000

*************2,672,646 *****************1,000

*************2,672,646 *****************1,000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras:
Autorizar cualquier acto o contrato cuya cuantia sea superior al
equivalente en pesos Colombianos a cincuenta mil dolares de los Es-
tados Unidos de America (US$50.000.00), liquidados a la tasa de cam-
bio representativa del mercado vigente el dia en que se surta la
aprobacion y para enajenar o gravar bienes inmuebles y demas activos
fijos de la sociØdad, cualquiera que sea la cuantia de la transac-
cion. Las demas que le sean propias y no esten atribuidas a otro or-
gano social y las que le correspondan en virtud de la ley. la socie-
dad tendra un Gerente General, quien ejercera la administracion y
representacion legal de la sociedad y tendra las siguientes atribu-
ciones, entre otras: Ejercer la representacion legal de la sociedad
en todos los actos y contratos que se requieran para el desarrollo
del objeto social, de conformidad con lo previsto en las leyes y en
los presentes estatutos. Aprobar y celebrar en nombre de la sociedad
todo acto o contrato cuya cuantia sea igual o inferior al equivalen-
te en pesos Colombianos a cincuenta mil dolares de los Estados Uni-
dos de America (US$50.000.00), liquidados a la tasa de cambio repre-
sentativa del mercado vigente el dia en que se surta la aprobacion a
celebracion del acto. Para enajenar, a cualquier titulo, bienes in-
muebles de la sociedad o constituir gravamenes sobre los mismos, de-
bera obtener la aprobacion de la junta directiva, cualquiera que sea
la cuantia de la transaccion; o las demas funciones que le corres-
pondan como representante legal por disposicion de la ley, de estos
estatutos. a de la junta directiva. El Gerente General tendra un su-
plente, designado por la junta directiva, quien lo reemplazara con
identicas facultades en sus faltas temporales, absolutas o meramente
acciedentales, sin que sea necesario para ello acreditar la ausencia
delprincipal--- --

CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha: 20080312 Hora Certificado 18:25:01

Operacion: 02CP20312099 PAGINA No. 4

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C E R T I F I C A

Que seg?n Acta No. 15 del 18 de Febrero de 2008 correspondiente a
la Asamblea de Accionistas en Bogota, de la sociedad:
GYNOPHARMS.A. --

cuya parte pertinente se inscribi? en esta C?mara de Comercio, el
25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron
hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales
1. Llobet Poal Manuel CC.******14,670,196
2. Zanatta Reherman Leonardo Andres CC.*******2,760,271
3. Munoz Marroquin Diego CC.*******7,688,292
4. Montealegre Gonzalez Andres Leonardo CC.******79,950,262

Suplentes
1. Agudelo Pelaez Luis Hernando CC.******14,238,997
2. Aroca Almanza Arleth Ayelina CC.******36,718,415
3. Penaranda Urbina Adriana Paola CC.******53,120,683
4. tovar Vasquez Ruth CC.******52,175,756

C E R T I F I C A

Que seg?n Acta No. 18 del 30 de Octubre de 2003 correspondiente a
la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A.
cuya parte pertinente se inscribi? en esta C?mara de Comercio, el
06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo,
fueron hechos los siguientes nombramientos:
Cargo/Nombre Identificaci?n
Gerente General.

Palacios Aragon Luis Alberto CE.*********319,788

C E R T I F I C A

Que seg?n Acta No. 49 del 03 de Marzo de 2008 correspondiente a la
Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A.
cuya parte pertinente se inscribi? en esta C?mara de Comercio, el
11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo,
fueron hechos los siguientes nombramientos:
Cargo/Nombre Identificaci?n Suplente del Gerente.
Mollajoli Centurion Andres Fernando CE.*********351,283

C E R T I F I C A

Que seg?n Acta No. 2 del 13 de Enero de 1998 correspondiente a la

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CERTIFICADO NACIONAL -1)

J C CAMARA DE COMERCIO DE BARRANQUILLA
CAMARA, DEC0MERa0DEBOGOTA Fecha: 20080312 Hora Certificado 18:25:01

- - Operacion: 02CP20312099 PAGINA No. 5

PILL

flAànblŁdØAcc1onistas en Barranquilla, de la sociedad: GYNOPHARM
S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio,
el 20 de Enero de 1998 bajo el No. 73.393 del libro respectivo,
fueron hechos los siguientes nombramientos:
Cargo/Nombre Identificaci?n
Revisor Fiscal Ppal.
Barros Cera William Alberto CC.*******8,715,941
Suplente del Revisor Fiscal.
Duarte Diaz David CC.******73,115,965

C E R T IF I CA

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inS-
crito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo
el No. 1.872 del libro repectivo, consta que el senor RUBEN MINSKI
GONTOVNIK C.C. No. 7.463.982, actuando coma PresIdente y represen-
tante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial,
Amplio y Suficienta a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-
732.070, para que en nombre y representacion de la sociedad suscri-
ba todas las declaraciones cambiarias a que esta obligada GYNOPHARM
S.A., en el giro normal de sus negocios y operaciones sociales. -----

CERTIFICA

Que segun Documento Privado de fecha 10 de Octubre del 2.000, ins-
crito en esta Camara de Comercio el 12 de junio del 2.002, bajo el
2.164 del libro respectivo,consta que el senor JORGE CASTELLANOS
MARTINEZ, identificado con C.C.No.19.460.089,actuando como represen-
tante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Am-
plio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la ce-
dula de ciudadania No.32.732.070 de Barranquilla, mediante docu-
mento privado de octubre 10/2000, inscrito en la Camara de Comer-
cio de Barranquilla bajo el No.1.872 del libro respectivo, para
que en representacion de GYNOFARM S.A, suscriba las declaracio-
nes cambiarias a los que esta obligada GYNOFARM S.A. en el giro
ordinario de sus negocios y operaciones sociales. ------------------

CERTIFICA

. 463.982, actuando corno Presidente y represen-tante legal de la sod
edad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficienta a KA
REN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombr
e y representacion de la sociedad suscriba todas las declaraciones c
ambiarias a que esta obligada GYNOPHARS.A.., en el giro normal de sus
negocios y operaciones sociales.---. --------------------------------

CERTIFICA

*** CONTINUA ***

CERTIFICADO NACIONAL

CANARA DE COMERCIO DE BARRANQUILLA

Fecha: 20080312 Hora Certificado 18:25:01

Operacion: 02CP20312099 PAGINA No. 6

Que en esta C?mara de Comercio no aparecen inscripciones posteriores
de documentos referentes a reforma, disoluci?n, liquidaci?n 0
nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su?ltima Renovaci?n fue el: 23 de Marzo de 2007.

La informaci?n sobre embargos de establecimiento se suministra en
Certificados de Matr?cula, la de contratos sujetos a registro, en
Certificados Especiales.

C E R T I F I C A

Que los actos de registro aqu? certificados quedan en firme cinco d?as h?biles despues de la correspondiente inscripci?n, siempre
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Superintendencia de Industria y Comercio.

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(12) United States Patent (10) Patent No.: US 69583,295 B!
Pflaum (45) Date of Patent: Jun. 24, 2003

(54) SALTS OF HMG-COA REDUCTASE 5,223,415 A 6/1993 Condcr ct at...............435/125
INHIBITORS 5.403,860 A 4/1995 Kurabayashi et at.........514/460
5,763,646 A 6/1998 Kumar et at................560/252

(75) Inventor: Zlatko Pflaum, Domzale (SI) 5,763.653 A 6/1998 Khanna et at...............560/252

(73) Assignee: LEK Pharmaceuticals d.d., Ljubljana FOREIGN PATENT DOCUMENTS
(SI) EP 0 456 214 Al 11/1991
EP 0 065 835 B1 11/1995

(*) Notice: Subject to any disclaimer, the term of this GB 2055 100 2/1981
patent is extended or adjusted under 35

U.S.C. 154(b) by 0 days. Primary ExaminerBrian J. Davis
(74) Attorney, Agent, or FirmBromberg & Sunstein LLP

(21) AppI. No.: 09/787,387 (57) ABSTRACT
(22) PCT Filed: Sep. 17, 1999
Lovastatin, pravastatin, simvastatin, inevastatin,

(86) pc’r No.: PCT/1B99/01554 atorvastatin, and derivatives and analogs thereof are known
)
§ 371 (c)(1), as HMG-CoA reductase inhibitors and are used as antihy-
(2), (4) Date: Apr. 25, 2001 percholesterolemic agents. The majority of them are pro-

duced by fermentation using microorganisms of different
(87) PCT Pub. No.: W000/17150 species identified as species belonging to Aspergillus,
Monascus, Nocardia, Amycolatopsis, Mucor or Penicillium

PCT Pub. Date: Mar. 30, 2000 genus, some are obtained by treating the fermentation prod-
(30) Foreign Application Priority Data ucts using the methods of chemical synthesis or they are the
products of total chemical synthesis. The present invention
Sep. 18, 1998 (SI)..P9800240 relates to the new amine salts of HMG-CoA reductase

(51) mt. C1.7.........................CO7C 69/13; C07C 69/30; inhibitors, the preparation thereof, the preparation of pure
C07C 211/07; C07C 211/14; C07D 309/30 HMG-CoA reductase inhibitors via amine salts thereof, the
(52) U.S. Cl........................ 548/537; 548/494; 549/292; use of the amine salts of 14MG-CoA reductase inhibitors in
560/248; 560/256 the process for semisynthetic preparation of HMG-CoA

reductase inhibitors, the use of the amine salts of l-IMG-CoA

(58) Field of Search..........................549/292; 560/248, reductase inhibitors in the process for biotechnological 560/256; 548/537, 494 modification of HMG-CoA reductase inhibitors as well as
(56) References Cited the conversion of the amine salts of HMG-CoA reductase

inhibitors into the pharmaceutically acceptable salts of the
U.S. PATENT DOCUMENTS HMG-CoA reductase inhibitors and the conversion of the
amine salts of HMG-CoA reductase inhibitors into the

4,319,039 A 3/1982 Albers-Schonberg.......560/256 HMGCoA reductase inhibitors in the lactone form. 4.342,767 A 8/1982 Albers-Schonberg et a!.....424/

250

4.346,227 A 8/t982 Terahara ci a!.............560/119 44 Claims, No Drawings

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SALTS OF HMG-COA REDUCTASE
INHIBITORS

TECHNICAL FIELD 5

Invastatin, pravastatin, simvastatin, mevastatin, atorvas-tatin and derivatives and analogs thereof are examples of known as l-IMG-CoA reductase inhibitors which are used as

antihypercholesterolemic agents. The majority of them are 10 produced biotechnologically by fermentation using micro-
organisms of different species identified as species belong-ing to Aspergillus, Monascus, Nocardia, Amycolat psis, Mucor or Penicillium genus, some are obtained by treating the fermentation products using the methods of chemical synthesis, thus leading to semi-synthetic substances, or they are the products of total chemical synthesis.
The present invention relates to a new industrial process
for isolation and/or of HMG-CoA reductase inhibitors via

salts thereof with specific amines. The invention enables a 20 user to obtain the pure amine salts of HMG-CoA reductase inhibitors from the fermentation broth in case the substances are produced by biotechnological (microbiological) processes, or from the reaction mixture in case the sub-stances are produced by semisynthetic or total chemical 25 synthesis. The step of forming salts with amine may be one of the steps in the process for isolation and/or purification of HMG-CoA reductase inhibitors or precursor substances thereof. The amines described in the present specification are very useful for the formation of salts in the composition 30 of media in processes for biotechnological modification of HMG-CoA reductase inhibitors or precursors thereof. The salts thus formed may be used as the starting substances or intermediates for the preparation of semisynthetic deriva-tives and analogs thereof, or by employing simple tech- 35 niques known from the literature, if required, to be con-verted into the pharmaceutically acceptable salts and lactones, respectively.
The processes for the isolation and purification of anti-hypercholesterolemic agents known from patent and tech- 0 nical literature include different combinations of extraction, chromatography, lactonization and crystallization methods. Some of them additionally include the isolation and purifi-cation via different salts. In U.S. Pat. Nos. 9,342,767 and 4,319,039, the ammonium salt of lovastatin (in the carboxy- 45 late form) is isolated directly from the organic phase which has been extracted from the fermentation medium. In the same patent the preparation of ethylenediamine, tetramethylammonium, potassium and N-methylglucamine salts as well as the salts of different amino acids such as so L-lysine, L-arginine and L-ornithine is also described. The aforementioned salts are prepared from the already purified substance and the option for their use in the process of isolation or purification is not mentioned. GB 2055100A " also describes the formation of the sodium and calcium salts 55 of lovastatin, which comprises the extraction in methanol, i, two steps of preparative liquid reverse -phase chromatography, crystallization from methanol and recrys-tallization from ethanol, and the conversion into the salt using an aqueous solution of sodium or calcium hydroxide. oo However, without including various chromatography methods, the methods described do not yield a product of the purity comparable to the product obtained by using the present invention. U.S. Pat. No. 4,346,227 discloses a pro-cess for the preparation of the sodium salt of pravastatin, 65 wherein chromatographic techniques are also used but the final product is obtained only after lyophilization which is

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not an economical process in a large scale production operations. EP 65,835 discloses the preparation of the L-ornithine and t-octylamine salts of tetrahydro-M4 or tctrahydro-IsoM-4 (wherein M4 denotes a specific 11MG-CoA reductase inhibitor, M4 and IsoM-4 representing the isomers hydroxylated at 6- and 3-biphenyl ring position, respectively, and ’tetrahydro" means that the condensed biphenyl ring system is fully hydrogenated) as final products, that is from the respectively purified sodium salts thereof, but not as intermediates via which the isolation would be carried out. Other salts of tetrahydro-M-4 or IsoM:4 with ammonia, an amino acid or an organic amine are also contemplated as final products, including octylamine, 2-ethylhexylamine, benzylamine, a-methyl-benzylamine, phenethylamine, dibenzylamine, N-mcthylbenzylamine, N,N-dimcthylbenzylamine, N,N-diethylbenzylamine, N-ethyl-N-methylbenzylamine, tribenzylamine, cyclopentylamine, cyclohexylamine cycloheptylamine, N-methylcyclopentylamine, N-ethylcyclohexylamine, N-ethylcycloheptylamine, dicyclohcxylamine, N,N-dimethylcyclopentylamine, N,N-dimethylcyclohexylamine, N,N-diethylcycloheptylamine, pyrrolidine, N-methylpyrrolidinc, piperidine, N-methylpiperidine and morpholine. GB 2073199A also discloses the preparation of different salts of HMG-CoA reductase inhibitors from the already isolated substance in the lactone form. U.S. Pat. Nos. 5,763,653 and 5,763,646 disclose the preparation of the cyclopropylamine and n-butylamine amides of lovastatin and their use in a process of chemical semisynthesis of simvastatin. U.S. Pat. No. 5,403,860 discloses, as final products, amine salts of octahy-dronaphthalene oxime derivatives of HMG-CoA inhibitors, the derivatives deriving from ML-236A, ML-23613, MB-530A and M13-53013. As final amine salts, t-octylamine, dibenzylamine, dicyclohexylaminc, morpholine, D-phenylglycine alkylester and D-glucosamine salts are mentioned.

In industry there exists a constant need for rationalization of the production and shortening of the production processes as well as for the use of least expensive starting raw materials or intermediate substances. To date the isolation of the final products in the case of HMG-CoA reductase inhibitors has been a multi-stage process wherein each step adds its share to the losses resulting in the final yield rarely greater than 60%. In addition, a product in the lactone form or lactone converted into the sodium salt is used as the starting substance in the process of semisynthesis (erg. in a process for preparing simvastatin) or biochemical conver-sion (e.g. in a process for preparing pravastatin). The prepa-ration of lactone is one of the least economical steps in the production of HMG-CoAreductase inhibitors since losses in the course of the conversion from the acid into the lactone form and optionally further into the salts are greater than 20%. Therefore, there is a constant need for the starting substances and/or the intermediate substances which would be sufficiently pure, with small losses during their conversion, low costs, and the preparation per se should be technologically simple.
In our developmental and research work we have surpris-ingly found that HMG-CoA reductase inhibitors form the salts with certain amines which crystallize from mother liquor once they are formed. It has surprisingly been found that crystals of the amine salt of the desired IIMG-CoA reductase inhibitor of high purity may he obtained from the liquors containing a large number of impurities and undes-ired HMG-CoA reductase inhibitor analogs. Contrary to the statements from U.S. Pat. No. 5,403,860 that lower yields

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are obtained when using the salts of HMG-CoA reductase inhibitor as starting or intermediate substances in a process for preparing the substances (la) mentioned below, we have surprisingly found that, when using the amine salts of HMG-CoA reductase inhibitors according to the present invention, the yields and the purity of the prepared HMG-CoA reductase inhibitors are equal to or greater than when using the HMG-CoA reductasel inhibitors in the lactone form.
Exemplified Formula la

R1

R1: C131 CILOIl, 011
a and b: both may be double bonds, one of them may be a single bond, both may be single bonds
Furthermore, we surprisingly discovered that in processes for the biotechnological modification of HMG-CoA reduc-tase inhibitors the formation of amine salts of HMG-CoA reductase inhibitors in the medium which derives from the fermentation liquor provides, in comparison with the mere metal salts as described in publicly accessible literature, an efficient means for the isolation and/or purification of 11MG-CoA reductase inhibitors by means of simple crystallization. The amines which are described in the present specification and which readily form salts with HMG-CoA reductase inhibitors are thus particularly suitable as auxiliary materials or processing aids for the isolation and/or purification of HMG-CoA reductase inhibitors. Furthermore, they can be excellently used as starting materials or intermediates of semisynthetic preparation or biotechnological modification of HMG-CoA rcductase inhibitors and, furthermore, for the conversion into pharmaceutically acceptable salts or into the lactone form of the respective HMG-CoA reductase inhibi-tors. Accordingly, the novel amine salts of HMG-CoA reduciase inhibitors of the present invention are also highly valuable as such.

The present invention provides:
a) the novel salts of HMG-CoA reductase inhibitors with organic amines, wherein those specific salts are excluded which are disclosed in the prior art, but in different contexts as mentioned above,
h) a process for the preparation of salts of HMG-CoA reductase inhibitors with amines,
e) a use of salts of l-IMG-CoA reductase inhibitors with amines as processing aids or starting substances or intermediate substances in various processes,
d) a process for the preparation of the pure HMG-CoA reductase inhibitors from/via amine salts thereof,
e) a process for the semisynthetic preparation of 1-1MG-CoA reductase inhibitors, wherein the amine salts of HMG-CoA reductase inhibitors are used as the starting substances,
t) a process for the biotechnological modification of HMG-CoA reductase inhibitors, wherein one of the

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components of the medium is the amine salt of HMG-
CoA reductase inhibitors,
g) a process for the conversion of the amine salts of HMG-CoA reductase inhibitors into the pharmaceuti-
5 cally acceptable salts of HMG-CoA reductase
inhibitors, and
h) a process for the conversion of the amine salts of HMG-CoA reductase inhibitors into HMG-CoA reduc-
tase inhibitors in the lactone form.
10 The amine which is used according to the present inven-tion for the formation of the salts with a HMG-CoA reduc-tase inhibitor is selected from the group consisting of organic amines of the following formulae I and It:

15

a)

R1 X R3 I /

N(CH2)--dH(CH2)1N

20 R2

wherein:

a!) R1, R2, R3 and R4 independently denote:

a hydrogen atom 25 a straight or a branched alkyl group having 1 to 8
carbon atoms, or
a cycloalkyl group having 3 to 8 carbon atoms, or
an arylalkyl group wherein the alkyl group is methyl or

ethyl and the aryl group is phenyl, which is option- 30 ally substituted by an N-alkyl or N,N-dialkyl group
wherein the alkyl group is alkyl having 1t4 carbon
atoms, or

an arylalkyl group which is optionally substituted by

one or more substituents, 35 a hydroxyalkyt group having 2 to 4 carbon atoms, or
an aminoalkyl group having 2 to 4 carbon atoms, which
are optionally substituted by an N-alkyl or N,N-
dialkyl group wherein the alkyl group is alkyl having

1 to 4 carbon atoms; 40 X denotes a hydrogen atom, a hydroxyl group, a halogen
or a methyl group;
in and n independently denote an integer from 0 to 5 or
a2) NR1R2 or NR1R4 denote a heterocyclic ring having 3
45 to 7 methylene groups, one of these groups being
optionally substituted by an oxygen or a sulphur atom
or an iminc group; X, in and n are as defined above;

6) 50 R1
NR’

R/

55

wherein:

hi) R’1, R’2, and R’3 are the same or different and denote hydrogen, alkyl, alkenyl, amino- or hydroxy- or alkoxy-substituted alkyl or alkenyl, or substituted
60 amino-substituted alkyl or alkenyl, provided that R’1,
R2, and R3 are not hydrogen at the same time; or
b2) R’1 and R, and optionally R’31 together with the nitrogen atom form an optionally substituted heterocy-
clic ring system including the nitrogen atom as a ring
65 member, and optionally including an additional hetero
atom, and if W3 is not part of the ring system it is independently selected from hydrogen, alkyl, alkenyl,

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amino- or hydroxy- or alkoxy-substituted alkyl, or substituted amino-substitu ted alkyl; or
b3) R’1 is an optionally substituted cyclic group of general formula III.

R(CHR4),,--- III

wherein m is zero or an integer from I to 5, R’ is optionally substituted aliphatic hydrocarbon cyclic sys-tem having 3 to 8 carbon atoms in the ring, R’4 is hydrogen, or alkyl, amino- or hydroxy- or alkoxy-substituted alkyl, or substituted amino -substituted alkyl, or a group of the same general formula as R1 as defined herein above; R’2 and R’3 are the same as R’1 or hydrogen, alkyl, alkenyl, amino- or hydroxy- or alkoxy-substituted alkyl, or substituted amino-substituted alkyl or alkenyl; or
M) R1 is an optionally substituted aryl group of general formula IV:

Iv

(CHR’5)

wherein R’5 is hydrogen or one or more substituents, and in is zero or an integer from 1 to 5; and R’2 and R’3 may be independently hydrogen, alkyl, amino- or hydroxy- or alkoxy-substituted alkyl, or substituted amino-substituted alkyl, or groups of the same general formula R.
Substitutions which are not explicitly specified are usual "inert" substituents, such as halogens, a hydroxyl group, alkyl having 1 to 4 carbon atoms, alkoxyl having t to 4 carbon atoms, acyloxyl having 1 to 4 carbon atoms and esterified carboxyl having 1 to 4 carbon atoms. Advantageous examples of amines which form the salt with IIMG-CoA reductase inhibitors are: (–)-1,2-dimethylpropylamine, 3-(2-aminoethylamino)- propylamin n-butylamine, secondary butylamine, tertiary butylamine (TBA), dibutylamine, tertiary amylamine, cyclopentylarine, cyclohexylamine, cycloheptylamine, dieyclohcxylaminc (DCHA), N-methylcyclohexylamine, N,N’-diisopropylethylenediamine (DIPEDA), N,N-diethylenediamine, N-methyl-1,3 -prop anediamine, N-methylethylenediamine, N,N,N’,N’-tetramethyl-1,2-diaminoethane, N,N,N’,N-tetramethyl-1,4-diaminobutane, N,N,N,N’-tetramethyl- 1,6-diaminohexane, 1,2-dipiperidinethane, dipiperidinemethane, 2 -amino-3, 3-dimethylbutane, N,N-dimethylcyclohexylamine, neopentylamine, adamantylamine, N,N-diethylcycohexylam me, N-isopropylcyclohcxylamine, N-methyl-cyclohexylamine, cyclobutylaniine and norhory-lamine. Preferably in terms of crystallization efficiency, combined with low toxicity and low costs, the amine is selected from the group consisting of n-butylamine, second-ary butylamine, TBA, dibutylamine,tertiary amylamine, cyclohexylamine, DCHA, N-methylcyclohexylamine and DIPEDA. The amine may particularly be selected from-the group consisting of TBA, DIPEDA, DCHA and N-methylcyclohexylamine.
The amines specified above are advantageous over the direct isolation via the salts with ammonia in terms of purification efficiency. Furthermore, amines having a larger organic group, and especially those having bulky groups, generally show a more readily crystallization and to a lower

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extent form salts with unwanted side products when com-pared with amines having small organic groups. Accordingly, amines having at least one hydrocarbon resi-due with secondary or tertiary carbon atoms, or with cyclic
S hydrocarbon structure (either aromatic or aliphatic), and
organic diamines are particularly suitable for the presenL,
in iii)fl.
Xny pe of HMG-CoA reductase inhibitors can be used
a ing to the present invention. Those HMG-CoA reduc-
10 tase inhibitors selected from the group consisting of f mevastatin, pravastatin, lovastatin, simvastatin, fiuvastatin / and atorvastatin have shown good results and are particu-
arly preferre
For isolating and purifying the desired HMG-CoA reduc-
15 tasc inhibitor, the amine salt is most effectively formed directly from the crude medium of the respective HMG-CoA reductase inhibitor, which crude medium is usually derived from a fermentation broth as the result of a biotechnological process or from a reaction mixture as the result of a
20 semisynthesis or the total synthesis and usually contains the
desired HMG-CoA reductase inhibitor together with unwanted side products and impurities. The crude medium may preferably contain the HMG-CoA reductase inhibitor in its acid from, and the formation of the amine salt may be
25 effected by simply adding the amine to the crude medium.
The crude medium may be an organic phase or a mixture of an organic or an aqueous phase where the impure IIMG-CoA reductase inhibitor is present in an organic solvent, such as ethyl acetate, ether or acetonitrile. Ethyl acetate is
30 preferred as the organic solvent. After the biotechnological
treatment, the crude medium in the organic phase is prefer-ably obtained from the fermentation broth by a process including the step of extracting the IIMG-CoA reductase inhibitor into the aforementioned organic solvent.
s The process for the preparation of the amine salts of l-IMG-CoA reductase inhibitors may include the following steps:
a) contacting the medium containing the HMG-CoA reductase inhibitor, which is preferably in the acid form
40 in an organic solvent, with at least one of the amines specified above,
b) optionally forming crystallization nuclei by known techniques,

45 c) filtering the crystals crystallized out,
d) washing the crystals with an organic solvent, and
e) drying the crystals.
The term "con includes the known techniques for
the preparation of the salts from substances with acid 50 properties and substances with alkaline properties. The crystallization is preferably carried out at a temperature between 0 and 300 C., more preferably between 4 and 22°
C.

Since the amines specified above effectively form salts with the HMG-CoA reductase inhibitors, they are also particularly suitable as auxiliary materials or processing aids in a process for preparing the HMG-CoA reductase inhibitor in a purified form. Previously isolated IIMG-CoA reductase inhibitors can be thus obtained in a higher purity. The so purified form is usually prepared by crystallization. Accordingly, the present invention provides a process for the isolation and/or purification of a l-IMG-CoA reductase inhibitor.

In further aspects of the present invention, the salt as
ss specified above is suitably used as the starting substance or
the intermediate substance in a process for preparing the HMG-CoA reductase inhibitor which is in a modified form,

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in a pharmaceutically active salt form or in the lactone form. Specifically, the modified form is obtained by chemical modification or biotechnological modification, which modi-fications are known to those skilled in the art. The pharma-ceutically active salt is preferably a metal salt, such as the sodium salt or the calcium salt.
In this connection, the term "a process for the semi-synthetic preparation of HMG-CoA reductase inhibitors" means the preparation of HMG-CoA reductase inhibitors using any of the known chemical modifications of the HMG-CoA reductase inhibitors. An example ofsuch process is the semisynthesis of simvastatin from lovastatin as the starting substance. Most preferably, the TBA salt of lovas-tatin is used as the starting substance.
Furthermore, the term "a process for the biotechnological modification of l-IMG-CoA reductase inhibitors" means the preparation of HMG-CoA reductase inhibitors using micro-organisms or enzymatic systems thereof for modifying IIMG-CoA reductase inhibitors. An example ofsuch process is the biotechnological conversion of mevastatin into pray-astatin. The amine salt is preferably the TBA salt. Furthermore, the term "a process for the conversion of the amine salts of HMG-CoA reductase inhibitors into the pharmaceutically acceptable salts of HMG-CoA reductase inhibitors" includes processes for the preparation of HMG-CoA reductase inhibitors by one of the known methods wherein the amine salts of HMG-CoA reductase inhibitors are used as the starting substance. Specific examples of converted salts are the sodium salts of pravastatin and fiuvastatin and the calcium salt of atorvastatin. Furthermore, the term "conversion of the amine salts of HMG-CoA reductase inhibitors into HMG-CoA reductase inhibitors in the lactone form" includes processes for the preparation of HMG-CoAreductase inhibitors in the lactone form by one of the known methods wherein the amine salts of HMG-CoA reductase inhibitors are used as the starting substance. Examples of HMG-CoA reductase inhibitors converted into the lactone form are lovastatin, mevastatin or sirnvastatin.

The present invention is illustrated but in no way limited by the following examples.

EXAMPLES

Example I

Preparation of Free Acid of Mevastatin and
Conversion Thereof into Salt Thereof with Tertiary Butylamine (IBA)

Mevastatin (200 g) was suspended in 30% volume! volume (v!v) aqueous acetonitrile solution (2500 ml), 3 equivalents of triethylamine were added and the mixture was heated to 800 C. and stirred for 30 minutes After the completed reaction, acetonitrile was evaporated, the remain-ing solution was acidified to pH 4 with phosphoric acid and extracted into ethyl acetate (2x10(X) ml). The pooled extracts were dried by the addition of 30 g of sodium sulphate, the desiccant was filtered off and the solution was concentrated

(950 ml). TBA (1.5 equivalents) was added to the isolution and crystallization was carried out for 30 minutes at 8° C. The crystals formed were filtered and washed with ethyl acetate (2x100 ml) and subsequently dried at 40° C. for 15 hours. The crystals obtained (the TBA salts of mevastatin 215 g) were white in color with a RPLC purity of 96.8%. The yield of the hydrolysis and crystallization was 91%.

Example 2

Preparation of the Sodium Salt of Mevastatin from
the TBA Salt of Mevastatin

The TBA salt of mevastatin (1 g), obtained by the process disclosed in example 1, was dissolved in 3 ml of ethanol

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(96% v/v) and sodium hydroxide (40 g/L of ethanol) was added. The resulting mixture was precipitated in the ethyl acetate (60 ml). After the crystallization (30 at 8° C. the crystals were filtered off, washed with ethyl acetate and
5 dried. The product: crystals of the sodium salt of mevastatin
(0.65 g) pate brown in color with a HPLC purity of 98%.

Example 3

Isolation of the TBA Salts of lovastatin from the

10 Fermentation Broth

A fermentation broth (160 L) obtained by the fermenta-tion with a microorganism Aspergillus terreus A1’CC 20544 and having a lovastatin content of 1 gIll, was transferred from is the fermenter into the tank (400 L) and pH was adjusted to 10 with the addition of 1 M aqueous sodium hydroxide 10 minutes of vigorous stirring the pH of the broth was decreased to 9 by adding 1 M sulphuric acid solution and the biomass was filtered off. The filtrate obtained was acidified
20 to a pH value of 6.5 with 1 M sulphuric acid solution and
160 L of ethyl acetate was added. The slurry was subse-quently stirred for 20 minutes. The aqueous and ethyl acetate phases were separated by extraction centrifuge and the ethyl acetate extract was concentrated in a rotavapor to the vol-
25 ume of 14 L. The concentration of lovastatin in the form of
free acid in concentrated ethyl acetate extract was 10.1 g/L. To the obtained lovastatin solution (IIPLC purity 72.7%) in the form of free acid in ethyl acetate (800 ml) 1.05 equiva-lents of TBA were added. After crystals were crystallized
30 out, they were filtered off, washed with ethyl acetate (2x50
ml) and dried in a vacuum oven at 35° C for 24 hours. The yield: 8.06 g of crystals of the TBA salt of lovastatin with a HPLC purity of 99.2%.

35 Example 4

Preparation of the Salt of Lovastatin with Tertiary Amylamine

Lovastatin (5 g) was treated according to the process for
40 hydrolysis disclosed in example I and sodium salt thereof
(4.8 g) was prepared and dissolved in 100 ml of water p11 was adjusted to 4 with phosphoric acid (10% aqueous solution) and the formed free acid of lovastatin was extracted from the water phase into ethyl acetate (2x1 00 ml).
45 The pooled ethyl acetate extracts were dried with sodium
sulphate, the solution was filtered off and concentrated to ca. 100 ml. To the solution, prepared in the above manner (ca. 100 ml), 1.05 equivalents of tertiary amylamine were added. After crystals were crystallized out, they were filtered off,
so washed with ethyl acetate (2x 10 ml) and dried in a vacuum
oven (35° C., 24 hours). The yield: 4.8 g of crystals of the tertiary amylamine salt with a UPLC purity of 98.6%.

Example S

cc . Preparation of Pravastatmn in the free Acid Form and Conversion into the ()-1,2-
Dimethylpropylamine Salt Thereof

Pravastatin (11 g, HPLC purity 97.2%) in the form of Na
60 salt was dissolved in water (100 ml) and p1-1 was adjusted to
4 with phosphoric acid (10% aqueous solution). The result-ing free acid was extracted from the water phase into ethyl acetate (2x100 ml). The pooled ethyl acetate extracts were dried with sodium sulphate, the solution was filtered off and
05 concentrated to a volume of ca. 100 ml.
To the concentrate (9 ml) thus obtained, 1.5 equivalents of a)-1,2-dimethyl-propylamine were added. After crystals

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were crystallized out, they were filtered off, washed with 20 ethyl acetate (2x10 ml) and dried in a vacuum oven at 35° C. The yield: crystals yellow in color with a HPLC purity of 98.28%.

Examples 6-13

The conversion of the free acid form of pravastatin into it ç,.,.,.-,i,,

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dissolved in 3 ml of water, instead of ethanolic solution of 0.43N NaOH, and subsequently an aqueous sodium carbon-ate solution (equivalent) was added. The obtained solution was diluted with 5 ml of ethanol and the resulting sodium
5 salt was precipitated with ethyl acetate. After 30 minutes at
8° C., crystals formed were filtered off and dried. The formed crystals of the sodium salt of pravastatin (0.65 g) were yellow in color.

with other amines. Pxnmnlo 17 The amines used and results are shown in the Table
below:

IIPLC
Ex. AMINE EFFECT purity

6 3-(2-aminocthylamino)- an oil is formcd*
propylaminc
7 N,N-diisopiopyl- pale yellow 99.3%
ethyleiiediamine crystals
8 N,N’-diethyl- yellow crystals 993%
ethyleriedianrine
9 N-methyl-1.3- an oil is formed*
propanediamine
10 N-methylethylenedianiine an oil is formed*
ti secondary-butylamine white crystals 989%
12 tertiary-butvlammne yellowish 97.4%
(TBA) crystals
13 tertiary-amylamine off-white 979%
crystals

from an oil formed, crystals are crystallised out overnight at 4 C

Example 14

Preparation of the Salt of Pravastatin with
Secondary Butylamine from the Crude Sodium Salt
of Pravastatin

According to the process described in example 5, prav-astatin in the free acid form was prepared from the sodium salt of pravastatin (HPLC purity 83.6%). Further the salt of pravastatin with secondary butylamine was prepared by the process described in example 5. White crystals with a HPLC purity of 97.3% were obtained.

Example 15

Preparation of the Sodium Salt of Pravastatin from
the TBA Butylamine of Pravastatin (1)

8 9 g of the TBA salt of pravastatin as obtained in example 12 were dissolved in 22 ml of ethanol (96%) and subse-quently precipitated in 450 ml of ethyl acetate. Crystalliza-tion was carried out at 8° C. for 60 minutes, the crystals formed were filtered off, washed with two 50 ml portions of ethyl acetate and dried at 40° C. for 5 hours. I g of the recrystallized TBAsalt of pravastatin, obtained in the above - described manner, was dissolved in 5 ml of ethanolic solu-tion of 0.43N NaOH and precipitated in 60 ml of ethanol. After 30 minutes at 8° C., crystals formed were filtered, off and dried. The formed crystals of the sodium salt of prav-astatin (0.75 g) were dark yellow in color.

Example 16

Preparation of the Sodium Salt of Pravastatin from
the TBA Salt of Pravastatin (2)

The process described in example 15 was repeated wherein 1 g of the recrystallized TBA salt of pravastatin was

10

Preparation of Pravastatin from the TEA Salt of
Mevastatin

Preparation of Inoculum For Production
The colonies of microorganism Amycolatopsis orientalis
15 ATCC 19795 were transferred to a sterile potter and homog-
enized. The resulting colonies were transferred to agar slopes and incubated in the thermostat at 26° to 30° C. for
7 to 14 days. During that time surfaces of agar slopes were overgrown by cultures of homogeneous, folded, smooth, 20 white to pale greyish-blue mycelium. Further, 10 ml of sterile water was poured onto the agar slopes, the culture was scraped off with the pipette and the contents transferred into the potter. A portion (0.5 to 1 ml) of the resulting culture was then inoculated into the vegetative medium.
25

Raw material Amount

Dextrin 10 g
30 Consumer’s glucose 5
Casamino acid 3
Yeast extract 4

Agar 15 g
Sterile water up to 1000 ml

35

Vegeative Phase of Fermentation
The inoculum grown on the slope at 260 to 30° C. for 10 days and prepared according to the above-described method was inoculated in a 500-ml Erlenmeyer flask containing 50
40 ml of the vegetative medium. After 24 hours of shaking at
220 rpm at 28° C., the culture was transferred onto the fermentation medium.

45 Raw material Amount

Corn starch for 20
fermentation
Soybean flour fot 14
fermentation
50 Glucose 10
Yeast extract 5 g
Nat-I.PO x 2H0 33

Tap water to 1000 ml

55 Conversion of the TBA Salts of Mcvastatin into Pravastatin
The contents of fifteen Erlenmeyer flasks with the culture, prepared according to the above -described method, were used to inoculate the fermenter (50 L) with 30 L of fermen-tation medium. After 20-hour fermentation, the solution of
60 the TEA salt of mevastatin and glucose (1200 g of glucose
and 70 g of TEA salt of mevastatin (assay of mevastatin: 80%) dissolved in 5 Lof water) was continually added to the medium at the flow rate 2 ml/min. During the fermentation 70% oxygen saturation of the medium was maintained by 65 stirring with the frequency between 300 and 600 rpm. Analyses of the concentration of pravastatin in the fermen-tation broth showed the total final concentration of prevas-

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tatin in the fermentation broth to he 690 g/kg of broth after 76 hours of fermentation at temperature between 24° and 30° C., indicating a 40% conversion of mevastatin into pravastain.
Fermentation Medium:

Raw material Amount

Corn starch for 20 g
fermentation

Soybean flour for 5 g
fermentation

Glucose 10 g
Yeast extract 5 g
Antifoam agent 10 g

All raw materials were dissolved in tap water, the pH was then adjusted to 7.4.

Example 18

Preparation of TEA Salt of Simvastatin

Simvastatin (1.95 g) was suspended in 50 ml of 30% (v/v) acetonitrile, triethylamine (1 ml) was added and the solution was heated for 20 minutes at 70° C. After completion of reaction acctonitrile was evaporated from the solution, the remaining solution was acidified to pH 4 with phosphoric acid. Simvastatin in the acid form was extracted into ethyl acetate (2x50 ml) and the pooled extracts were dried with 2 g of sodium sulphate. The desiccant was filtered off and the ethyl acetate solution was concentrated to 20 ml. To the solution 1.05 equivalents of TEA were added and crystal-lization was carried out for 1 hour at 8° C. The product was filtered off and dried at 40° C. for 1 hour. The -yield: 2 g of the TEA salt of simvastatin.

Example 19

Conversion of the TBA Salt of Sinvastatin into Simvastatin Lactone

The TEA salt of simvastatin (1.6 g), obtained by the process disclosed in example 18, was dissolved in water (36 ml), the solution was then acidified to pH 3.7 with an aqueous phosphoric acid solution and simvastatin in the acid form was extracted into ethyl acetate (2x50 ml). The pooled extracts were dried with sodium sulphate (2 g) and the desiccant was then filtered off. The ethyl acetate solution was concentrated to 20 ml.

To the solution trifluoroacetic acid (0.5 nil) was added and the reaction mixture was heated for 25 minutes at 50° C. After completion of the reaction, the ethyl acetate solution was extracted with 50%(w/w) aqueous solution of ammo-nium hydrogen carbonate. The organic phase was dried with sodium sulphate (2 g), the desiccant was filtered off and the ethyl acetate solution was concentrated to 4 ml. Crystalli-zation was carried out for 1 hour at 8° C. The product was then filtered off and dried at 40° C. for 1 hour. The yield: 0.9 g of simvastatin in the acid form.

Example 20

Preparation of Free Acid of Simvastatin

Simvastatin (20 g) was dissolved in the mixture of water (80 in]) and SM KOH (18 ml). The solution was stirred in nitrogen atmosphere for two hours at room temperature. After that 120 ml of ethyl acetate was added and pH was adjusted to 2-3 with 5% aqueous solution of HCI. Ethyl

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acetate phase was washed with mixture of water (100 ml), 5% aqueous solution of HC1 and 5% aqueous solution of NaCl (50 ml). The obtained ethyl acetate phase was then dried for three hours with addition of 20 g MgSO4 anhydrite
s and filtrated.

Preparation of Amine Salt

After that 18 ml of N-methylcyclohexylamine was added

10 into the ethyl acetate phase. After two days at temperature
between 0 and 5° C. crystals of simvastatin N-methylcyclo-hexylamine salt were formed. Obtained crystals were fil-tered off and washed with 20 ml of ethyl acetate, 40 ml ethyl acetate/n-heptane (1:1) and 40 ml of pentane. The yield: 20.5
g of N-methylcyclohexylamine salt of simvastatin. The yield calculated to the starting simvastatin was 79%.
The same results were obtained also with cyclohexy-laminc (by the use of the same method).

20 Example 21

Preparation of Pravastatin in Purified Form

Pravastatin (30 g, HP[.0 purity 90.2%) in the form of Na salt was dissolved in water (100, ml) and p1l was adjusted
25 to 3 with HCl (10% aqueous solution). The resulting free
acid was extracted from the water phase into ethyl acetate (3x200 ml). The pooled ethyl acetate extracts were dried with sodium sulphate, the solution was filtered off and 7.604
g of N-methylcyclo-hexylamine was added (drop by drop at
30 intensive stirring). After crystals were crystallized out, they
were filtered off and recrystallized from the mixture of ethyl acetate/methanol. The yield: 21 g of crystals of pravastatin N-methylcyclohexylamine salt with a HPLC purity of 99.28%.
35

Example 22

Preparation of Free Acid of Atqrvastatin

Calcium salt of atorvastatin (3 g) was suspended in tOO ml 40 water. The pH was adjusted with phosphoric acid to 4 and
after that free acid of atorvastatin was extracted with ethyl acetate (3x100 ml). Combined ethyl acetate extract was dried and 2.7 g of oil containing atorvastatin in the free acid

form was obtained. 45
Preparation of Amine Salt

1 g of atorvastatin in the free acid form was dissolved in acetonitrile (100 ml) and 1.1 molar equivalents of TI3A was
50 added. The obtained mixture was concentrated to 30 ml and
after four hours at 8° C. the TEA salt of atorvastatin crystallized. White precipitate was filtered off and dried in a rotary evaporator. Yield: 1 g of TEA salt of 5 atorvastatin.

55 Example 23
1 g of atorvastatin in the free acid formjwas jiolve methanol (20 ml) and 1.1 molar equivalents of dicyclohexy-lamine (DCHA) in 50 ml of n-hexane was added. After four hours at 8° C. the DCHA salt of atorvastatin crystallized.. oo White precipitate was filtered off and dried in a rotary evaporator. Yield: 1.1 g of DCHA salt of atorvastatin.
What is claimed is:
1. A salt of an HMG-CoA reductase inhibitor with an amine, characterized in that said salt is an intermediate or a
65 starting substance in a process for preparing the HMG-CoA
reductase inhibitors and that said amine is selected from the group consisting of amines of the following formulae I and

II;

13

R1 X R3

I / N(CH,)CFt(CH--N
R2

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wherein:

al) R1, R21 R. and R4 independently denote:
a hydrogen atom;
a straight or a branched alkyl group having I to 8 carbon atoms;
a cycloalkyl group having 3 to 8 carbon atoms;
an arylalkyl group wherein the alkyl group is methyl or ethyl and the aryl group is phenyl, which is option-ally substituted by an N-alkyl or N,N-dialkyl group wherein the alkyl group is alkyl having 1 to 4 carbon atoms;

an arylalkyl group which is optionally substituted by one or more substituents selected from the group consisting of a halogen, a hydroxyl group, an alkyl having 1 to 4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having 1 to 4 carbon atoms or an esterified carboxyl having 1 to 4 carbon atoms;

a hydroxyalkyl group having 2 to 4 carbon atoms; or an aminoalkyl group having 2 to 4 carbon atoms, which are optionally substituted by an N-alkyl or N,N-dialkyl group wherein the alkyl group is alkyl having
1 to 4 carbon atoms;
X denotes a hydrogen atom, a hydroxyl group, a halogen or a methyl group;
in and n independently denote an integer from 0 to 5; or a2) NR,R2 or NR3R4 denote a heterocyclic ring having 3 to 7 methylene groups, one of these groups being optionally substituted by an oxygen or a sulfur atom or
an imine group; and X, in and n are the same as defined above;

b)

R’1

NR’

R/

wherein:

bi) R1, R’2, and R’3 are the same or different and denote hydrogen, alkyl, alkenyl, amine or hydroxy- or alkoxy-substituted alkyl or alkenyl, or substituted amino-alkyl
or alkenyl, wherein the amino group is substituted by one or more substituents selected from the group con-sisting of a halogen, a hydroxyl group, an alkyl having I to 4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having 1 to 4 carbon atoms or an esterified carboxyl having I to 4 carbon atoms, pro-vided that R1, R’- and R’3 are not hydrogen at the same time; or
b2) R’1 and R’2, and optionally R’3, together with the nitrogen atom form a heterocyclic ring system includ-ing the nitrogen atom as a ring member, and optionally including an additional hetero atom, and if R’3 is not part of the ring system it is independently selected from hydrogen, alky, alkenyl, amino- or hydroxy or alkoxy-

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substituted alky, or substituted amino-alkyl wherein the amino group is substituted by one or more substituents selected from the group consisting of a halogen, a hydroxyl group, an alkyl having t to 4 carbon atoms, an
5 alkoxyl having 1 to 4 carbon atoms, an acyloxyl having
1 to 4 carbon atoms or an esterified carboxyl having 1
to 4 carbon atoms; or

b3) R’1 is a group of general formula 111,

10 R(CHR4),,---. ttt

wherein in is zero or an integer from 1 to 5, R is an aliphatic hydrocarbon cyclic system having 3 to 8 carbon atoms in the ring, optionally substituted by one
15 or more substituents selected from the group consisting
of a halogen, a hydroxyl group, an alkyl having 1 to 4 carbon atoms, an alkoxyl having I to 4 carbon atoms,
an acyloxyl having 1 to 4 carbon atoms or an esterified carboxyl having 1 to 4 carbon atoms, R’4 is hydrogen,
20 alkyl, amino- or hydroxy- or alkoxy-substituted alkyl,
substituted amino-alkyl or alkenyl, wherein the amino
group is substituted by one or more substituents selected from the group consisting of a halogen, a hydroxyl group, an alkyl having Ito 4 carbon atoms, an
25 alkoxyl having 1 to 4 carbon atoms, an acyloxyl having
I to 4 carbon atoms or an esterified carboxyl having 1
to 4 carbon atoms, or a group of the same general formula as R1 as defined herein above; R’-, and R’3 are
the same as or hydrogen, alkyl, alkenyl, amino- or
30 hydroxy- or alkoxy-substituted alkyl, or substituted
amino-alkyl wherein the amino group is substituted by
one or more substituents selected from the group con-
sisting of a halogen, a hydroxyl group, an alkyl having
1 to 4 carbon atoms, an alkoxyl having 1 to 4 carbon
35 atoms, an acyloxyl having I to 4 carbon atoms or an
esterified carboxyl having 1 to 4 carbon atoms, or alkenyl; or
b4) R’1 is an optionally substituted aryl group of general

formula IV: 40
tv

(CFIR5--

45

wherein R5 is hydrogen or one or more substituents selected from the group consisting of a halogen, a hydroxyl group, an alkyl having I to 4 carbon atoms, an
so alkoxyl having 1t4 carbon atoms, an acyloxyl having
1 to 4 carbon atoms or an esterified carboxyl having 1
to 4 carbon atoms, and on is zero or an integer from 1
to 5; and R’2 and R3 may be independently hydrogen,
alkyl, amino- or hydroxy- or alkoxy-substituted alkyl,
55 or substituted amino-alkyl wherein the amino group is
substituted by one or more substituents selected from
the group consisting of a halogen, a hydroxyl group, an
alkyl having 1 to 4 carbon atoms, an alkoxyl having I
to 4 carbon atoms, an acyloxyl having 1 to 4 carbon
u atoms or an esterified carboxyl having 1 to 4 carbon
atoms, or groups of the same general formula R’1;
provided that
when the HMG-CoA reductase inhibitor is lovastatin,
the amine is not tetramethylamine or ethylencdianine,
when the HMG-CoA reductase inhibitor is tetrahydro-M4 or tetrahydro-IsoM-4, the amine is not

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octylamine, 2-ethyihexylamine, benzylarnine, cr-methyl-benzylamine, phenethyline, dibenzylamine, N-methylbenzylamine, N,N-dimethylbenzylanine, N,N-diethylbenzylamine, N-ethyl-N- met hylbenzylamine, tribenzylamine, cyciopentylamine, cyclohexylamine, cycloheptylamine, N-niethylcyclopentylamine, N-ethylcyclohexylamine, N-ethylcycloheptylamine, dicyclohexylamine, N,N-dimethylcyclopentylamine,
N,N-dimethylcyclohexylamine, N,N-
diethylcyclobeptylamine, pyrrolidine,
N-methylpyrrolidine, piperidine,
N-methylpiperidine or morpholine; and
when the HMG-CoA reductase inhibitor is the octahy-dronaphthalene oxime derivative of ML-236A, ML-23613, MB-530A or MB-530B, the amine is not t-octylamine, dibenzylamine, dicyclohexylamine or morpholine.
2. The salt of a FIMG-CoA reductase inhibitor with an amine according to claim 1, wherein the amine is selected from the group consisting of (–)-1,2-dimcthylpropylaminc, 3-(2-aminoethylamino)-propylamine, n-butylamine, sec-ondary butylamine, tertiary butylamine, dibutylamine, ter-tiary amylamine, cyclopentylamine, cyclohexylamine, c ye I oh e p1 y lam iDe, dicyclohexylamine,
N-methylcyclohexylarnine, N,N’-
diisopropylethylenediamine, N,N’-diethylenediamine, N-methyl-1,3-propanediamine, N-methylethylenediamine, N,N,N’,N’-tetramethyl-1,2-diaminoethane, N,N,N,N’- tetramethyl-1,4-diarninobutane, N,N,N’,N-tetramethyl-1,6-d jam inohexane, 1,2-dipiperidineth ane, dipiperidinemethane, 2-amino-3,3-dimethylbutanc, N,N-dimethylcyclohexylamine, neopentylamine, adamantylamine, N,N-diethylcyclohexylamine, N-isopropylcyclohexylamine, N-methylcyclohexylamine, cyclobutylamine and norborylamine.
3. The salt of a HMG-00A reductase inhibitor with an amine according to claim 1, wherein the amine is selected from the group consisting of n-butylamine, secondary butylamine, tertiary butylamine, dibutylamine, tertiary amylamine, cyclohexylamine, dicyclohexylamine,
N - methyl eye to hex y lam inc and N, N -
diisopropylethylenediamine.
4. The salts of a HMG-CoA reductase inhibitor with an amine according to claim 1, wherein the IIMG-CoA reduc-tase inhibitor is selected from the group consisting of mevastatin, pravastatin, lovast atm, simvastatin, fluvastatin and atorvastatin.
5. A process for preparation of the salt of an HMG-CoA rcductasc inhibitor with an amine, characterized in that the amine is added to a crude medium of the HMG-CoA reductase inhibitor and that said amine is selected from the

group consisting of amines of the following formulae I and
II:

R1 X R3 I /
(CH2)-- CH- (C112)jrN

R2 R4

wherein:

al) R1, R,, R. and R4 independently denote:
a hydrogen atom;
a straight or a branched alkyl group having 1 to 8 carbon atoms;

16 a cycloaikyl group having 3 to 8 carbon atoms;

an arylalkyl group wherein the alkyl group is methyl or ethyl or the aryl group is phenyl, which is optionally substituted by an N-alkyl or N,N-
dialkyl group wherein the alkyl group is an alkyl
having 1 to 4 carbon atoms;
an arylalkyl group which is optionally substituted by
one or more substituents selected from the group
consisting of a halogen, a hydroxyl group, an alkyl
10 having 1 to 4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having 1 to 4
carbon atoms or an esterified carboxyl having 1 to
4 carbon atoms;
a hydroxyalkyl group having 2 to 4 carbon atoms; or
15 an aminoalkyl group having 3 to 4 carbon atoms,
which are optionally substituted by an N-alkyl or N,N-dialkyl group wherein the alkyl group is an
alkyl having 1 to 4 carbon atoms;
X denotes a hydrogen atom, a hydroxyl group, a
20 halogen or a methyl group;
m and n independently denote an integer from 0 to 5;
or

a2) NR1R1 or NR3R4 denote a heterocyclic ring having
3 to 7 methylene groups, one of these groups being
1-5 optionally substituted by an oxygen or a sulfur atom
or an amine group; and X, m and n are the same as
defined above;

5)

30 R1

R/

35

wherein:

bI) R’1, R’2, and R’3 are the same or different and denote hydrogen, alkyl, alkenyl, amino- or hydroxy- or alkoxy-substituted alkyl or alkenyl, or substituted
40 amino-alkyl or alkenyl, wherein the amino group is
substituted by one or more substituents selected from
the group consisting of a halogen, a hydroxyl group,
an alkyl having 1 to 4 carbon atoms, an alkoxyl
having I to 4 carbon atoms, an acyloxyl having 1 to
45 4 carbon atoms or an esterified carboxyl having I to
4 carbon atoms, provided that R,, R., and R’3 are
not hydrogen at the same time; or
b2) R’ and R’,, and optionally R, together with the nitrogen atom form a heterocyclic ring system
50 including the nitrogen atom as a ring member, and
optionally including an additional hetero atom, and if
R3 is not part of the ring system it is independently
selected from hydrogen, alkyl, alkenyl, amino- or hydroxy- or alkoxy-substituted alkyl, or substituted
55 amino-alkyl wherein the amino group is substituted
by one or more substituents selected from the group consisting of a halogen, a hydroxyl group, an alkyl
having I to 4 carbon atoms, an alkoxyl having I to
4 carbon atoms, an acyloxyl having 1 to 4 carbon
60 atoms or an estcrified carboxyl having [to 4 carbon
atoms; or

b3) R1 is a group of general formula III,

R-(CHR’4),,,- 111

wherein m is zero or an integer from 1 to 5, R is an
aliphatic hydrocarbon cyclic system having 3 to 8
carbon atoms in the ring optionally substituted by

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17 one or more substituents selected from the group

consisting of a halogen, a hydroxyl group, an alkyl having 1 to 4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having 1 to 4 carbon atoms or an esterified carboxyl having I to 4 carbon atoms, R’4 is hydrogen, alkyl, amino- or hydroxy- or alkoxy-substituted alkyl, substituted amino-alkyl wherein the amino group is substituted by one or more substituents selected from the group consisting of a halogen, a hydroxyl group, an alkyl having I to 4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having 1 to 4 carbon atoms or an esterified carboxyl having 1 to 4 carbon atoms, or a group of the same general formula as R1 as defined herein above; R’2 and R3 are the same as R’1 or hydrogen, alkyl, alkenyl, amino- or hydroxy- or alkoxy-substituted alkyl, or substituted amino-alkyl or alkenyl, wherein the amino group is substituted by one or more substituents selected from the group consisting of a halogen, a hydroxyl group, an alkyl having 1 to 4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having 1 to 4 carbon atoms or an esterified carboxyl having 1 to 4 carbon atoms; or

b4) R’1 is an optionally substituted aryl group of general formula IV:

IV
R5’1

(CFiR5

wherein R5 is hydrogen or one or more substituents, selected from the group consisting of a halogen, a hydroxyl group, an alkyl having 1t4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having I to 4 carbon atoms or an esteritied carboxyl having 1 to 4 carbon atoms, and in is zero or an integer from 1 to 5; and R’2 and R3 may be inde-pendently hydrogen, alkyl, amino- or hydroxy- or alkoxy-substituted alkyl, or substituted amino-alkyl wherein the amino group is substituted by one or more substituents selected from the group consisting
of a halogen, a hydroxyl group, an alkyl having 1 to
4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having I to 4 carbon atoms or an esterified carboxyl having 1 to 4 carbon atoms, or groups of the same general formula R’r
6. The process according to claim 5, wherein the amine is selected from the group consisting of (–)-1,2-dimethylpropylaniine, 3-(2-aminoethylamino)- propylamine, n-butylamine, secondary butylamine, tertiary butylamine, dihutylamine, tertiary amytamine, cyclopentylamine, cyclohexylamine, cycloheptylamine, dicyclohexylamine, N-methylcyclohexylamine, N,N-diisopropylethylenediamine, N,N-diethylcnediamine, N-methyl- 1,3-propanediamine, N-methylethylenediamine, N,N,N,N-tetramethyl-1,2-diaminoethane, N,N,N’,N-tetramethyl-1,4-diaminobutane, N,N,N’,N’-tetramethyl-116-di am in oh cx an e, 1,2 - dip i per i dine than e, dipiperidinemethane, 2-amino-3,3-dimethylbutane, N,N-dimethylcyclohexylamine, neopentylamine, adamantylamine, N,N-diethylcyclohexylamine, N-isopropylcyclohexylamine, N-methylcyclohexylamine, cyelohutylaniine and norhorylamine.
7. The process according to claim 5, wherein the amine is selected from the group consisting of n-butylamine, second-

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ary butylamine, tertiary butylamine, dihutylamine, tertiary amylamine, cyclohexyla mine, dicyclohexyla mine, N-methylcyelohexylamine and N,N-diisopropylethylenediamine.
5 8. The process according to claim 5, wherein the HMG-CoA reductase inhibitor is selected from the group consist-ing of mevastatin, pravastatin, lovastatin, simvastatin, lluv-astatin and atorvastatin.

9. The process according to claim 5, wherein said crude
to medium is derived from a fermentation broth containing the
crude HMG-CoA reductase inhibitor.
10. The process according to claim 5, wherein said crude medium has been obtained from the fermentation broth by a process including a step of extracting the crude HMG-CoA
15 reductase inhibitor into an organic solvent.
11. The process according to claim 5, wherein said crude medium is derived from a reaction mixture containing the crude HMG-CoA reductase inhibitor.
12. The process according to claim 11, wherein said
20 reaction mixture has been obtained by semi or total synthesis
of the HMG-CoA reductase inhibitor.
13. The process according to claim 5, wherein said crude medium is present in an organic solvent which is selected from the group consisting of ethyl acetate, ether and aceto-
25 nitrile.

14. The process according to claim 5, wherein th c IIMG-CoA reductase inhibitor in said crude medium is in the acid form.
15. The process according to claim 5 comprising the
30 following steps:
a) contacting the medium containing the l-IMG-CoA reductase inhibitor with the amine,
h) optionally: conventionally forming crystallization

nuclei, 35 c) filtering the crystals crystallized out,
d) washing the crystals with an organic solvent, and
e) drying the crystals.
16. The process according to claim 15, wherein the

40 crystallization is carried out at temperature between 0 and
30° C.

17. The process according to claim 16, wherein the crystallization is carried out at temperature between 4 and 22° C.

45 18. A process for preparing a desired HMG-C’oA reduc-tase inhibitor comprising the steps:
1) providing an amine salt of an IIMG-CoA reductase inhibitor as a processing aid, starting substance, or an intermediate substance wherein the starting substance
50 or intermediate substance is:
i) in a purified form;
ii) in a modified form;
iii) in a pharmaceutically active salt form; or
iv) in a laclone form,
characterized in that said amine salt is formed from an amine selected from the group consisting of amines of
the following formulae I and II:

60

R1 X

I / N(CH2) CH(CII,)1N
R1

65

wherein:

al) R, R., R3, and R,1 independently denote:

b)

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19 a hydrogen atom;

a straight or branched alkyl group having 1 to 8 carbon atoms;

a cycloalkyl group having 3 to 8 carbon atoms;
an arylalkyl group wherein the alkyl group is methyl or ethyl or the aryl group is phenyl, which is optionally substituted by an N-alkyl or N,N-dialkyl group wherein the alkyl group is an alkyl having 1 to 4 carbon atoms;
an arylalkyl group which is optionally substituted by
one or more

substituents selected from the group consisting of a halogen, a hydroxyl group, an alkyl having 1 to 4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having 1 to 4 carbon atoms or an esterified carboxyl having 1 to 4 carbon atoms;
a hydroxyalkyl group having 2 to 4 carbon atoms; or an aminoalkyl group having 3 to 4 carbon atoms, which are optionally substituted by an N-alkyl or N,N-dialkyl group wherein the alkyl group is an alkyl having 1 to 4 carbon atoms;
X denotes a hydrogen atom, a hydroxyl group, a halogen or a methyl group;
m and It independently denote an integer from 0 to 5; or a2) NR1R2 or NR3R4 denote a heterocyclic ring having 3 to 7 methylene groups, one of these groups being optionally substituted by an oxygen or a sulfur atom or an amine group; and X, m and n are the same as defined above;

R1

NR’3

R(

wherein:
bi) R’1, R’2, and R3 are the same or different and denote hydrogen, alkyl, alkenyl, amino- or hydroxy- or alkoxy-substituted alkyl or alkenyl, or alkenyl, or substituted amino-alkyl or alkenyl, wherein the amino group is substituted by one or more substitu-ents selected from the group consisting of a halogen, a hydroxyl group, an alkyl having 1 to 4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having 1 to 4 carbon atoms or an esterified carboxyl having 1 to 4 carbon atoms, provided that R’1, W21 and R’3 are not hydrogen at the same time;
or

b2) R1 and R., and optionally R’, together with the nitrogen atom form a heterocyclic ring system including the nitrogen atom as a ring member, and optionally including an additional hetero atom, and if R’3 is not part of the ring system it is independently selected from hydrogen, alkyl, alkenyl, amino or hydroxy- or alkoxy-substituted alkyl, or substituted amino-alkyl wherein the amino group is substituted by one or more substituents selected from the group consisting of a halogen, a hydroxyl group, an alkyl having 1 to 4 carbon atoms, an alkoxyl having 1 to 4 carbon atoms, an acyloxyl having 1 to 4 carbon atoms or an esterified carboxyl having 1 to 4 carbon atoms; or

b3) R1 is a group of general formula III,

20

wherein m is zero or an integer from 1 to 5, R’ is an aliphatic hydrocarbon cyclic system having 3 to 8 carbon atoms in the ring, optionally substituted by one or more substituents selected from the group consisting of a halogen, a hydroxyl group, an alkyl
having 1 to 4 carbon atoms, an alkoxyl having I to
4 carbon atoms, an acyloxyl having 1 to 4 carbon
atoms or an esterified carboxyl having 1 to 4 carbon
atoms, R’4 is hydrogen, alkyl, amino- or hydroxy- or

10 alkoxy-substituted alky, substituted amino-alkyl
wherein the amino group is substituted by one or
more substituents selected from the group consisting
of a halogen, a hydroxyl group, an alkyl having ito
4 carbon atoms, an alkoxyl having 1 to 4 carbon

atoms, an acyloxyl having 1 to 4 carbon atoms or an 15 esterified carboxyl having I to 4 carbon atoms, or a
group of the same general formula as R1 as defined
herein above;
R’ and W3 are the same as or hydrogen, alkyl,
alkenyl, amino- or hydroxy- or alkoxy-substituted
20 alkyl, or substituted amino-alkyl or alkenyl, wherein the amino group is substituted by one or
more substituents selected from the group consist-
ing of a halogen, a hydroxyl group, an alkyl
having I to 4 carbon atoms, an alkoxyl having I
25 to 4 carbon atoms, an acyloxyl having I to 4 carbon atoms or an esterified carboxyl having ito
4 carbon atoms; or
h4) R’1 is an optionally substituted aryl group of general formula IV:

30 Iv

(CHR,3-

35

wherein R’, is hydrogen or one or more substituents,
selected from the group consisting of a halogen, a hydroxyl group, an alkyl having Ito 4 carbon atoms,
an alkoxyl having 1 to 4 carbon atoms, an acyloxyl
40 having Ito 4 carbon atoms or an esterified carboxyl
having 1 to 4 carbon atoms, and m is zero or an
integer from 1 to 5; and R, and R3 may be inde-pendently hydrogen, alkyl, amino- or hydroxy- or ailcoxy-substituted alkyl, or substituted amino-alkyl
45 wherein the amino group is substituted by one or
more substituents selected from the group consisting
of a halogen, a hydroxyl group, an alkyl having ito
4 carbon atoms, an alkoxyl having 1 to 4 carbon
atoms, an acyloxyl having I to 4 carbon atoms or an
so esterified carboxyl having 1 to 4 carbon atoms, or
groups of the same general formula R’1.
19. The process according to claim 18, wherein the amine
is selected from the group consisting of (–)-1,2-dimethylpropylamine, 3-(2-aminoethylamino)-
55 propylamine, n-butylamine, secondary butylamine, tertiary
hutylamine, dibutylamine, tertiary amylamine, cyclopentylamine, cyclohexylamine, cycloheptylamine, dicyclohexylamine, N-methylcyclohexylamine, N,N-diisopropylethylenediamine, N,N’-diethylenediamine,
oo N-methyl-I,3-propanediamine, N-methylethylcnediamine,
N,N,N’,N’-tetramethyl-1,2-diamineoethane, N,N,N,N’- tetramethyl-1,6-diaminohexane, I,2-dipiperidinethane, dipiperidincmethane, 2-amino-3,3-dimethylbutane, N,N - dimethylcyclohexylamine, neopentylaminc,
65 adamantylamine, N,N-diethylcyc]ohexylamine,
N-isopropylcyclohexylamine, N-methylcyclohexylamine,
III cyclobutyl amine and norborylamine.

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21

20. The process according to claim 18, wherein the amine is selected from the group consisting of n-butylamine, secondary butylamine, tertiary butylamine, dibutylamine, tertiary amylamine, cyclohexylamine, dicyclohexylamine, N-methylcyclohexylaminc and N,N’- diisopropylethylcnediamine.
21. The process according to claim 18, wherein the IIMG-CoA reductase inhibitor provided as a starting sub-stance or intermediate substance is selected from the group consisting of mevastatin, pravastatin, lovastatin, simvastatin, fiuvastatin and atorvastatin.
22. The process according to claim 18, wherein said purified form is prepared by crystallization.
23. The process according to claim 18, wherein said modified form is prepared by chemical modification.
24. The process according to claim 18, wherein said modified form is prepared by biotechnological modification.
25. The process according to claim 18, wherein said pharmaceutically active salt form is a metal salt.
26. The process according to claim 25, wherein said metal salt is sodium salt or calcium salt.
27. A process for the isolation and/or purification of a HMG-CoA reductase inhibitor, characterized in that the amine salt of the HMG-CoA reductase inhibitor as defined in claim 18 is used for preparing and isolating the 11MG-CoA reductase inhibitor by means of crystallization.
28. The process according to claim 27, wherein the amine salt of mevastatin, pravastatin, lovastatin, simvastatin, flu-vastatin or atorvastatin is prepared and isolated.
29. The process according to claim 28, wherein the TBA salt of mevastatin, pravastatin, lovastatin, simvastatin, flu-vastatin or atorvastatin is prepared and isolated.
30. A process for the preparation of a semisynthetic HMG-CoA reductase inhibitor, characterized in that a start-ing substance used is an amine salt of a HMG-CoA reductase inhibitor as defined in claim 18.
31. The process according to claim 30, wherein an amine salt of lovastatin is used as the starting substance for the preparation of simvastatin.
32. The process according to claim 31, wherein the TBA salt of lovastatin is used as the starting substance.
33. A process for the biotechnological modification of an HMG-CoA reductase inhibitor by using microorganisms or enzymatic systems thereof, characterized in that one of the components used in a medium is an amine salt of an HMG-reductase inhibitor as defined in claim 18.
34. The process according to claim 33, wherein an amine salt of mevastatin is used as a starting substance in the medium.

35. A process for the biotechnological modification of an HMG-CoA reductase inhibitor according to claim 34, wherein an amine salt of pravastatin is produced by said biotechnological process.

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36. ’[he process according to claim 35, wherein the amine salt of pravastatin produced is the TBA salt.
37. A process for the preparation of a pharmaceutically acceptable salt of an HMG-CoA reductase inhibitor, char-acterized in that the HMG-CoA reductase inhibitor in the form of a pharmaceutically acceptable salt is prepared by using as a starting substance an amine salt of an IIMG-CoA reductase inhibitor as defined in claim 18.
38. The process according to claim 37, wherein the

10 pharmaceutically acceptable salt prepared is a metal salt.
39. The process according to claim 38, wherein the HMG-CoA reductase inhibitor prepared is the sodium salt of pravastatin or fiuvaslatin.
40. The process according to claim 38, wherein the

HMG-CoA reductase inhibitor prepared is the calcium salt 15 of atorvastatin.
41. A process for the preparation of an HMG-CoA reduc-
tase inhibitor in a lactone form, characterized in that an amine salt of an HMG-CoA reductase inhibitor as defined in claim 18 is used as a starting substance for the preparation
20 of the HMG-CoA reductase inhibitor in the lactone form.
42. The process according to claim 41, wherein the HMG-CoA reductase inhibitor prepared in the lactone form is lovastatin, mevastatin or simvastalin.
43. A process for isolating and/or purifying a desired
25 HMG-CoA reductase inhibitor comprising:
obtaining an unpurified form of the desired IIMG-CoA reductase inhibitor;
adding an amine as described in claim 18 to form an amine salt of said desired llMG-CoA reductase

j inhibitor, wherein the amine acts as a processing aid to isolate and/or purify the desired IIMG-CoA reductase
in the form of an amine salt; and
crystallizing said desired HMG-CoA reductase inhibitor
as an amine salt.

5 44. A process for isolating and/or purifying a desired HMG-CoA reduclase inhibitor according to claim 43, wherein the amine is selected from the group consisting of (–)-1,2-dime thylpropylamine, 3-(2-aminoethytamino)- propylamine, n-butylamine, secondary butylamine, tertiary 40 butylamine, dibutylamine, tertiary amylamine, cyclopentylamine, cyclohexylamine, cycloheptylarnine, dicyclohexylamine, N-methylcyctohexylamine, N,N’- diisopropylethylenediamine, N,N-diethylenediamine, N-methyl-1,3-propanediamine, N-methylethylenediamine,
45 N,N,N’,N-tetramethyl-1,2-diamineoethane, N,N.N,N-
tetramethyl-1,6-diaminohexane, 1,2-dipiperidinethane, dipiperidinemnethane, 2-amino-3,3-dimethylhutane, N,N-dimethylcyclohexylamine, neopentylamine, adamantylamine, N,N-diethylcyclohexylamine,
50 N-isopropylcyclohexylamine, N-methylcyclohexylamine,
cyclobutylamine and norborylamine.

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ance Notes on Codes andAbbreviatio"appearing at the begin-
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(54) Title: HYDROLYSIS OF [R(R*,R*)]2(4FLUOROPHENYL)M DIHYDROXY5-(1-METHYLETHYL)-3-PHENY1.L [(PHENYLAMINO)CARBONYL]-IH-PYRROLE-1-HEPTANOIC ACID ESTERS WITH CALCIUM HYDROXIDE
(’1

(57) Abstract: The present invention provides a process for preparing atorvastatin hemi-calcium from an atorvastatin ester derivative with calcium hydroxide. The process is conveniently incorporated into a process for preparing atorvastatin hemi-calcium from an acetonide protected, ester protected f-dihydroxy heptanoic acid precursor compound by a first acid hydrolysis step followed by base hydrolysis with calcium hydroxide. The latter process may be performed as a one-pot process.

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HYDROLYSIS OF IR (Ri,
METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYLI-1H-PYRROLE-I-IIEPTANOIC ACID ESTERS WITH CALCIUM HYDROXIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

This invention claims the benefit under 35 U.S.C. 1.119(e) of provisional
applications Serial Nos. 60/249,319, filed November 16, 2000; 60/312,144, filed August 13, 2001 and provisional application Serial No. 60/326,529, filed October 1, 2001, which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to compounds that suppress cholesterol biosynthesis
in humans by competitively inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase and, more particularly, to processes for preparing pharmaceutically appropriate salts for oral administration ofsuch compounds.

BACKGROUND OF THE INVENTION

[R (R*, R’)]-2-(4-fluoropheny1)-,ô-dihydroxy-5-(I -methylethyl)-3-phenyl-4-[(phenylamino)carbonyl}-1}{-pyrrole-1-heptanoic acid ("atorvastatin") is an inhibitor of cholesterol biosynthesis in humans. It is one of a class of drugs called statins. Statins suppress cholesterol biosynthesis by competitively inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase ("HMG-CoA reductase"). HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, which is the rate determining step in the biosynthesis of cholesterol. Goodman and Gilman, The Pharmacological Basis of Therapeutics 841 (MacMillan PubI. Co.: New York 7th ed. 1985). Decreased production
of cholesterol stimulates LDL receptor activity and consequently reduces the
concentration ofLDL particles in the bloodstream. Reducing LDL concentration in the bloodstream decreases the risk of coronary artery disease J.A.MA. 1984, 251, 351-74.
30 Racemic trans-5-(4-fluorophenyl)-2-(1 -methylethyl)-N,4-diphenyl- 1 -[2-tetrahydro-4-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-I H-pyrrole- carboxamide ("the
racemic atorvastatin lactone") was reported to be a useful inhibitor of cholesterol

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biosynthesis in U.S. Patent No. 4,681,893, in 1987. The racemic lactone was synthesized according to the chemical process summarized in Scheme 1.

Scheme 1

0 0 0 0
F F
C r F

J

0 OCH2CH3

(a) 0OCH2CH3 H,CH2CO 0 HO 0

0

NH CFO,0
ME

0

(e)

HO 0
HO OCH3 HO

rC’O’o

, H

F
CO

4

(cs:t(ans) 1:9 rel

(a) Et3N, CH3CN; (b) isobutyryl chloride, Et3N, CH2Cl2; (c) NaOH, MeOH:water; (d) 90°C; (e) 1) HCI, DOH, 2) PTSA, acetone:water; (f) 1) NaN, BuLl, ThIF; (g) 1) B(n-Bu)3, THF, 2)NaBH4; 3) aq. NaOHJ1-1202; (h) A, tol. (I) recryst. tot./EA;

Example 2 ofthe ’893 patent describes the preparation ofthe sodium salt of (R*, -methyletbyl)-3-phenyl-4-
[(phenylamino)carbonyl] -1 H-pyrrole- 1 -heptanoic acid ("racemic atorvastatin sodium") by treating the racemic lactone with sodium hydroxide in THF:water, as shown in Scheme 2.

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Scheme 2

HO HO

6 6

0 HO

ret

(a) NaOH, THF:water.

ret

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U.S. Patent No. 5,273,995 discloses atorvastatin, the pure [R (Re, R*)] enantiomer of 2-(4-fluoropheny1)-,ô-dihydroxy-5-(1 -methylethyl)-3-phenyl-4-[(pheny1amino)carbony1] -1H-pyrrole-1-heptanoic acid. The 995 patent describes a stereoselective preparation (Scheme 3) of atorvastatin wherein the absolute configuration ofthe side chain hydroxy group closest to the pyrrole ring is set by a stereoselective aldol condensation. After chain extension with tert-butyl acetate, reduction ofthe P ketone proceeds under substrate stereocontrol to orient the 3 hydroxy group cis to the hydroxy

group.

F

01OX

(b)

Scheme 3

Ph 1 (a) I O
+ Oh I
L Ph j

NJ

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(d)

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F F

0 (e) 0 OH N OH ON OH N OH Ca2

(a) 1) LDA, S-2-acetoxy-1,1,2-triphenylethanol, MgBr2, THF, 2) 4NaOCI-131 MeOH:THF; (b) tert-butyl acetate, LDA,
5 THF; (c) 1) BEt3, NaBH4, THF, 2) NaOH, THF:MeOH, 3) A, tot., 4) recryst. (d) 1 eq. NaOH (s), 5:1 MeOH:water; (e)
0.5 eq. CaC1321-120.

The ’995 patent describes a preparation of atorvastatin hemi-calcium, which is the
salt form ofthe drug that has been approved by the U.S. Food and Drug Administration
10 for oral administration to human patients. To prepare atorvastatin hemi-calcium, the ’995
patent teaches that the sodium salt is prepared first by dissolving the lactone in methanol
and water and adding a little less than one equivalent ofsodium hydroxide to the solution until the lactone has been opened as determined by high performance liquid
chromatography (HPLC). The ’995 patent then teaches that the hemi-calcium salt may be
15 prepared from the sodium salt by treating it with one equivalent or a slight excess of
calcium chloride dihydrate (CaC12’2H20) (steps d and e of Scheme 3). To an atorvastatin sodium salt solution whose exact concentration has been determined by HPLC is slowly added an equivalent or slight excess of CaC122H20 at elevated temperature while
agitating the solution. After completing the addition, atorvastatin herni-calcium is
20 obtained as a precipitate by cooling the solution. The ’995 patent also describes how the
pure R, R stereoisomer may be obtained from a mixture ofRR and SS stereoisomers obtained from the ’893 patent process.
U.S. Patent No. 5,298,627 discloses an improved, more convergent, process for
preparing atorvastatin in which the side chain bearing the 3,6-dihydroxycarboxylic
25 acidwhich is essential for biological activity--is incorporated in a single step (Scheme 4)
rather than being elaborated from a propanal side chain as disclosed in the ’893 and ’995

patents.

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Scheme 4

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OH 0 OH 0 0 OH OH 0 ’< 0
NC. OR Ph NC.LJL...JL.Ph......NC,,L,,tJ? Ph_-.-NC.Ph
(a) Ph Ph Ph
Ph
F__(
HN
o P h

)

(d) ______________________ 6 - H2N (a) Ph
6

(1)

Ca2+

2

(a) LDA, THF; (b)B(OCI-13)Et2, NaB!-!4, 2:1 THF:CI-130F1; (c) 2,2-dimethoxypropane, MSA; (d) NH,, Raney-Ni, MeOH; (e) pivalic acid, THF:tol.; (f) 1 N Rd. MeOH; (g) 2 N NaOH; (h) Ca(OAc),.

The convergent step ofthe process is a Paal Knorr reaction (step e). After the convergent step, the acetonide protecting group on the 3 and hydroxyls is cleaved with acid (step f). The ’627 patent teaches that the sodium salt maybe prepared from the N,N-diphenyl amide without intermediate isolation ofthe lactone by treating it with sodium hydroxide in a mixture ofmethanol and water (step g). The hemi-calcium salt is then prepared by dissolving the sodium salt in a solution of calcium acetate (Ca(OAc)2) at room temperature and crystallizing the hemi-calcium salt from the solution by cooling. The ’627 patent also describes preparations in which other NN-disubstituted acetamides are used in the first step in otherwise similar processes. The ’627 process is said to be well adapted for large scale production of atorvastatin.

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Brower, P.L. et al. Tet. Lett. 1992, 33, 2279-82 states that (4R-cis)-1,1-dimethylethyl-6-cyanomethyl-2,2-dimethyl- 1,3-dioxane-4-acetate is an ideal intermediate
for preparing atorvastatin because it is highly crystalline and readily obtainable by recrystallization in high purity. After extensive optimization ofthe Paal-Knorr reaction, atorvastatin hemi-calcium was prepared from the highly crystalline intermediate in 60% yield following a procedure generally similar to steps (d) through (h) of Scheme 4. Baumann, K.L. et at. Tet. Lett. 1992, 33, 2283-2284. Conversion ofthe Paal Knorr reaction product to atorvastatin hemi-calcium was carried out without isolation of intermediate products by deprotection ofthe acetonide with aqueous HC1/methanol, dilute base hydrolysis ofthe tert-butyl ester (anchimeric assistance) and treatment ofthe derived sodium salt with Ca(OAc)2 as shown in Scheme 5. As in the process ofthe ’627 patent previously described, the carboxyl protecting group was cleaved with sodium hydroxide and atorvastatin hemi-calcium was prepared by treating the sodium salt with calcium

acetate.

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(a) HC1, MeOH; (b) NaOH; (c) Ca(OAc)2

Scheme 5

o_o. I
HO HO
HO

JI

HO.) I

F- L-o,2

V6 aL

U.S. Patents Nos. 5,003,080; 5,097,045; 5,124,482; 5,149,837; 5,216,174; 7,, 5,245,047 and 5,280,126 disclose methods ofmaking atorvastatin free acid and lactone 7
and/or stereoisomers thereof. Roth, B.D. et al. J Med Chem. 1991, 34, 357-66 discloses preparations of atorvastatin lactone and other pyrroi-i-yl ethylmevalonolactones with variable substituents on the pyrrole ring.

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Kearney, A.S. et al. "The Interconversion Kinetics, Equilibrium, and Solubilities
ofthe Lactone and Hydroxyacid Forms ofthe HMG-CoA Reductase Inhibitor, CI-981 "
Pharm. Res. 1993, 10, 1461-65 reports that the carboxylic acid group of atorvastatin has a
of 4.46. The acidic proton ofthe carboxylic acid group ofintermediate compounds
used to prepare atorvastatin by the 893 and 995 patent processes must be masked during
the chain elaboration steps. The carboxyl group is also protected during the Pan! Knorr reaction in the 627 patent and Baumann et al. processes. Forming an ester is a well
known way ofprotecting a carboxylic acid group and masking its acidic proton. Green,
T.W.; Wuts, P.G.M. Protective Groups in Organic Synthesis 3rd. ed., chapter 5 (John
10 Wiley & Sons: New York 1999) ("Greene & Wuts"). It is also known, generally, that
carboxylic acids that have been protected as esters may be deprotected by hydrolyzing the ester with a strong base. Id. at 377-78.
Sodium hydroxide is a strong base with a dissociation constant of 6.37 (pKb= -
0.80), Handbook ofChemistry and Physics 81st ed 8-45 (CRC Press: Boca Raton 2000-
15 01), and its use as a reagent for deprotecting ester-protected carboxylic acids is taught in
the art. Green & Wuts, p. 377. Calcium hydroxide (Ca(OH)2), with a first dissociation constant of 3.74 x 10-3 (pK=2.43) and second dissociation constant of4.0 x 102 (pKb’
1.40), is a much weaker base than sodium hydroxide. Handbook ofChemistry and Physics 63rd ed D-170 (CRC Press: Boca Raton 1983).
20 Calcium hydroxide is not listed among the reagents that have been used to hydrolyze esters in a well known compendium offunctional group transformations in
organic synthesis. Larock R.C. Comprehensive Organic Transformations 2nd ed.,
Section NITRILES, CARBOXYLIC ACIDS AND DERIVATIVES, Sub-sect. 9.17, pp. 1959-68 (Wiley-VCH: New York 1999). Its use as a general reagent for deprotecting ester-
25 protected carboxylic acids is not taught by a well known reference book on methods for
protecting and deprotecting organic functional groups. Greene & Wuts. pp. 377-79. In
fact, the 995 patent cautions against using an excess ofsodium hydroxide to prepare the sodium salt in order to prevent forming calcium hydroxide when calcium chloride is later added to a solution ofthe sodium salt. It appears not to have been appreciated that an
30 ester-protected form of atorvastatin can be converted directly to atorvastatin hemi-calcium
without first treating the ester with a strong base like sodium hydroxide to hydrolyze it.

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The present invention meets a long-felt need for a more direct, practicable,
convenient and high yielding route to atorvastatin hemi-calcium from a carboxylic acid ester derivative of atorvastatin.

SUMMARY OF THE INVENTION

It has now been discovered that an atorvastatin carboxylic acid ester derivative can
be converted directly to atorvastatin hemi-calcium with calcium hydroxide. The calcium hydroxide performs two functions. It is a basic catalyst for hydrolyzing the carboxylic
acid ester and it supplies calcium ion to coordinate with atorvastatin carboxylate anions to
10 form atorvastatin hemi-calcium.

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Accordingly, the present invention provides a process for preparing atorvastatin hemi-calcium by converting an atorvastatin ester derivative offormula:

wherein R1 is a lower alkyl group, to atorvastatin hemi-calcium with calcium hydroxide. The process is advantageously practiced in a process provided by this invention
for converting a dioxanyl derivative of atorvastatin offormula:

old

wherein R1 is as previously defined, to atorvastatin hemi-calcium, hereafter referred to as the sequential acid-base hydrolysis process. The sequential acid-base hydrolysis process may be conveniently practiced by following one ofthe exemplary embodiments.

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In one exemplary embodiment, the sequential acid-base hydrolysis process is
performed in two steps with intermediate isolation of an atorvastatin ester derivative. The isolated atorvastatin ester derivative may be the direct product ofhydrolysis ofthe
dioxane and have the structural formula 1. Another atorvastatin ester derivative resulting
5 from ester transposition with an alcohol solvent and/or atorvastatin lactone may also be
obtained, optionally in mixture with some atorvastatin free acid. First, the dioxane 2 is converted to one or more ofthese atorvastatin ester derivatives with an acid catalyst, preferably acetic acid. The atorvastatin ester derivative or mixture thereofis then isolated
in condensed form, as a solid or oil. Second, the isolated atorvastatin ester
10 derivative(s) is converted to atorvastatin hemi-calcium with calcium hydroxide and,
optionally, a phase transfer agent.
In another exemplary embodiment, dioxane 2 is hydrolyzed in a mixture of an acid
catalyst and a mixed solvent comprising a C1-C4 alcohol offormula R2-OH and water to
form the atorvastatin ester derivative 1 or another atorvastatin ester derivative, optionally
15 in mixture with some atorvastatin free acid. The ester derivative(s) is then converted to
atorvastatin hemi-calcium with calcium hydroxide in a solution of a C1-C4 alcohol. The
steps ofthe second embodiment ofthe sequential acid-base hydrolysis process are advantageously practiced in a single reaction vessel, as a"one-pot" process. In either embodiment ofthe acid-base process, atorvastatin hemi-calcium, or a solvate thereof, may
20 be separated from the solvent and dissolved substances by precipitation.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Some ofthe terms used in this disclosure have the following ascribed meanings.
A C1 -C4 alcohol is a compound ofthe formula R2-OH wherein R2 is methyl, ethyl,
25 propyl, isopropyl, n-butyl, s-butyl or t-butyl.
An "ester derivative" is a compound resulting from replacement ofthe hydroxyl
proton of a carboxylic acid with a substituent bonded to the hydroxyl oxygen atom
through carbon. Unless otherwise excluded by a formula, an ester derivative includes a lactone, which is a cyclic ester in which the ester group in incorporated into a ring. Ester
30 derivatives also include compounds where the substituent bonded to the hydroxyl oxygen
is C1-C4 alkyl group.

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In its first aspect, the present invention provides a process for preparing
atorvastatin hemi-calcium by converting an atorvastatin ester derivative offormula:

wherein R1 is a C1 to C4 alkyl, to atorvastatin hemi-calcium with calcium hydroxide. An unexpected advantage ofthis process is that the calcium hydroxide fulfills two roles. It functions as a basic catalyst for hydrolysis ofthe ester and supplies calcium ion that coordinates to atorvastatin anions. Another significant practical advantage ofthe process is that the amount of calcium hydroxide does not have to be as carefully controlled as the amount ofsodium hydroxide and calcium chloride used in other processes.
The atorvastatin ester derivative 1 may be provided in pure form or in mixture
with other atorvastatin ester derivatives. In a second aspect ofthe invention, described below, a mixture ofintermediate atorvastatin ester derivatives are formed from a dioxanyl precursor compound. These atorvastatin ester derivatives include, in addition to those of fonnula 1, those derived from transposition of atorvastatin ester derivative 1 with a C, -C4 alcohol solvent offormula R2-OH. In addition, atorvastatin ester derivative 1 may be provided in mixture with atorvastatin lactone, which may form from atorvastatin free acid, small amounts ofwhich are in equilibrium with the ester in the acidic aqueous solvents used in the second aspect ofthis invention.
In the invention’s first aspect, hereafter referred to as the base hydrolysis process,
the atorvastatin ester derivative 1, optionally in mixture with other atorvastatin ester derivatives, is dissolved or suspended in a mixed solvent comprising a C1-C4 alcohol and water. A preferred alcohol is ethanol and a preferred solvent mixture contains about 5% to about 15% water in ethanol, more preferably about 10% water and about 90% ethanol (vlv). Whether the atorvastatin ester derivative 1 dissolves in the mixed solvent depends upon such factors as the choice of C1 -C4 alcohol, the proportion ofwater, the temperature

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and the purity ofthe atorvastatin ester derivative. Calcium hydroxide is suspended in the
mixed solvent and the base hydrolysis reaction mixture is maintained until the atorvastatin
ester derivative 1 has been consumed. Consumption of atorvastatin ester derivative 1 may
be monitored by any conventional means like TLC, HPLC, NMR and the like. After the
5 atorvastatin ester derivative 1 has been consumed, atorvastatin hemi-calcium is recovered
from the base hydrolysis reaction mixture by any means. It is unnecessary to add another source of calcium to provide a Ca2 ion for the atorvastatin hemi-calcium salt.
According to a preferred procedure for practicing the base hydrolysis process, the atorvastatin ester derivative 1 is added in an amount sufficient to provide about 10
10 mmoles L’ to about 1 mole L1 ofthe mixed solvent.

Preferably, about 1 equivalent to about 6 equivalents of calcium hydroxide with
respect to the ester derivative 1 is used. More preferably, from about 1 to about 2
equivalents is used.
Calcium hydroxide is only sparingly soluble in the C1 -C4 alcohol:water mixed
15 solvent and only a minor proportion ofit will be in solution available to catalyze the
hydrolysis at any one time. To accelerate the base hydrolysis, a phase transfer catalyst
may be added to increase the solubility ofthe calcium hydroxide. Phase transfer catalysts
are well known in the art and include, for instance, tetra-n-butylammonium bromide ("TBAB"), benzyltriethylammonium chloride ("TEBA"), tetra-n-butylammoniurn
20 chloride, tetra-n-butylanmonium bromide, tetra-n-butylanimonium iodide,
tetra-ethylammonium chloride, benzyltributylammonium chloride,
benzyltributylammonium bromide, benzyltriethylammonium bromide, tetramethylanimonium chloride and polyethylene glycol. A most preferred phase transfer catalyst is TBAB. When used, the phase transfer catalyst should be used in a
25 substoichiometric amount, preferably from about 0.05 to about 0.25 equivalents, more
preferably about 0.1 equivalents, with respect to atorvastatin ester derivative 1.
The mixture may be heated to up to the reflux temperature ofthe mixed solvent in
order to accelerate the reaction. A preferred temperature range is from about 30°C to
about 70’C.

30 After consumption of atorvastatin ester derivative 1, atorvastatin hemi-calcium or solvate thereofis recovered from the base hydrolysis reaction mixture. As part of

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recovering the atorvastatin hemi-calcium, the reaction mixture should be filtered to remove excess suspended calcium hydroxide. The reaction mixture preferably is filtered hot to prevent precipitation of atorvastatin hemi-calcium on the calcium hydroxide filtercake.

After filtration to remove suspended calcium hydroxide, atorvastatin hemi-calcium
may be recovered from the filtrate by precipitation. According to a preferred recovery technique, atorvastatin hemi-calcium is caused to precipitate from the filtrate by slow addition ofwater. A volume ofwater roughly equivalent to the volume ofthe filtrate is
added over about an hour’s time. Preferably, the slow water addition is also conducted at
10 elevated temperature, e.g. from about 40°C to about 65°C. Precipitating atorvastatin
hemi-calcium by slow water addition yields atorvastatin hemi-calcium in a crystalline trihydrate state and prevents formation of a gelatinous precipitate. Alternatively, atorvastatin hemi-calcium may be recovered by any conventional means. After any necessary purification steps, the recovered atorvastatin hemi-calcium may be used as an
15 active ingredient to formulate a pharmaceutical product.

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In a second aspect ofthe invention, the base hydrolysis process for converting atorvastatin ester derivative 1 to atorvastatin hemi-calcium is preceded by acid hydrolysis
of a dioxane offormula:

R1

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wherein R1 is as previously defined. This two-step process (which may be conducted in single reaction vessel) is hereafter referred to as the sequential acid-base hydrolysis

process.

Dioxane 2 is an important intermediate in the preparation of atorvastatin. For
25 example, it is an intermediate in the Baumann et al. process. Dioxane 2 is a protected
form of atorvastatin with an acetonide protecting group on the,ô-dihydroxy groups and
an ester group masking the carboxylic acid proton.

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According to one preferred embodiment ofthe sequential acid-base hydrolysis
process, dioxane 2 is converted into an atorvastatin ester derivative or mixture thereof, which is then isolated as a solid or oil before being carried forward to prepare atorvastatin hemi-calcium according to the base hydrolysis process ofthe invention. In this
embodiment, the dioxane ring of dioxane 2 is cleaved with a catalyst selected from the group consisting of acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, zinc bromide and hydrochloric acid. Procedures for practicing this process using these catalysts are illustrated in Example 1. In its most preferred mode, this embodiment uses acetic acid as an 80% solution in water (Example I (a)-(c)). Dioxane 2 is suspended in the aqueous acetic acid and stirred at room temperature until a clear solution is obtained. The acetic acid is then evaporated under reduced pressure. Remaining traces of acetic acid may be removed by azeotroping with toluene, leaving a residue of atorvastatin ester derivative 1 as a solid or as a viscous oil containing residual toluene. The residue may also contain amounts of atorvastatin lactone and atorvastatin free acid.
As further illustrated in Example 2, the residue may be converted to atorvastatin hemi-calcium by suspending in the C1 -C4 alcohol:water mixed solvent and adding from about I to about 6, more preferably in this embodiment from about 4 to about 6 equivalents of calcium hydroxide and a phase transfer agent. After the atorvastatin ester derivative 1 has been consumed, the mixture is filtered to remove excess calcium hydroxide. Atorvastatin bemi-calcium or solvate thereofmay then be recovered by precipitation, e.g., by cooling the solution and/or adding water (for example as previously described for the base hydrolysis process), filtering and drying. The filtrate also may be further purified by recrystallization using known techniques or by chromatography.
In another preferred embodiment ofthe sequential acid-base hydrolysis process,
both the acid hydrolysis ofthe 1,3-dioxane ring of dioxane 2 and the subsequent base hydrolysis ofthe ester are performed in a mixed solvent of a C1 -C4 alcohol and water. Thus, this embodiment ofthe sequential acid-base hydrolysis process may be advantageously practiced entirely in one reaction vessel without a change ofsolvent or isolation of an atorvastatin ester intermediate or mixture ofintermediates. An additional advantage ofthis "one-pot" embodiment is that it enables further reduction ofthe amount of calcium hydroxide used, yet without demanding strict adherence to a predetermined

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exact molar ratio. The one-pot embodiment also does not involve using a phase transfer agent and uses a mineral acid to cleave the 1,3 dioxane ring, thus reducing the cost of reagents.
In the one-pot embodiment ofthe sequential acid-base hydrolysis process, dioxane
2 is suspended in the mixed alcohol:water solvent in a vessel that is able to withstanding a vacuum and is equipped with a heater and a distillation head. The mixed solvent is pH adjusted to about I or less with hydrochloric acid or other mineral acid. Hydrochloric
acid is preferred because a small amount of calcium chloride is formed when calcium hydroxide is added to the reaction mixture. Calcium chloride is readily soluble in the
10 mixed solvent and therefore easily separated from the product when atorvastatin hemi-
calcium is precipitated from the reaction mixture. The mixed solvent is conveniently prepared and pH adjusted by mixing dilute aqueous hydrochloric acid with the C1 -C4 alcohol, from 1.5 % to 10 % hydrochloric acid being preferred.
Dioxane 2 is preferably added in an amount of about 0.12 moles L’ ofthe C1-C4
15 alcohol. The resulting suspension may be heated to accelerate hydrolysis ofthe dioxane.
Preferred temperatures for the hydrolysis are mildly elevated, ranging from about 30°C to about 50°C, more preferably about 40°C.
Under acidic aqueous conditions, the dioxane 2 and free diol 1 are in equilibrium.
Under the preferred reaction conditions, the mixed solvent contains something on the
20 order of a ten fold molar excess of water over the amount of acetone that would be
produced by complete hydrolysis. A significant amount ofthe dioxane would remain in
the reaction mixture if acetone were not removed. Therefore, it is desirable to remove acetone that is liberated by the acid hydrolysis from the reaction vessel by evaporation
To meet this purpose at the preferred reaction temperatures, the reaction vessel should be
25 maintained under sufficiently reduced pressure to distill offthe liberated acetone.
Aspirator vacuum is generally sufficient. Alcohol and water vapors may be drawn off by
the distillation head along with the acetone. Make up alcohol may be added to the
mixture to maintain a constant volume. Consumption of dioxane 2 may be monitored by HPLC chromatography, or by observing the formation of a clear solution and allowing a
30 period of about 9 to 11 hrs for consumption of dissolved dioxane 2.

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Acid hydrolysis of dioxane 2 produces atorvastatin ester derivative 1 as a direct product. However, other reactions occur to a greater or lesser extent under these
conditions. Transesterification occurs with the alcohol solvent component to form atorvastatin ester derivatives offormula:

OH OH 0

0 C 3

wherein R7 is the alkyl substituent ofthe C1 -C4 alcohol, and may be the same or different from R1 In the presence ofwater, some atorvastatin free acid forms. The free acid in turn
10 lactonizes, although a proportion remains in equilibrium as the free acid with the lactone
and with the other atorvastatin ester derivatives.

After dioxane 2 has been completely consumed, calcium hydroxide is added to the
resulting solution. The rate of hydrolysis ofthe atorvastatin ester derivatives by calcium hydroxide depends upon a variety offactors including the temperature, concentration of
15 the ester derivatives in the mixture, the exact composition ofthe mixture, all ofwhich can
vary in accordance with the invention. The rate of hydrolysis also depends upon the
quantity and particle size ofthe calcium hydroxide used. With these considerations in
mind, an optimal set of base hydrolysis conditions using calcium hydroxide has been developed.
20 The total atorvastatin ester derivative concentration, which is taken as equal to the concentration ofdioxane 2, is adjusted to from about 0.10 to about 0.15 M, by continuing
to distill solvent or by adding more C1 -C4 alcohol and/or water. Any amount of calcium hydroxide in excess of about 3/4 molar equivalent with respect to the dioxane 2 may be
used. However, in the one-pot embodiment ofthe sequential acid-base hydrolysis
25 process, preferably from about 1 to about 2 equivalents, more preferably about 1.5 molar
equivalents of calcium hydroxide with respect to the atorvastatin ester derivatives (or
dioxane 2) is used. Calcium hydroxide may be added in one or more than one portion.
Further, the reaction mixture is preferably heated to from about 50°C to about 70’C, more

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preferably about 70°C. Under these conditions, the atorvastatin ester derivative(s), i.e. compound 1, transposed ester 3, and atorvastatin lactone are substantially completely hydrolyzed within a few hours. The consumption ofthe atorvastatin ester derivatives may be monitored by HPLC. Using these conditions, atorvastatin hemi-calcium can be later precipitated from the base hydrolysis reaction mixture substantially free ofimpurities, i.e. containing less than 0.05%, atorvastatin ester derivative 1.
After the atorvastatin ester derivatives have been consumed, excess suspended
calcium hydroxide should be filtered from the mixture ifit is desired to precipitate atorvastatin hemi-calcium from the base hydrolysis reaction mixture with minimal
10 contamination by calcium hydroxide. The reaction mixture preferably is filtered hot to
prevent precipitation of atorvastatin hemi-calcium on the calcium hydroxide filtercake.
Using the preferred amount of 1 to 2 equivalents of calcium hydroxide in the one-pot
process also minimizes losses due to precipitation of atorvastatin hemi-calcium on the calcium hydroxide filter cake and increases the purity ofthe atorvastatin hemi-calcium
15 recovered from the solution by precipitation.
Further, according to the preferred mode ofpracticing the one-pot sequential acid-
base hydrolysis process, atorvastatin hemi-calcium is caused to precipitate from the
filtrate by slow addition ofwater as previously described with reference to the base
hydrolysis process. The precipitate may be carried forward and used in a pharmaceutical
20 product.
The filtering characteristics and purity ofthe atorvastatin hemi-calcium may be
further improved by redissolving the crystalline product in the aqueous alcohol reaction mixture by heating to a temperature sufficient to cause all the precipitate to dissolve,
resulting in a clear solution. The solution should then be slowly cooled over several hours
25 and held, preferably at ambient temperature, until no more crystals are observed to form.
After filtering and drying, and any necessary purification steps, the atorvastatin hemi-
calcium or solvate thereofmay be used as an active ingredient in a pharmaceutical
product.
Having thus described the present invention with reference to certain ofits
30 preferred embodiments, it will now be further illustrated with the following examples

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which offer highly specific procedures that may be followed in practicing the invention but which should not be construed as limiting the invention in any way.

EXAMPLES
General

Unless otherwise indicated, reagents were used as received. [R(R*,R*)]2(4 fluorophenyI)-3,-dioxane-5-(1 -methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]- 1 H-pyrrole- 1 -tert-butylheptanoic ester (dioxane 2, R1 = t-Butyl) was prepared by a
condensation reaction between the corresponding diketone and the corresponding chiral
10 amine to form the pyrrole ring. It also may be prepared by known methods. Brower, P.L.

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et al. Tet. Lett. 1992, 33, 2279-82; Baumann, K.L. et al. TeL Lett. 1992, 33, 2283-84. The following HPLC conditions were used to determine the composition ofmixtures obtained
in the acid hydrolyses reported in the examples: Waters Spherisorb S3 ODS I (7.6x1 00
mm), 70:30 acetonitrile:water, 0.6 ml mm:1, 20 p1 sample, UV detection?."254).

Example 1: Preparation ofAtorvastatin Ester Derivative(s) From Dioxane 2
a) Dioxane 2 (R1 = t-Bu) (2.0 g, 3.06 mmole) was suspended in an 80% aqueous
solution of acetic acid (50 ml) in a flask equipped with a magnetic stirrer. The mixture
was stirred at ambient temperature for 20 hours until a clear solution was obtained. The
20 clear solution was evaporated to dryness and traces of acetic acid were removed by
azeotropic distillation with toluene (3x50 ml) to obtain a powder containing atorvastatin t-butyl ester 1 (R1=t-Bu), atorvastatin free acid and atorvastatin lactone.
b) Dioxane 2 (R1 = t-Bu) (10.0 g, 15.3 mmole) was suspended in an 80% aqueous
solution of acetic acid (150 ml) in a flask equipped with a magnetic stirrer. The mixture
25 was stirred at ambient temperature overnight until a clear solution was obtained. The
clear solution was evaporated and the traces of acetic acid were removed by azeotropic distillation with toluene (3x100 ml) to obtain an oil containing toluene, atorvastatin t-
butyl ester 1 (R1=t-Bu), atorvastatin free acid and atorvastatin lactone.
c) In a flask equipped with a magnetic stirrer, dioxane 2 (R1 = t-Bu) (1.0 g, 1.53
30 mmol) was suspended in 80% aqueous acetic acid (10 ml) containing p-toluenesulfonic
acid (40 mg, 0.21 mmole). The mixture was stirred at ambient temperature for 18 hours.

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The white precipitate that appeared was filtered, wash with water (3x1 5 ml), and dried in
a vacuum oven at 50°C for about 4 hours to yield a powder containing atorvastatin t-butyl
ester 1 (R1=t-Bu), atorvastatin free acid and atorvastatin lactone.
d) To a flask equipped with a magnetic stirrer, dioxane 2 (R1 = t-Bu) (0.5 g, 0.76
5 mmole) was dissolved in a 1:1 mixture oftrifluoroacetic acid:tetrahydrofuran (4ml) in the
presence of catalytic amount ofwater. The reaction mixture was stirred at ambient temperature for 24 hours. The solution obtained was evaporated and traces of
trifluoroacetic acid were removed by azeotropic distillation with ether (3x1 0 ml) leaving a white solid residue (0.3 g). Based on HPLC analysis, the white solid was a mixture of
10 atorvastatin free acid and atorvastatin lactone in the ratio of40:60.
e) A flask equipped with a magnetic stirrer was charged with dichloromethane (5
ml), dioxane 2 (R1 = t-Bu) (0.2 g, 0.30 mmole) and zinc bromide (241 g, 1.07 mmole, 3.5
eq). The reaction mixture was stirred at ambient temperature for 24 h. Water (30 ml) was added and the mixture was stirred for an additional 3 hours. The aqueous layer was
15 extracted with dichioromethane (3x1 0 ml) and the organic layer was dried with sodium
sulfate and filtered. The organic layer was then evaporated under reduced pressure to give
a powder (150 mg). Based on HPLC analysis, the powder was a mixture of atorvastatin
free acid and atorvastatin lactone in the ratio of 57:43.

f) In a flask equipped with a magnetic stirrer, dioxane 2 (R1 = t-Bu) (0.2 g, 0.31
20 mmole) was suspended in a 90% aqueous solution of acetic acid (4 ml). The mixture was
stirred at 60°C for 5 days. The resulting solution was evaporated to dryness and traces of acetic acid were removed by azeotropic distillation with toluene (3x1 5 ml) leaving a
powder residue. Based on HPLC analysis, the powder was a mixture of atorvastatin free
acid and atorvastatin lactone in the ratio of 54:46.

25 g) In a flask equipped with a magnetic stirrer, dioxane 2 (R1 = t-Bu) (0.2 g, 0.31
mmole) was dissolved in a mixture of 3% aqueous solution of hydrochloric acid (1 ml)
and methanol (2 ml). The mixture was stirred at 100°C for 3.5 hours and then stirred overnight at ambient temperature. The resulting solution was evaporated to dryness to
obtain a powder. Based on HPLC analysis, the powder was a mixture of atorvastatin free
30 acid and atorvastatin lactone in the ratio 54:46.

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Example 2: Preparation ofAtorvastatin Hemi-calcium from The Ester Derivative(s).
a) A saturated solution of calcium hydroxide (8 ml) containing tetrabutyl ammonium
bromide (10 mg, 0.031 mmole) was added to a solution ofthe powder obtained in
Example 1(a) (200 mg, 0.32 mmole) in ethanol (8 ml). The mixture was stirred and
heated to 45°C for 24 hours. Additional saturated calcium hydroxide solution (4 ml) was
then added. After 20 more minutes ofstirring at ambient temperature, HPLC ofthe
reaction mixture showed that the reaction was complete. A white precipitate from the reaction mixture was filtered under vacuum and dried at 65°C for about 18 hours to give atorvastatin hemi-calcium (142 mg, 77%).
10 b) The oil obtained from Example 1(b) was dissolved in a mixture of ethyl alcohol
(100 ml) and water (20 ml). Calcium hydroxide (6.22 g, 84.0 mmole, 5.5 eq.) and tetrabutyl ammonium bromide (0.46 g, 1.43 mmole, 0.05 eq.) were added. The mixture was heated to 45°C for 3 hours until the reaction was complete. While the mixture was
still hot, it was filtered under vacuum to remove excess calcium hydroxide. The mixture
15 was then cooled to ambient temperature, after which, while stirring, water (200 ml) was
added. A white precipitate that formed was filtered under vacuum and dried at a
temperature of about 65°C for about 18 hours to give atorvastatin hemi-calcium (7.44 g, 84%).

20 Example 3: Preparation ofAtorvastatin Hemi-calcium from Dioxane 2 in One-Pot
a) Dioxane 2 (R t-Bu) (20 g, 30.6 mmole) was suspended in a mixture of 1.5%
HC1 (50 ml, 0.067 eq. HC1, 11.2 eq. water) and absolute ethanol (250 ml) in a cylindrical reactor equipped with a distillation apparatus and a mechanical stirrer. The suspension
was heated to 40°C and then the pressure inside the reactor was reduced to 500-600 mbar
25 for 9-11 hrs while a vapor mixture of acetone, ethanol and water was continuously
distilled off. Make-up of absolute Ethanol (35-40 ml.) was added every hour. After 9-11 hours, dioxane 2 (R1 = t-Bu) had been more than 99.9 % consumed according to HPLC
and the suspension had become a clear solution.
Without any further treatment, Ca(OH)2 (3.4 g, 46 mmole, 1.5 eq.) was added.
30 The reaction mixture was heated to 70°C for 4-5 hrs. Then, the excess of Ca(OH), was
collected by filtration. To the hot filtrate (65°C), water (350 ml) was added slowly using
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a dosing pump over about 1/4 of an hour to 1 hour. During the addition, atorvastatin hemi-calcium precipitated. The atorvastatin hemi-calcium can be filtered at this point, but that was not done in order to obtain a product with optimal filtering characteristics and a low level ofimpurities.
5 After the addition ofwater was complete, the reaction mixture was heated to reflux (84’Q until the mixture clarified. The mixture was then cooled to 20°C over 3 hrs
and stirred at this temperature for an additional 20 hrs. The solid was then filtered to give
45.0 g ofwet cake ofAtorvastatin hemi-calcium. The wet cake was dried at 65°C for 24
hrs to give atorvastatin hemi-calcium (16.7 g, 95%) with a water content ofbetween 2.8%
10 and 6.6% as determined by Karl-Fisher analysis.
b) Dioxane 2 (R1 = t-Bu) (20 g, 30.6 mmole) was suspended in a mixture of 10% HC1 (7.6 ml, 0.68 eq. HCI, 12.4 eq. water) and methanol (135 ml) in a cylindrical reactor
equipped with a distillation apparatus and a mechanical stirrer. The suspension was heat
to 35°C for 3 hrs, while the pressure inside the reactor was reduced to 820 mbar and a
15 vapor mixture of acetone, methanol and water was continuously distilled off. Make-up of
methanol (35 ml) was added every V2 hour. After 3 hrs dioxane 2 (R1 = t-Bu) had been
more than 99.9 % consumed according to HPLC and and the suspension had become a
clear solution.

Without any further treatment, Ca(OH)2 (3.4 g, 45.9 mmole, 1.5 eq), water (5m1)
20 and methanol (45m1) were added. The reaction mixture was heated to 70°C for 2 hrs. The
excess of Ca(OH)2 was collected by filtration and the Ca(OH)2 cake was washed with methanol (2x 1 Omi). To the hot filtrate (650C), water (300m1) was slowly added using a dosing pump over 45 minutes. During the addition, atorvastatin hemi-calcium salt precipitated. The atorvastatin hemi-calcium can be filtered at this point, but that was not
25 done in order to obtain a product with optimal filtering characteristics and a low level of
impurities.
After the addition, the reaction mixture was heated to reflux temperature (78’Q
for V2 hour. The mixture was then cooled to 20°C over 3 hrs and stirred at this
temperature for another 20 hrs. The solid was then filtered and dried at 65°C for 48 his to
30 give atorvastatin hemi-calcium (16.9 g, 96%) with a water content of 3.2% by Karl Fisher
analysis.
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CLAIMS

We claim:

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1. A process for preparing atorvastatin hemi-calcium comprising:
a) providing an atorvastatin ester derivative offormula:

or

wherein R1 is a C1-C4 alkyl group, and
b) converting the atorvastatin ester derivative to atorvastatin hemi-calcium
with calcium hydroxide.
2. The process of claim I wherein the atorvastatin ester derivative is provided in a
mixture with a second atorvastatin ester derivative.

3. The process of claim 2 wherein the atorvastatin ester derivative is provided as a
solute in a C1 -C4 alcohol offormula R2-OH wherein R2 is a C1 -C4 alkyl group
selected independently ofR1, and wherein the second atorvastatin ester derivative
is ofthe formula:

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4. The process of claim 2 further comprising recovering the atorvastatin hemi-
calcium substantially free of atorvastatin ester derivatives.
5. The process of claim 2 wherein the second atorvastatin ester derivative is
converted into atorvastatin hemi-calcium with the calcium hydroxide.
6. The process of claim 1 wherein the mixture further comprises atorvastatin free
acid in an amount ofless than about 10% with respect to the atorvastatin ester derivative and is converted into atorvastatin hemi-calcium with the calcium hydroxide.
7. The process of claim 1 wherein the calcium hydroxide is a molar excess of
calcium hydroxide with respect to the atorvastatin ester derivative.
8. The process of claim 7 wherein the molar excess is greater than about 0.75 and
less than about 6 molar equivalents with respect to the atorvastatin ester
derivative.

9. The process of claim 8 wherein the converting comprises adding the atorvastatin
ester derivative to a mixed solvent comprising about 5 % to about 20 % water in
C1 -C4 alcohol and suspending the calcium hydroxide in the mixed solvent.
10. The process of claim 9 wherein from about 10 mmole to about 1 mole of
atorvastatin ester derivative per liter ofmixed solvent is added.
11. The process of claim 9 wherein the converting further comprises adding a phase
transfer agent to the mixed solvent.
12. The process of claim 11 wherein the phase transfer agent is selected from the
group consisting oftetra-n-butylarnmonium bromide, benzyltriethylammonium chloride, tetra-n-butylammonim-n chloride, tetra-n-butylammonium bromide, tetra-n-butylammonium iodide, tetra-ethylammonium chloride, benzyltributylammonium chloride, benzyltributylammonium bromide, benzyltriethylammonium bromide, tetramethylammonium chloride and
polyethylene glycol.
13. A process for preparing atorvastatin bemi-calcium comprising the steps of:
a) mixing an atorvastatin ester derivative, phase transfer catalyst, and from
about 0.75 to about 6 equivalents of calcium hydroxide with respect to the

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atorvastatin ester derivative in a mixed solvent comprising from about 5 %
to about 20 % water in a C1 -C4 alcohol,
b) heating the mixture to from 50°C to 70°C for a period oftime sufficient to
hydrolyze the atorvastatin ester derivative,
C) filtering the mixture to remove excess calcium hydroxide,
d) adding water to the filtrate to precipitate atorvastatin hemicalcium, and
e) separating atorvastatin hemi-calcium from the filtrate.
14. A process for preparing atorvastatin hemi-calcium or solvate thereof comprising the steps of:
a) forming a solution of an atorvastatin ester derivative selected from the
group consisting of:

OH OH

F

OH OH

C

F and

wherein R1 and R2 are each a C1-C4 alkyl group, by converting a dioxane of formula:

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to the atorvastatin ester derivative with an acid catalyst in a mixture of
water and a C1 -C4 alcohol offormula R2-OH,
b) adding calcium hydroxide to the solution to convert the atorvastatin ester derivative to atorvastatin hemi-calcium, and
C) recovering the atorvastatin hemi-calcium or solvate thereoffrom the
solution.

15. The process of claim 14 wherein the C1-C4 alcohol and water mixture has a pH of
less than about 1, the acid catalyst is hydrochloric acid and R2 is ethyl.
16. The process of claim 14 further comprising evaporating acetone liberated by the
conversion ofthe dioxane to the atorvastatin ester derivative.
17. The process of claim 16 wherein the acetone is evaporated under reduced pressure.
18. The process of claim 14 wherein the calcium hydroxide is a molar excess of
calcium hydroxide relative to the dioxane.
19. The process of claim 18 wherein the molar excess is from about 1.5 to about 6
molar equivalents.
20. The process of claim 18 wherein the excess portion ofthe calcium hydroxide is
filtered from the solution before recovering the atorvastatin hemi-calcium or
solvate thereof.

21. The process of claim 20 wherein the atorvastatin hemi-calcium or solvate thereof
is recovered by precipitation and removal ofthe C1-C4 alcohol and any dissolved substances.

22. The process of claim 21 wherein the atorvastatin hemi-calcium is caused to
precipitate by slow addition of water.

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DESCRIPCION

Forma cristalina de La sal hernicÆlcica del Æcido

letil)-3-fenil-4 (feniLamino)carbonilJ_ 1 H-pirrol- 1-heptanoico (atorvastatina).

Estado de la tcnica

La presente invención se refiere a una forma nueva cristalina de atorvastatina que es conocicla per
el nombre quIlnico de Sal hemicÆlcica de Æcido 1-metiletil)-
10 3-fenil-4- [(fenilainino)carbonil]- 1H-pirrol- 1-heptanoico efectivo corno agente farrnacØutico, a los mØtodos
para su producción y aislamiento, a las composiciones farmacØuticas que incluyen este compuesto, a un sc porte farniacØuticamente aceptable y a los mØtodos farmacØuticos de tratarniento. El compuesto crist.aliiio nuevo de la presente iiivención es efectivo como inhibidor de La enzima 3-hidroxi-3-metilglutaril-coenzima
A reductasa (reductasa HMG-CoA), resultando de este modo efectivo como ageiite hipolipidØmico e hi-
15 pocolesterolØmico.

La patente de Estados Unidos nüinero t681.893 que se incorpora en la presente como referencia(muestra ciertas trans-6-[2-(3- o 4-carboxamido -sustituidas- pirroL-1-il)a1qui1-4--hidroxi-piran-2-onas que incLuyen trans(–)-5-(1_fluorofenil)-2_(1_rnetiletil)-N,1-difeniL-1- [(2-tetrahidro-1-hidroxi-6-oxo-2H-piran-2-
20 il)etil]- IH-pirrol-3-carboxamida.

La pateiite de Estados Unidos niimero 5.273.995 que se incorpora a la presente como, referencia muestra el enantiómero que tiene la forma R del Æcido de ciclo abierto de trans- 5-(l-fluorofenil)-2-(1-inetiletil)_N,4_difenil_1- (2-tetrahidro_4_hidroxi-6_oxo_2H_piran2-i1)etil]- 1H-pirrol-3-carboxainida, es decir,
25 Æcido [R_(R*,R*)1_2_ (4-fluorofenil)-3,-dihidroxi-5-(1-meti1eti1)-3-fenil-4- F(fenilamino)carbo1i11-111-pirrol-
1-heptaiioico.

Las patentes de Estados Unidos iiuinero 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5.280,126; 5,397,792; y 5,342,952 qtw se IIRorporan en Ia
30 presente come, refereiicia rnuestrari varios procesos y los productos iiiteruiedios para preparar La atoras-
La tin a.

La atorvast,aCina se ireiart (X)TflO sii sal calcica, es (lecir, sal (’alcica (IC aCi(IO IH_(R*,B *)I_2.(4. fluorofenil)-0,3-dihidroxi-5-(1-nietiletil)-3-fenil-4- [(tenilarnino)carbonil]-1FI-pirrol- 1-heptanoico (2:1). La
35 sal cÆlcica es aconsejable piiesto que permite que la atorvastatina Sc encileutre convenientemente for-
mulada en, por ejemplo, comprirnidos, cÆpsulas, pastillas, polvos y sirnilares para [a administración oral. Adicionalmente, existe]a necesidad de prodiicir atorvastatina en una forma piira y cristalina que facilite que las formulacioucs cumplan con los requisites y las especificaciones farinacØuticas exac-
tas.
40

AdcmÆs, el proceso por el que La atorvastatina es producida dcbc ser capaz de Ilevar a caho una producción a gran escaLa. AdicionaLmente, es conveniente que el producto SC encuentre dc manera que permita una fÆcilflltración y secado. Finalmente, CS econ6n1icarnente aconsejabic que el producto pernia-nczca estable durantc largos perIodos de tiempo sin necesidad de contar con unas condiciones especificas
4.5 de almacenamiento.

Los procesos niencionados anteriormente en Las patentes de Estados Unidos muestran una atorvas-tatina amorfa que posee unas caracterIsticas de flltración y de secado inadecuadas para ser producida a graii escala y que dehe ser protegida del calor, la luz, el oxigeno y la humedad.
50

WO-A-94/16693 muestra una composlclón farrnacØutica
hiperlipidemia que contiene una formuLación ventajosa pan
zirna HMG-CoA, el HemicaLcio CI-981 de la formula (IA) cc
Co.

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60

oral para tratar la hipercoLesteroleinia o . estabilizar ci inhibidor A de La coen-n cantidades eficaces de carhonato c6ld-

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US-A-5 316 765 muestra un rnØtodo para mejorar Ia reducción dc la, cocnzinia Qio en pacientes quo padcccn miocardiopatla y quo rccibcn un inhibidor de la HMG-CoA reductasa quo inciuyc la adrniiiis-20 tración sirnuitÆnea dc dicha cocnzirna Qio inhibidora de la HMG-CoA reductasa on una concentración suficientc para elevar ci nivel dc sucro dc la cocnzima Quo por lo menos en 2.0fig/m, on ci quc al igual que en ci mencionado inhibidor de HMG-CoA reductasa pueda utilizarse el CI-981 con la siguiente formula:

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F

HO

CO2 Ca2

H

CO

Tetrahedron Letters, Vol. 33, N 17, pp. 2283-2284,1992, Bairn ann, Kelvin-el al, (lescribeli I sIiitesis del C1-981 y ci interinedio quiral cave (2):
45

0

P

50 CO CM 0

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2

60 EP-A-0 409 281 muestra Æcido R(R*,R
I (fenhiarnino)-carbonill-1 H-pirrol- 1-heptanoico o (2R_trans)_5_(4_fluorofenil)-2-(1-nletiletil- N,4-difeniI- 1-

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[2(tetrahidro_4-hidroxi-6-oxo2II-piran2-il)etil]-1II_pirrol-3-carboxamida; un proceso para su prepara-don y las sales derivadas farrnacØuticainente aceptables.

Acabamos de descubrir de forma sorprendente e imprevista que la atorvastatina puede ser preparada
5 en forma cristalina. De este modo, la presente invención proporciona la atorvastatina en una forina niteva
cristalina design ada Forma I.

La Forma I del hidrato de la atorvastatina consiste en partIculas mÆs pequeæas y una distribucióii
inÆs uniforine del taniaæo que el anterior producto amorfo y muestra caracterIsticas mÆsfavorables (Ic
10 liltrado y secado. Aclicionalmente, la Forma I del hidrato de Ia atorvastatina es iuÆs puray estabie que
ci producto amorfo.

Resumen de la invencidn

15 En consecuencia, la presente invcnción proporciona:

1. La forma cristalina I del hidrato de la atorvastatina (es decir, sal hernicÆlcica del ªcido [R(R*,R*) 1_2_(4_fluorofenil)-I3,_dihidroxi_5_(1_metiietil)_3-fenil-4-(feniiamiflo) carbonil]- IH-pirrol-1-heptanoico) que posee un espectro de difracción de polvo de rayos X que contiene los siguientes
20 valores 20, medidos mediante una radiación CuKa; 19.485 y 21.626;

2. La forma cristalina I del hidrato de atorvastatina segdn ci punto 1, donde ci espectro de clifraccióu
de polvo de rayos X contiene adeniÆs lossiguientes valores 20 medidos mediante una radiación
CuK: 17.075 y 23.734;

25 3. La forma cristalina I del hidrato de atorvastatina segdn el punto 2, donde ci anterior espectro de
difracción de polvo de rayos X contiene ademÆs los siguientes valores 20 medidos mediante una radiación CuK0: 9.150, 9.470, 10.266, 11.853, 21.960, 22.748 y 23.335;

4. La fornia cristalina I del hidrato de atorvastatina, que tiene un espectro de difraccidn de polvo de
30 rayos X que contiene ademÆslos siguientes valores 20 medidos mediante radiación CuK: 9.150,
9.470, 10,266, 10.560, 11.853, 12.195, 17.075, 19.485, 21.626, 21.960, 22.7481 23.335, 23.734, 24.438,
28.915 y 29.234;

5. La forma cristalina I del hidrato de atorvastatina, que tiene un espectro de (hfraccióll de polvo de
35 rayos X que contiene adeniÆs los siguientes valores 20 medidos mediante radiacióii CiiK: 11.853 o
21.960;

6. La forum cristalina I del hidrato dc atorvastatina; caractcrizado per una resonancia magntica nuclear 13 C en estado sólido que posee los siguientes cambios quImicos cxprcsados on partcs por
40 millóii: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5. 127.6,
129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (ainplio), 178.4 y 182.8

7. La forma cristalina, I del hidrato (IC atorvastatina segilu (’ilaiqitidra (IC los 1)11111 OS anteriores (]UC contiene (Ic 1 a 8 moles de agna;

45 8. La forum cristalina I del hidrato de atorvastatina segthi cualquiera de los puntos anteriores que
contiene 3 moles de agua;

9. Una composición farmacØutica que contiene la forma cristalina I del iiidrato de atorvastatina seglin cualquiera de los puntos anteriores mezclada al inenos con on excipiente, un diluyente o un soporte
50 farmacØuticainente aceptable;

10. Una composidion farmacØutica segiin ci punto 9 en forma de comprimidos, pIidoras, grÆnulos dis-persabies, sellos para rnedicamentos, cÆpsulas, poivos, pastillas, supositorios o enemas de retención;

55 ii. El uso de la forma cristalina I del hidrato de atorvastatina segdn cualquiera de los 1)UfltOS 1 a 8 cii
medicina.

Como inhibidor del HI\’IC-CoA, Ia nueva forma cristalina de la atorvastatina es efectiva como agente

60 hipolipidØmico e hipocolesterolØmico.

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Breve descripción de los dibujos

La invención es descrita ademds por los ejemplos no limitativos que se refieren a las figuras anexas 1
y 2, cuyos detalles breves se ofrecen a continuación.
5

Figura I

Difractograina de la forma I del hidrato de atorvastatina molido durante 2 minutos (eje Ys=0) a una intensidad maxima de 3767,50 cuentas por segundo (cps).
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Figura 2

Espectro de la resonancia magnØtica nuclear ’3C en estado sólido con bandas laterales de giro identi-ficadas por tin asterisco de la forms I del hidrato de atorvastatina.
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Descripción detallada de la invención

La forms (ristalina [del hidrato (IC alorvas aIiiia I)Iie(Ie (:ara(;terizarse por ci espectro de (liira(CiOII
de polvo de rayos X y/o por los espectros de la resonancia magnØtica nuclear en estado sólido (NMB).
20

Difracrión de poivo de rayos X

La forma I del hidrato de atorvastatina se caracterizó por sti espectro de diiracción de polvo de rayos
X. [)c cstc inodo, ci espectro dc difracción dc rayos X de la forma I del hidrato de atorvastatina fue
25 medido mediante un difractómetro Siemens 11-500 con una radiación CuKa.

Equipo

Difractóinetro Kristalloflex Siemens 11-500 con una interfaz compatible con IBM, Software DIFFRAC
30 Al’ (SOCABIM 1986,1992).

Rcndijas I y II a V de radiación CuKa (20 mA, 40 kV, As 1.5406 A) cicctrónicaincntc filtradas mediante el detector Psi Peltier de silicona enfriada [Si(Li)] de Kevex (Rendijas: HI at V and IV at 0.15).

Metodo!ogia

Cada dIa se aplica silicona estÆndar para controlarla alineación del tubo de rayos X.

Escaneado acoplado 0/20 continuo: 4,00° a 40,00’ con un Indice de escaneado de 20 de 6°/nun: 03
40 seg/0,04° paso.

Muestra extraIda del vial y presionada en placas de cuarzo de fondo espectral cero en un soporte de
Al. Amplitud de la muestra: 13-15mm.

45 Las muestras se almacenan y utilizan a temperatura ambiente.

Molido/Tamizado

El molido se utiliza para minimizar las variaciones de intensidad en el difractograina mostrado aqul.
50 Sin embargo, si el molido alteraba significativamente el difractograma o aumentaba ci contenido amorfo
de Ia muestra, se utilizaba el difractogrania de Ia muestra no molida. El molido se realizó en un pequefio niortero dc Ægatay con una mano de mortero. El mortero se sujetó durante el molido y se aplicó tins ligera presióu a Ia mano de mortero.

55 La tabla 1 indica los espaciadores d de 20 y las intensidades relativas de todas Ia lIneas en una muestra sin moler con una intensidad relativa dc >20 % para la forma cristalina I del hidrato de atorvastatina. La tabla 1 tambiØn indica las intensidades relativas de las misma lIneas en un difractograrna medido tras
2 minutos de molido. Las intensidades de la inuestra molida durante 2 minutos son niÆsrepreseiitativas

del espectro de difracción sin orientaciOn preferida. Asiinismo, se debe considerar que en esta tabla los
60 ndnieros gerierados por ordenador no estÆn redondeados.

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TABLA 1

lnteri.sidades y ubicaciones del valor md.zimo do toda.s las Ilneas do difraeción eon una intensidad relativa superior at 20 % para
to forma 1 del hidrato de atorvastatina

20 d

Intensidad relativa

(>20%) No molido

Intensidad relativa
(>201/(,)* Molido 2
Minutos

9.150 9.6565 37.42 42.60
9.470 9.3311 46.81 41.94 10.266 8.6098 75.61 55.67 10.560 8.3705 24.03 29.33 11.853 7.4601 55.16 41.74 12.195 7.2518 20.03 21.62 17.075 5.1887 25.95 60.12 19.485 4.5520 89.93 73.59 21.626 4.1059 100.00 100.00 21.960 4.0442 58.64 49.44 22.748 3.9059 36.95 45.85
23.335 3.8088 31.76 44.72
23.734 3.7457 87.55 63.04
24.438 3.6394 23.14 21.10
28.915 3.0853 21.59 23.42
29.234 3.0524 20.45 23.36

* La colunina de la segunda intensidad relativa muestra las intensidades relativas
is de las lIneas de difracción en el difractograma original tras 2 minutos de inolido.

Resonancia magnØtwa nuclear en estado sólido (NMR)

Metodologla
40

Todas las mediciones en estado sólido ’C NMR se lievaron a cabo niediante Un espectróinetro Bruker AX-250, 250 MHz NMR. Los espectros de alta resolución fueron obtenidos utilizando un desacoplamiento do protones de alta potencia y una polarización cruzada (CP) con rotación sobre el dngulo mÆgico(MAS) aproximadamente a 5 kHz. El Ængulo mÆgicofue ajustado utilizando la seæal Br de KBr inecliante la 45 delección de las baiidas laterales, tal y corno fue descrito por Frye y Macid (Frye LT.S. and Macic! G.E., J. Maq. Res., 1982;48:125). Aproximadamente, do 300 a 450 mg de muestras enipaquetadas en tin rotor en Forma (Ic cartiicho fiieroii tit ili’/aAIOS para cada experiirwnto. Las variaci000s ftieroii referenciadas coino tetrakis externo (trinietilsilil)silano (seæal de nietilo a 3.5 ppni) (Muntean J.V. and Stock L.M.,.1.!tloq Res., 1988;2(;:54).
50

La t ably 2 niuestra ci espectro NMR en estado soiido (le iii forrita cristalina 1 (101 hidrato do atorvas-
tatiiia.

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IN

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TABLA 2

20 Afribución del dtomo de carbono y variación qulmica para la
forma I del hidrato de atorvatatina

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Ca2+

Atribución (7 kHz) Variación quImica

C12 o C25 182.8

C12 o C25 178.4

C16 166.7 (amplio)
159.3

Carbonos arornÆticos

C2-05, C13-C18, C19-C24, C27-C32 137.0
134.9
131.1
129.5
127.6
123.5
120.9
118.2
113.8

CS. CIO 73.1
70.5
68.1
64.9

Carbonos de metileno

C6, C7, C9, Cli 47.4
41.9
40.2

C33 26.4
25.2

C34 21.3

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La forma cristalina I del hidrato de carbono de Ia presente invención existe en formas hidratadas. La forma cristalina I del hidrato de atorvastatina contiene airededor de 1 a 8 moles de agua. Preferiblemente, la forma I del hidrato de atorvastatina contiene 3 moles de agua. La presente invención proporciona un proceso para la preparación de la forma cristalina I del hidrato de atorvastatina que comprende la crista-lización de la atorvastatina a partir de una solución en solventes bajo condiciones que producen ci hidrato de atorvastatina en forma cristalina I.

Las condiciones precisas en las que el hidrato de atorvastatina en forma cristalina I es formada pueden
ser empIricamente determinaclas y solamente es posible proporcionar un ndmero de mØtodos que se hayau demostrado apropiados en la prÆctica.

AsI, por ejemplo, el hidrato de atorvastatina en forma cristalina I puede prepararse rnediaiite cris-talización bajo condiciones controladas. En particular, puede prepararse bien a partir de una solución acuosa de la sal bÆsica correspondieiite como por ejeiuiplo una sal del inetai alcalino, por ejeunplo litio,
15 potasio, sodio o siunilares; preferibleunente, la sal sódica por adición de una sal cÆlcicacomo, por ejemplo,
acetato calcico y similares, o inediaiite la suispeIlsionl (Ic la atorvastatina arnorfa en agua. En general, es preferido ci iiso (Ic un sosolvente hidroxIiico comb, por ejeniplo, tin alcanol inferior como ci nielaiiol 3’
sini iiares.

20 Cimando Cl iriaterial de partida para la I)FCI)(I01I (IC lii forma cristalina I (Iesea(ia dcl Illoiralo) de ator-vastatina es una solución de la sal sódica correspondiente, tuna preparación preferida incluye ci trataflhieflt() de una sotución dc la sal sódica on agua que contcnga no menos de alrcdcdor dc 5%, prefcriblcmentc de 5% a 33%, v/v metanol, particularmente preferido airededor de 10% a 155 v/v rnctanol, con una soliición acuosa de acctato cÆlcico, prefcriblcmente a una tcmperatura elevada dc hasta unos 70C tat como, per
25 ejemplo, unos 45-60C, particularmente preferido hasta 47-52’C. Es preferible usar acetato cÆlcico y, en
general, 1 mol dc acetato cÆlcico a 2 moles dc la sal sódica de atorvastatina. Bajo cstas condiciones, Ia forrnación de sal cticica asi como Ia cristalización deberIan ilevarse a cabo a una temperatura elevada, por ejemplo euitre las gamas de temperaturas mcncionadas antcriormcntc. Sc ha cicscubierto que puede resultar ventajoso incluir en la solución de partida una pequeæa cantidad de inetil-terbutilØter (MTBE)
30 tat como, por ejemplo, unos 7% peso en peso. Sc ha visto freciientcmcnte descahic aæadir "semillas" de
la forma cristalina I del hidrato de atorvastatina a la solución de cristalización para producir de manera consistcnte la forma cristalina I del hidrato de atorvastatina.

Cuando el material de partida es amorfo o una combinación de amorfo y de forma cristalina I del
35 hidrato de atorvastatina, la forma cristalina I del hidrato de atorvastatina deseada puede ser obtenida
suspendiendo el sólido en agua conteniendo aproximadamente hasta un 40% v/v tat como, por ejemplo de aproximadamente 0% a 20% v/v, particularmente preferido alrededor de 5% a 15% v/v de cosolvente tat como, por ejemplo, metanol, etanol, 2-propanol, acetona y similares hasta cornpletar la conversion a la forma requerida, seguida por la filtraciOn. Frecuentemente, se ha visto deseable afladir "sernillas" de
40 la forma cristalina I del hidrato de atorvastatina a la suspension para asegurar la conversion completa
a la fornia cristalina I del hidrato de atorvastatina. Alternativamente, tuna costra humedecida en agua cousistente principaimente en atorvastatina amorfa puede calentarse a temperatiuras elevadas tat como, por ejemplo, hasta unos 75C, particularmente preferido alredcdor de 65-70C, hasta que una cantidad significativa de la forma cristalina I del hidrato de atorvastatina estØ presente, a partir de lo cual se puede
45 formar una pasta con la mezcla amorfo/forma cristalina I, tat y como se describe anteriorment.e.

La forma cristalina I del hidrato de atorvastatina es significativamente rnds fdcil de aislar que la ator-vastatina amorfa y puede ser filtrada del medio de cristalización tras ser enfriada 3, lavada y secada. Por ejemplo, el filtrado de una pasta de 50 ml de forma cristalina I del hidrato de atorvastatina se compietó on 10 segundos. kJna muestra de similar tamaiio de atorvastatina amorfa tardó mÆs deuna hora on filtrarse.

Los compuestos de la presente invención pueden ser preparados y administrados en una amplia vane-
dad de formas de dosificaciOn oral y parenteral. Dc este modo, los compuestos de la presente invención pueden ser administrados por inyección, es decir, por via intravenosa, intramuscularmente, por via in-55 subcutÆnea, por viaintraduodenal o intraperitonealmente. Asiniismo, los compuestos de la presente invención pueden ser administrados por inhalaciOn, por ejemplo por via intranasal. Adiciorial-niente, los compuestos de la presente invención pueden ser administrados por via transdØrniica. Send obvio para aquellos expertos en la materia que las siguientes formas de dosificación pueden comprenider como componerite activo, o los compuestos o una sal farmacØuticamente aceptable del comnpuesto de la
60 presente inveiición.

Para preparar composiciones farmacØuticas del compuesto de la presente iiivención los soportes far-

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macØuticamente aceptables pueden ser sóiidos o iIquidos. Las preparaciones en forma sólida inciuyen polvos, coniprimidos, pIldoras, cÆpsulas, selios para medicamentos, supositorios y grÆnulosdispersibles. Un soporte sólido puede ser una o mÆs sustancias quo pueden tambiØn actuar como diluyentes, ageiites aromatizarites, solubilizantes, lubricantes, agentes de suspension, aglutinantes, conservantes, agentes de-
5 siutegrantes o material do encapsulación.

En polvos, ci soporte es un sólido finamente dividido quo se encuentra mezclado con ci componente activo finarnente dividido.

10 En comprimidos, ci componente activo so encuentra mezclado con el soporte quo tiene las propiedades aglutinantes necesarias en las proporciones adecuadas y compactadas on la forma y tainaæo deseaclos.

Preferibleiriente, los polvos y comprimidos contienen del dos o el diez a aproximadamente el setenta
por cieiito del cornpuesto activo. Los soportes adecuados son carboiiato magnØsico, estearat() InagnØsico,
15 talco, azOcar, lactosa, pectina, dextrina, almidón, gelatina, tragacaiito, metilcelulosa, carboximetilcelu-
losa sodica, ima cera (IC l)ajo pilillo (10 fusion, rrianteca (Ic cacao, y siinilares. El lØriiiitio "l)rl)ara(on" se eiitieiide (1110 mci tiye ia ioruiiiilaci(ii del coinpiiesto activo coli ci material (IC eiicapsiilacioii (X)Ti1O tin so-porte (1IiC pro1)orcioiia hUla capsitla cit la (1110 ci (OUIpOTlehIt0 aetiVO, (01) 0 5111 I)tT0S sopoiles, Osta TO(Iea(1O por on soporte, con ci quo, do este modo, se encuentra asociado. Dc forma similar se inciiiyen los sellos
20 para medicanientos y pasti las. Los cornpriniidos, polvos, (:apstiias, pildoras, sollos para i iiedicahrwiltos y
pasti 1 las pueden ser i iti Ii zados en formas do dosi fi cación idas adecuadas para]a adniin istraciOn por via
oral.

Para preparar supositorios, una ccra do bajo punto do fusiOn, como por cjemplo, una mexcia de
25 glicØridos dc Æcidos grasos o manteca do cacao, es derretida y ci componente activo es dispersado ho-
mogØncamcntc on la misma por agitación. Entonces, la mczcla homogØnca fundida es vcrticia on moldes con un tamaæo adecuado, dejada enfriar y consecuentemente solidificada.

Las preparaciones en forma]iquida inciuyen soluciones, suspensiones, enemas de retención y emuisio-
o nos, por ejemplo, agua o soluciones acuosas de propiknoglicoL Para Ia inyección parcntcrai, las prepara-
ciones lIquidas pueden ser formuladas en solución mediante una soluciOn acuosa de polietilenoglicol.

Las soluciones acuosas adecuadas para Ia administración oral pueden ser preparadas disolviendo ci componente activo en agua y aæadiendo los colorantes, sabores, estabilizantes y agentes espesantes ado-
5 cuados de la forma deseada.

Las suspensiones acuosas adecuadas para el uso oral pueden ser producidas mediante La dispersion
en agua del componente activo finamente dividido con un material viscoso, como gomas naturales o sintØticas, resinas, metilcelulosa, carboximetilcelulosa sódica, y otros agentes de suspeilsiOn bien conoci-
40 dos.

Asimisino, se incluyen preparaciones en forma sóiida destinadas a convertirse, justo antes do su uso,
en preparaciones en forma lIquida para la administración oral. Este tipo do formas lIquidas inciuyen soluciones, suspensiones y einuisiones. Estas preparaciones pueden contener, adeniÆs del componente
,15 activo; coloraiites, sabores, estabilizadores, tampones, edulcorantes artificiales y naturales, dispersantes,
espesantes, agentes de solubiiización, y similares.

Preferiblemente, la preparación farmacØutica se produce en forma de dosificación unitaria. En este
tipo de forma, la preparaciOn es dividida en dosis unitarias que contienen las cantidades apropiadas del
50 componente activo. La forma do dosificación unitaria puede ser una preparación empaquetada, en la que
ci paquete contiene poqueæas cantidades do preparación, como comprimidos, cÆpsulas, polvos en frascos o ampollas. Asimismo, Ia forma do dosificación unitaria puede ser una cÆpsuia, compriinido. sello para medicamentos o pastilla, o puede ser Ia cantidad apropiada do cuaiquiera de los mismos en forma enipa-quetada.
55

La cantidad die componente activo en una preparación do dosiflcaciOn unitaria puede ser variada o ajustada do 0,5 a 100 rug, preferiblemente do 2,5 a 80 mg, segiin la aplicación y la potencia del componente activo. La composiciOn tambiØn puede, si se desea, contener otros agentes torapØuticos compatibles.

60 En su uso terapØutico como agonto hipolipidØinico y/o hipocolesteroiØinico, la forma cristalina I del hidrato de la atorvastatina utilizado en ci mØtodo farmacØutico do esta invonción, es administrada en una dosificación inicial do aproximadamente 2,5 a 80 mg diarios. Es preferido un margen do dosis diana de

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aproximadamente 2,5 a 20 mg. Sin embargo, las dosificaciones pueden variar dependiendo de los requi-sitos del paciente, la gravedad de la enfermedad de la que estÆsiendo tratado y del compuesto que estÆ siendo einpleado. La (Ieterminación de la dosificación apropiada en una situación particular se encuentra dentro de la profesioiialidad en este carnpo. Generalmente, el tratamiento es iniciado con dosificaciones mÆs pequeæas, que son inferiores a la dosis optima del compuesto. Posteriormente, la dosificaciOn va aurnentando poco a poco hasta alcanzar el efecto óptimo en dicha circunstancia. Convenienteinente, la dosificaciOn diana total puede ser dividida y administrada en dosis a to largo del dIa, si asI se desea.

Los siguientes eemnplos no lirnitativos ilustran los mØtodos preferidos del inventor para preparar los
10 compuestos de la invenciOn.

Ejeimiplo 1

Sal hemicalcica de Æcido [R-(R*, R*)]-2-(4-flu orofermzl)-/3,5, dihidrojii_5-(1-’rnetiletit)-3-fenil- 4-/(fe7lzlairmi-
15 no)carbonil/-IH-pirrol- l-heptanoico (Formma I del hidrato de atorvastatina)

1’VTe,to(l() A

Una mezcla de

20 2H-piraii-2-il)etil-1 H-prrroi-3-carboxamnida (lad ona (Ic atorvastatina) (Palente de Estados Ufli(IOS N
5,273,995) (75 kg.), nietilterhutilØter (MTBE) (308 kg), metanol (190 L) es hecha reaccioflar con una solución acuosa dc hidróxido de sodio (5,72 kg en 950 L) a 48-58°C durante 40 a 60 minutos para formar la sat sOdica de cicto ahierto. Una vez enfriada a 25-35°C, el estrato orgÆnicoes descartado,.y ci estrato acuoso es nucvamcntc cxtraIdo con M’I’BE (230 kg). El estrato orgÆnico es descartado, y la, solución
25 acuosa de M’lBE dc sal sódica es calentada a 47-52°C. A esta soluciOn se le aæade una solución de
hemnihidrato dc acetato cÆlcico (11,94 kg) disuclto en agua (410 L), durante at rncnos 30 minutos. La mezcla es sembrada con una pasta de la forma cristalina I de la atorvastatina (1,1 kg en 11 L de agua y 5 L de metanol), justo despuØs de la adición de la solución dc acetato cÆlcico. Entonces, la mezcla es calentada a 51-57°C durante at menos 10 minutos, y posteriormente enfriada a 15-40°C. La mezcla es
30 filtrada, lavada con una soluciOn dc agua (300 L) y dc metanol (150 L), seguida dc tin cnjuague con agua
(450 L). El sólido es secado at vaclo a 60-70°C durante 3 a 4 dIas para producir la forma cristalina I de la atorvastatina (72,2 kg).

MØtodo B
35

La atorvastatina amorfa (9 g) y Ia forma cristalina I del hidrato de atorvastatina (1 g) se mezclan a alrededor de 40°C en una mezcla de agua (170 L) y metanol (30 nil) durante on total de 17 horas. La mezcla es filtrada, enjuagada con agua y secada a 70°C bajo presión reducida para producir la forma cristalina I del hidrato de atorvastatina (9,7 g).
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REIVINDICACIONES

1. Forma cristalina I del hidrato de atorvastatina (es decir, sal hemicÆlcica del Æcido [R(R*,R*)I_ 2-(4-fluorofenil)-8,5-dihidroxi-5-(1-metiletil)-3-fenil-4- [(fenilamino)carbonil]-1H-pirrol-1-heptanoico), que 5 posee un espectro de difracción de polvo de rayos X que contiene los siguientes valores 20, medidos me-diante una radiación CuK0 de: 19,485 y 21,626.

2. Forma cristalina I del hidrato de atorvastatina segdn la reivindicación 1, donde ci espectro de difracción de polvo de rayos X contiene ademÆslos siguientes valores 20 medidos usando una radiación CuK: 17,075 y 23,734.3.

3. Forma cristalina I del hidrato de atorvastatina segdn la reivindicación 2, donde el anterior espectro
de difracción de polvo de rayos X contiene ademÆs lossiguientes valores 20, medidos usando una radiación 9,150, 9,470, 10.266, 11.853, 21.960, 22.748 y 23.335.
15

4. Forma cristalina I del hidrato de atorvastatina, que tiene un espectro de difraccióii de polvo de rayos X que contiene ademÆslos siguientes valores 20, medidos usando una radiación CuKa: 9.150, 9.170, 10.266, 10.560, 11-853, 12.195, 17.075, 19.485, 21.626, 21.960, 22.748, 23.335, 23.734, 24.438, 28.915 ’
29.231.
20

5. Forma cristalina I del hidrato de atorvastatina, que tiene un espectro de difracción de polvo de rayos X, que contiene al menos uno de los siguientes valores 20, medidos usando una radiación CuK0:
11.853 21.960.

25 6. Forma cristalina I del hidrato de atorvastatina, caracterizado por una resonancia inagnØtica nu-clear 13C cii estado sólido que posee los siguientes cainbios quIrnicos expresados en panes por rnillóii:

21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (ampl io), 178.4 y 182.8.
30

7. Fonina (rIstalilia I del hidrato (le atorvastatina segi’ni (Iialqluera (le las reiviidIl(aclOTies aiiteriores contenieiido 8 moles (le agua.

S. Forma cristalina I del hidrato de atorvastatina segdn cualquiera de las reivindicaciones anteriores
35 conteriiendo 3 moles de agila.

9. Composicion farmacØutica coniprendiendo la forma cristalina I del hidrato de atorvastatina me7-
dada con al mciios un excipiente, diluyente o soportc farmacØuticamcnte accptablcs.

40 10.Composicion farmacØutica scgdn la rcivindicación 9, en forma dc comprimidos, pildoras, grÆnulos dispersablcs, scllos para rncdicamcntos, cdpsulas, polvos, pastilias, supositorios o enemas de retcnción.

11. Uso dc I forma cristalina I del hidrato dc atorvastatina, segün cualquicra de las reivindicaciones
I a 8 en mcdicina.
45

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NOTA INFORMATIVA: Conforrne a la reserva del art. 167.2 del Convenio de Patentes Europeas (CPE)
y a la Disposición Transitoria del RD 2424/1986, de 10 de octubre, relativo a la
55 aplicacióii del Convenio de Pat cute Europea, las patentes europeas que desiguieii a Espafia y solicitadas antes del 7-10-1992, no producirÆn ningæn cfCct,() en Espaa en
la medida en que confieran protección a productos quImicos y farmacØuticos corno
tales.

60 Esta informacidn no prcjuzga que la patente cstØ o no incluida en la mencionada
reserva.

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86 Nimero de solicitud europea: 96924367.4
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Fecha de publicación de la solicitud: 24.06.1998

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TItuIo: Forma cristaliria III de la sal hemicÆlcica del Æcido (R_(R*,R*))2_(4_fluorofenil)_/3_di hidroxi-5-(1-metil-etil)-3-fenil-4-((Fenilamino)carbonil)-1H-pirrol-1-heptanoico (atorvastati-
na).

Prioridad: 17.07.1995 US 601454

Fecha de la publicación de la menci6n BOPI
16.04.2002

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'Titular/es: WARNER-LAMBERT COMPANY
201 Tabor Road
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motivada; sólo se considerar6 cot-no formulada una vez que se haya realizado el pago de la tasa de
oposición (art. 99.1 del Convenio sobre concesión de Patentes Europeas).

Vent de fescielos Ofldna EspaioIa de Patentee y Mareas. C/Paaam, 1 - 28036 Madrid

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DESCRIPCION

Forma cristalina III de Ia sal hemicÆlcica delÆcido IR-(R*,R*)I-2-(4-fluorofenj1)-I-o-dihidroxi-5(1rne til_etil)_3-fenil_4_ [(fenilamino)carbonil]_ 1H-pirrol- 1-heptanoico (atorvastatina).
5

Estado de la tcnica

La presente invención se refiere a una forma nueva cristalina de atorvastatina, que es conocida por el nombre quImico de sal hernicÆlcicade Æcido[R(R*,R*)]-2-(4-fluorofenil)-/3,ö,dihidroxi-5-(1-metiletil)-3-fe-
10 nil-4-[(fenilarnino)carboiiil]_ 1H-pirrol- 1-heptanoico corno agente farrnacØutico, a los inØtodos para su pro-
ducción y aislamiento, a las coniposiciones farrnacØuticas que incluyen este compuesto, a un soporte farina-cØuticamente aceptable y a los mØtodos farinacØuticos de trataniiento. El compuesto cristalino nuevo de la presente invención es efectivo como inhibidor de la enzima 3-hidroxi-3-metilglutaril-coenzima A reductasa (reductasa de HMG-CoA) resultando de este moclo efectivo coino agente hipolipidØinico e hipocolestero-
15 lØniico.

La patente de Estados Unidos ndmero 4.681 893 que se incorpora en la presente corno referencia, inuestra ciertas trans-6-[2-(3 o 4-carboxamido-sustituidas-pirrol-1-il)alquil]-4--hidroxi-piran-2-onas que in-cluye trans (–)-5-(1-fluorofenil)-2_(1_metiletil)_N,4-difenil- 1-F(2-tetrahidro-4-hidroxi-6-oxo-2H-piran-2-il)-
20 etill- IH-pirrol-3.-carboxarnida.

La patente de Estados Unidos ndrnero 5,273,995 que se incorpora a la presente como refereiicia, muestra ci enantióinero que tiene forma la R del Æcido deciclo abierto de trans-5- (4_fluorofenil)_2-(1-me-tiletil)-N,4-difenil-1- [(2-tetrahidro-4-hidroxi-6-oxo-2H-piran-2-ii)etil]-1H-pirrol-3-carboxamida, es clecir,
25 Æcido [R_(R*,R*)]_2_(l-fluorofenil)-/3,5-dihidroxi-5-(1-metiletil)-3-fenil-4- [(fenilamino)carboiiil]-1H-pirrol-
1 H-iieptanoico.

Las pateiites de Estados Unidos niimero 5.003.080; 5.097 045; 5.163,024; 5.124.482; 5.119.837; 5.155.251: 5.216.174; 5.245.047; 5.248.793 5.280.126; 5.397.792 y la, lilliflerO 5.342.952, qiw se in(-or-
30 poran eli in presente como refereiicia, niuestrau varios procesos y los productos iiiterniedtos para preparar
la al,orvastatina.

La atorvastatina es prepara(la coilS) sti sal calcica, es (ICcir, sal cÆlcica de iicido [R-(R *,E *_)1_2_(4_ fluorofenil)-ö-dihidroxi-5-(1-metiletil)_3_fenil_4- [(fenilamino)carbonil]-IH-pirrol-1-heptanoico (2:1). La
35 sal cÆlcica es aconsejable puesto que permite que la atorvastatina se enduentre convenientemente for-
mulada en, por ejemplo, pastillas, cÆpsulas tabletas polvos, y similares para la aclministración oral. Adicionalmcntc, existe la necesidad de prodiicir atorvastatina en una forma piira y cristalina, que facilite que las formulacioiies cumplan con los requisitos y las cspccificacionCs farmacØuticas exactas.

40 AdcniÆs, ci proceso por el quo Ia atorvastatina es producida, dcbc ser capaz dc Ilevar a cabo una producción a gran escala. Adicionalmentc, es convenicntc quo el producto so encucntre de mancra quo permita una fÆcil filtración y secado. Finalmcntc, es económicamcntc aconsejahlc que ci producto perma-nczca CstabiC durantC largos perIodos do ticmpo, sin ncccsidad de contar con unas condicioncs CspCcificas
dc aimaccnamicnto.
45

Los procesos mencionados anteriormente en las patentes de los Estados Unidos, muestran una ator-vastatina arnorfa que posee unas caracterIsticas de filtración y de secado inadecuadas para ser proditcida
a gran escala, y que dehe ser protegida del calor, la iuz, el oxIgeno y la huinedad.

50 WO-A-94/16693 muestra una composición farmacØutica oral para tratar Ia hipercolesterolemia o hi-perlipidemia que contiene una forrnulación ventajosa para estabilizar ci inhibidor A de la coenzinia 11MG-CoA, el Hemicalcio (’1-981 de la formula (IA) con cantidades eficaces de carhonato cOicico.

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(IA)

US-A-5 316 765 muestra un mØtodo para perfeccionar la reducción de la coenzima Qio en pacientes
que padecen rniocardiopatIa y que reciben un inhibidor de Ia IIMG-CoA reductasa, ciue incluye la admi-20 nistración simultÆnea de dicha coenzirna Qio inhibidora de la HMG-CoA reductasa, en una concentración suficiente para elevar el mvel de suero de la coenzirna Qio por lo menos en 2.0 pg/mi, en el que al igual que en el mnencionado inhibidor de HMG-CoA reductasa pueda utilizarse ci CI-981 con la siguiente formula:

HO 25
O2 Ca112

LOH

30 F(J

35

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C
Tetrahedron Letters, Vol. 33, N. 17, pp. 2283-2284, 1992, Baumann, Kelvin et al, describe la sIntesis
del C1-981 y ci intermedio dave quiral (2):

091 an e

5 0CN M

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55

EP-A-0 409 281 muestra 6cido [R(R*,R’)]-2(4-fluorofenil)-3-dihidroxi-5-(1-metiietil)-3-fenii-4-[(fe-niiarnino)carbonil]- 1H-pirroi- 1-heptanoico o (2R-trans)-5- (4-fluorofcnil)-2- (1-mctiletil)-N,4-difcnil- 1- [2-(tetrahidro-4-hidroxi-6-oxo-2-piran-2-il)etil]-1-pirroi-3-carboxamida; ml proceso para su preparaciOn y las

sales derivadas farmacØuticarnente aceptables. 60
Acabamos de descubrir de forma sorprendente e imprevista, que la atorvastatina puede ser preparada
en forma cristalina. Dc este inodo, la presente invención proporciona la atorvastatina en una forma nueva

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cristalina designada forma III. La forma III de la atorvastatina posee unas caracterIsticas fIsicas diferentes con respecto at anterior producto amorfo.

Resumen de la inveneión

En consecuencia, la presente invención proporciona:

1. La forma cristalina III del hidrato de atorvastatina (es decir, sal hemicÆlcica del dcido [R(R*,R)] 2-.(4-fluorofenil)-i3,ö-dihidroxi-5-(1-metiletii)-3-fenil-4- [(fenilamino)carbonil]- 1H-pirrol- 1-heptanoi-
10 co), que posee un espectro de difracción de polvo de rayos X que contiene los siguientes valores 20,
medidos inediante una radiación CUKQ de: 8,451 y 19,984;

2. La forma cristalina III del hidrato de atorvastatina segdn ci punto 1, doride ci espectro de difracción
de polvo de rayos X contiene adeinÆs los siguientes valores 20, medidos mediante una radiación CuK

1.5

de: 16,619, 20,294 y 24,405;

3. La forma cristalina III del hidrato de atorvastatina segdn e] punto 2, donde el anterior espectro
de difracción de polvo de rayos X contiene ademÆs lossiguientes valores 20, medidos mediante una radiación Cu1(, 4,123, 17,731 y 18,267;

20 4. La forma cristalina III del hidrato de atorvastatina, que tiene un espectro de difracciOn de polvo
de rayos X que contiene adernÆslos siguientes valores 20 medidos mediante la radiación CuKa de:
4,123; 4,993; 5,768; 7,670; 8,451; 15,962; 16,619; 17,731; 18,267; 18,870: 19,480; 19.984; 20,294;
21,105; 21,670; 23,318; 24,405; 24,967 y 25,397;

25 5. La forma cristalina III del hidrato de atorvastatina que tiene un espectro de difracción de polvo
de rayos X, que contiene at menos uno de los siguientes valores 20, medidos utilizando La ra(liación
CuK, de: 16,619 o 19,984.

6. La forma cristalina III del hidrato de atorvastatina, caracterizado per una resonancia magnØtica
30 nuclear 13C en estado sólido que posee los siguientes cambios quImicos expresados en partes por
millón:

19,9; 22,1; 24,1; 27,0; 35,4; 40,4; 44,1; 65,6; 67,3; 69,8; 114,9; 117,2; 122,2; 124,3; 128,9; 131,8:
135,2; 140,1; 161,0; 166,7 y 184,9;

3.5 7. Una composición farmacØutica que contiene la forma cristalina III del hidrato de atorvastatina,
segdn cualquiera de los artIculos anteriores, mezclada con at menos un excipiente, un diluyente o
tin soporte farmacØuticamente aceptable;

8. Una composiciórl farmacØutica segdn el artIculo 7 en forma de comprimidos, pIldoras. grÆnulosdis-

40 persables, sellos para medicainentos, cÆpsulas, polvos, pastillas,supositorios o enemas de retención;

9. Uso (IC la forma cristalina III del hidrato de atorvastatina, segdn cualquiera de los puntos 1 a 7 en medicina.

45 Como un inhibidor del HMG-CoA, la nueva forma cristalina de la atorvastatina es efectiva coino
agente hipolipidØmico y hipocolesterolØmico.

Breve descripción de los dibujos

50 La invención es descrita ademÆs per los ejemplos no limitativos que se refieren a las figuras aiiexas I
a 2 cuyos detalles breves se ofrecen a continuación.

Figural Difractograma de la forma III del hidrato de atorvastatina (eje Y=-0) a una inlensidad maxima
de 2815 cuentas por seguiidos (cps).

55 Figura 2 Espectro de la resonancia magnØtica nuclear 13C en estado sólido con bandas laterales (Ic
giro identificadas por el asterisco de la forma III del hidrato de atorvastatina.

Descripción detallada de la invención

60 La forma cristalina Ill del hidrato de atorvastatina puede caracterizarse por el espectro de difracción
de polvo de rayos X y/o por los espectros de Ia resonancia magnØtica nuclear en estado sólido (NMR).

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Difracción de polvo de rayos X

Hidrato de atorvastatina en forma III

El hidrato de atorvastatina se caracterizó por su espectro de difracción de polvo de rayos X. De este inodo ci espectro de difracción de rayos X de la forma III de la atorvastatina fue inedido mediaute tin difractómetro Siemens D-500 con una radiación Cuk.

Equipo
10

Difractómetro Kristalloflex Siemens D-500 con una interfaz compatible con IBM, software = Dl-FFRAC AT (SOCABIM 1986, 1992).

Rendijas I y II a F de radiación CuK (20. mA, 40,cvA=1; 5406 A) eleclróuicauieiite liltradas
15 mediante ci detector Psi Peltier de silicona enfriacia [Si(Li)1 de Kevex (Rendijas: 111 a 1 y IV a 0,15).

[tie todoiog’ia

Cada dIa se aplica silicomia estÆiidar para controlar laalineación del tubo de rayos X.
20

Escaneado acoplado 20 continuo 4,00 a 40,00 con un Indice de escaneado de 20 de 6/min: paso 0,4 scg/0,04

Muestra extralda del vial y prcsionada en piacas dc cuarzo de fondo cspectral ccro en tin soporte de
25 Al. Amplitud de la muestra 13-15 mm.

Las muestras son almacenadas y utilizadas a temperatura ambiente.

La tabla 1 indica los espaciadores d de 20 y las intensidades relativas de todas las lIneas en una
30 mucstra sin moler con una intensidad relativa superior a! 25% para la forma cristalina Ill del hidrato de
atorvastatina. Asimismo, se debe considerar que en esta tab]a los ndmeros generados por ordenador no estÆn rcdondcados.

TABLA 1

35 Intensidades y ubicaciones del valor md,ximo de todas las lIneas de difraccion con una intensidad relativa superior at 25 % para to forma III del hidrato de atorvastatina

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20 d Intensidad relativa (>25 %)

4,123 21,4140 49,20
4,993 17,6832 30,82
5,768 15,3099 28,69
7,670 11,5173 25,49
8,451 10,5173 100,00
15,962 5,5478 32,59
16,619 5,3298 62,34
17,731 4,9981 49,29
18,267 4,8526 45,12
18,870 4,6989 39,52
19,480 4,5531 36,59
19,981 1,1393 70,31
20,294 4,3722 69,54
21,105 4,2061 37,69
21,670 4,()976 36,5()
23,318 3,8117 38,63
24,405 3,6442 65,54
24,967 3,5635 27,20
25,397 3,5041 33,75

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MetodologIa

Todas las mediciones en estado sólido 13c NMR se lievaron a cabo mcdi ante un espectrómetro Bruker AX-250, a 250 NMR MHz. Los espectros de alta resolución fueron obtenidos utilizaiido un desacopla-5 miento de protones de alta poteiicia y una polarización cruzada (CP) con rotación sobre el Ængulo mÆgico (MAS) a aproximadamente 5 kHz. El Ængulo mÆgicofue ajustado utilizando Ia seæal Br de KBrmediante la detección de las bandas laterales, tal y como fue descrito por Frye y Macid (Frye J.S. y Maciel G.E. J. Maq. Res. 1982; 48:125). Aproximadamente, de 300 a 450 mg de muestras empaquetadas en un rotor en forma de cartucho fueron utilizadas para cada experimento. Las variaciones qulmicas fueron 10 referenciadas como tetrakis externo (trimetilsilil)silano (serial de metilo a 3,50 ppm) (Muntean J.V and Stock L.M., J. ilIag. Res. 1988; 76:51).

La tabla 2 muestra el espectro NMR en estado sólido de la forma cristalina III del hidrato de at.or-vastathia.
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20 1

29 27

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2

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F

Md

2

Ca2

35 TABLA 2
Atrihución del dtomo de carbono y variación qwImica para la forma III del hidralo de atorvaslatina

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Atribución Variación quImica

Banda lateral de giro 214,8
209,3
202,3

C12 o C25 184,9

C12 o C25 166,7

C16 161,0 (dØbil, amplio)

Carhorios aromÆti cos
C2-05, C13-C18, C19-C24, C27-C32 140,1
135,2
131,8
128,9
121,3
122,2
117,2
114,9

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TABLA 2 (Continuación)

Atri5uci6n del Ætomo de carbono y variación qulmica para la forma 111 dcl hidrato de atorvastatina

Atribucióii Variación quImica

C8, ClO 69,8
67,3
65,6

Carborios de metileno
C6, C7, C9, Cli 44,11
40,4
35,4

C33 27,0
24,1

C34 22,1
19,9

25 La forma cristalina III del hidrato de atorvastatina de la presente invención existe en formas hidrata-
das.

Asimismo, la presente invención proporciona un proceso para la preparacióri de la forma cristalina 111
del hidrato de atorvastatina, que comprende la exposición de la atorvastatina a una humedad relativa
30 alta, bajo condiciones que producen ci hidrato de atorvastatina en forma cristalina Ill.

Las condiciones precisas en las que la atorvastatina cii forma cristalina III es forrnada pueden ser empiricamente determinadas y solamente es posible proporcionar un mØtodo que se haya deinostrado

35 apropiado en la prÆctica.

AsI, por ejemplo, cuando ci material de partida es la forma cristalina III de la atorvastatina descrita
cii la solicitud de patente de Estados Unidos litulada: "sal cÆicica cristalina de dcido LR-(R,R)1-2-(4-fluorofenil)-0,6-dihidroxi-5-(1-metiietil)-3 -fenii-4- F(feniiamino)carbonill- 1H-pirrol-1-heptanoico (2:1)" (Ic propiedad compartida, referenda del represenlaiite PD-5250-01-FUT iidmero de serie 08/945 812, en la
40 actualidacl US-A-5 969 156 (las formas cristaiinas III y IV de la atorvastatina estÆutanibiØn descritas cii
esta sol ci Itid), là forma cristalina Ill deseada de la atorvastatiria piled(’ ser obleiiida expoiiiend() el sol 1(10
it una, hurnedad relativa de un 95% dumrante 11 dIas.

La forma cristalina II de la atorvastatina puede ser obtenida a partir de urn amorfo, de una combi-
45 iiacióu (IC urn amorfo y (IC inia forma cristalina I (IC la alorvastalitia. As(, por ejenuIpiO, cuando el niaterial
de partida es amorfo, o irna comhinación de amorfo y de forma 1, o la forma cristalina I de là atorvas-tatina, la forma cristalina 11 descada de la atorvastatina puede ser obtenida suspendiendo ci sólido en metanol conteiiiendo aproximadamente de urn 40 it un 50% de aguia hasta completar la conversion de la

.50

forma requerida seguicio de filtración.

La forma cristalina 1 de Ia atorvastatina puede ser preparada mediante cristalizaciOn bajo condiciones controladas. En particular puede ser preparada it partir de una solución acuosa de la, sal hdsica corres-pondicnte como por ejcmplo, una sal del metal aicalino, por ejcinpio, litio, potasio, sodio, o sinijiares; ainonio, o una sal de amina; preferihiemente, Ia sal sódica por adición de una sal cÆlcica como per ejem-
55 plo, acctato cÆlcicoy simiiarcs, o mediante la suspension de la atorvastatina amorfa en agua. En general,
es preferido ci uso de on cosoivente hidroxIlico como por ejeniplo, un aicanol inferior como ci metanoi y
simil arcs.

El compuesto de la presente inivención puede ser preparado y administrado en una amnplia variedad de
60 formas de dosificaciOri oral y parenteral. Dc este modo, el compuesto de la presente invención puede ser
administrado por inyecciOn, es decir, por via intravenosa. intraniuscularmente, por via intracutÆnea,sub-cutimnea, per via intraduodenal o intraperitonealmente. Ashnisrno, ci compuesto de la presente inveneiOn

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puede ser administrado per inhalación, por ejemplo, por via intranasal. Adicioiialniente, ci compuesto de la presente invención puede ser administrado por via transdØrmica. SerÆ obviopara aquellos expertos en la niateria, que las siguientes formas de dosificación pueden comprender como componente activo, o los compuestos o una sal farmacØuticarnente aceptable correspondiente del compuesto de la presente
5 invención.

Para preparar composiciones farmacØuticas del coinpuesto de la presente inveiición los soportes far-rnacØuticamente aceptables pueden ser sólidos o liquidos. Las preparaciones en forma sólida inciuyen polvos, comprimidos, pIldoras, cÆpsulas, sellos para medicamentos, supositorios y grÆnuios dispersibles. Un soporte sólido puede ser una o nia sustancias que pueden tainbiØn actuar como diluyentes, agentes aromatizantes, solubilizantes, lubricantes, agentes de suspension, agiutinantes, conservalites, agentes dc-siiitegrantes o material de encapsulacióii.

En P0tV0S, ci soporte es un sólido finameuite dividido que se euicuentra iiiezciado con el coinponente
15 activo finament e dividido.

En J)astill as, ci componente activo se enciieiitra inezci 11(10 (On Cl soporte (lIIC 11(9 ic las propie(1a(ivs agliitiiiantes necesarias en las proporciorles adecuadas y coinpactadas CII Ia fornia y lallIatI() deseiuk)s.

20 Preferibieuneiile, los poivos y pastilias contienen del (los o ci (liez a aproxiiriadainente ci setejita por
ciento del compuesto activo. Los soportes adecuados son carhonato magnØsico, estearato magnØsico, talco, azdcar, lactosa, pectina, dextrina, almidón, gelatina, tragacanto mctiicciuiosa, carboximetilcelu-losa sOdica, una cera dc hajo punto dc fusion Manteca dc cacao, y similares. I-il tØrrnino "preparación"
so coticude quo incluyc la formulación del compuesto activo con ci material dc cncapsulación como un
25 soporte que proporcione una cÆpsuia en Ia que ci componente activo, con o sin otros soportes, estÆ ro-
dcado por un soportc, con ci quo, dc cstc modo, se cncucntra asociado. Dc forma similar se incluycn los sellos para unedicaunentos y tabietas. Las pastillas, polvos, cÆpsulas,sellos para medicamentos y tahletas pueden ser utilizados on formas dc dosificación sólidas adecuadas para la administración por via oral.

30 Para preparar supositorios, una cera de bajo punto dc fusiOn, como pot cjernplo, una inczcla dc
giicØridos de Æcidos grasos o manteca dc cacao, es derretida y ci componente activo es dispersado homo-gØneamcntc on là misma por agitación. Entonces, la mczcla homogØnca fundida Cs vertida on moldes con un tamaOo adecuado, dejada enfriar y consecuentemente solidificada.

35 Las preparaciones on forma IIquida incluyen soluciones, suspensiones, enemas de retención y eniulsio-
ules, por ejeunplo, agua o soluciones acuosas dc propilenoglicol. Para la inyecciOn pareuiteral, las prepara-ciones liquidas pueden ser formuladas en solución mediante una soiución acuosa de polietileuuoglicol.

Las soluciones acuosas adecuadas para la administración oral pueden ser preparadas disolviendo ci
40 componente activo en agua y aæadiendo los colorantes, sabores, estabilizantes y agentes espesantes ade-
cuados de la forma deseada.

Las suuspensiones acuosas adecuadas para ci uso oral pueden ser producidas mediante la dispersion en
agua del componente activo finamente dividido con un material viscoso, como gonias naturaies o sintti-cas, resinas, metilcelulosa carboxiinetilcelulosa sOdica, y otros agentes dc suspension bien conocidos.

Asimisnio, se inciuyen preparaciones en forma sólida que estÆn creadaspara convertirse, justo antes dc
sit uso, en preparaciones on forma lIquida para la adrninistración oral. Este tipo dc formas lIquidas inclu-yen soluciones, suspensiones y emulsiones. Estas preparaciones pueden contener ademÆs del componente
o activo, colorantes, sabores, estabilizadores, tampones, edulcorantes artificiales y naturales dispersantes,
espesantes, agentes de solubilizaciOn, y similares.

Preferiblemente, la preparación farmacØutica se produce en forma dc dosificación unitaria. En este
tipo de forma. la preparaciOn es dividida en dosis unitarias que contienen las cantidades apropiadas (id
55 componente activo. La forma de dosificación unitaria puede ser una preparación eunpaquetada. en la
que ci paquete contiene pequeOas cantidades dc preparaciOn como pastillas, cÆpsulas, polvos on frascos o ainpoilas. Asimismo Ia forma de dosificación unitaria puede ser una cÆpsula, pastilla, sello para medica-nientos o tableta, o puede ser la cantidad apropiada de cualquiera de los mismos en forma empaquetada.

60 La cantidad de componente activo en una preparaciOn de unit dosis puede ser van a(la o ajust ada (IC
0,5 a 100 mg, preferihiemente de 2,5 a 80 mg, segOn la aplicación y la potencia del componente activo. La composición tambiØn puede, si se desea, contener otros agentes terapØuticos compatibles.

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En su uso terapØutico corno agente hipolipidØmico y/o hipocolesterolØrnico, la forma cristalina III del hidrato de la atorvastatina utilizado en el mØtodo farinacØutico de esta invención, es administrada en una dosificación inicial de aproxirnadarnente 2,5 a 80 mg diarios. Es preferido un margen de dosis diana de
5 aproximadaniente 2,5 a 20 mg. Sin embargo, las dosificaciones pueden variar (lepelidienclo de los requi-
sitos del paciente, la gravedad de La enfermedad de la que estÆ siendo tratado y del compuesto que estÆ siendo empleado. La deterrninación de la dosificación apropiada en una situación particular se encijeutra dentro de la profesionahdad en este cainpo. Generalmente, e1 tratarniento es iniciado con dosificaciones mÆs pequeæas, que son inferiores a la dosis optima del compuesto. Posterionnente, la dosificación va
10 aumentando poco a poco hasta alcanzar el efecto óptimo en dicha circunstancia. Convenientemeute, la
(losificacion diana total puede ser dividida y adrninistrada en dosis a to largo del dIa, si asI Se desea.

Los siguientes ejeinpios no limitativos ilustran los mØtodos prefenidos del inventor para preparar los cOnipUeslOs de la invenciOn.
15

Ejeiriplo I

Sal he’ffliC(RCiLO de (icidO
no)earhonil]- I 1-1-pzrroi- 1 -heptanoieo (Forma. I de la atorvastatina)
20

Una rnezcla de (2H_trans)-5-(4_fluiorofenil)-2_(1_met,iletil)_N,4_difenil-1-F2-(tetrahidro-4-hidroxi-6-ox(>- 2H-piran-2-il)etilj-1H-pirrol-3-carboxamida (lactona de atorvastatina) (Patcntc dc Estados I’iiidos N 5,273,995) (75 kg.), metilterbutileter (MIRE) (308 kg), inetanol (190 L) es hecha reaccionar eon una solución acuosa de hidróxido dc sodio (5,72 kg en 950 L) a 48-58CC durante 40 a 60 minutos para forniar
25 Ia sal sOdica de ciclo abierto. Una vez enfriada a 25-35C, el estrato orgÆnicoes descartado, y el estrato
acuoso cs nucvamcntc extraido con MTBE (230 kg). EL estrato orgÆnico cs dcscartado, y Ia so!ución acuosa de MIHE de sal sódica es ealentada a 47-52’’. A esta solución se le aæade una solución de hemihi-drato de acetato cÆlcico (11,94 kg) disucito on agua (410 L), durante at menos 30 minutos. La mczcla es sembrada con una pasta de Ia forma cristalina I de La atorvastatina (1,1 kg en II L de agua y 5 L de
30 inetanol) jiisto dcspuØs de la adición de Ia solución de acctato cÆlcico. Entonces, la inczcla es calentada
a 51-57’C durante at menos 10 minutos, y posteniormente enfriada a 15-46C. La mezcla es filtrada, lavada con una soluciOn de agua (300 L) y de metanol (150 L), seguida de un enjuaguc con agua (450 L). El sOlido CS secado at vacIo a 60-70C durante 3 a 4 dIas para producir Ia forma cristalina I de la atorvastatina (72,2 kg).
35

Ejemplo 2

Sal hemicÆlcica de Æcido/R(R* dihidroxi-5-(J-metiletil)-3-fenil-/(fenilamino)- carbonilJ-IH-pirrol-J-heptanoico (Forma II de la atorvastatina)
40

Uria mezcla de la forma amorfa y cristalina I de la atorvastatina (100 g) fue suspendida en una mezcta
de metanol (1200 inL) y agua (800 mL), y agitada durante 3 días. El material fite filtrado y secado a 70-C bajo presiOn reducida para producir la forma cristalina II de la atorvastatina.

5 Ejemplo 3

Sal hemiedleica de deido /R(R*,R)J-2-(4-fluorofenil)-3,ö. dihidroxi-5-(1-metileiil)-4-fenil-i-/(feniiami-no)carbonil]-JH-pirrol-1-hepianoico (Forma III del hidrato de Ia atorvastatina)

50 La forma II de la atorvastatina (Ejemplo 2) es introducida a travØs de un filtro de malla del 50 hasta un flltro de nialla del 100 y expuesta en una botella hinnidificadora a una hurnedad relativa del 95 5 durante 11 dIas para producir la forma cristalina III del hidrato de la atorvastatina.

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REIVINDICACIONES

1. Forma cristalina III del hidrato de atorvastatina (es decir, sal hemicÆlcica del Æcido IR(R*.B*)J
2- (4-fluorofenil)-/3,ö.dihidroxi-5-(1-rnetiletil)-3-fenil-4-t(fenilamino)carbonilj- 1H-pirrol- 1-heptanoico), que
5 posee un espectro de difracción de polvo de rayos X que contiene los siguientes valores 20, medidos me-
diante una radiación CuK de: 8,451 y 19,984.

2. Forma cristalina III del hidrato de atorvastatina segün Ia reivindicación 1 donde ci espectro de difracción de polvo de rayos X contiene ademÆslos siguientes valores 20, medidos usando una radiación
10 CuK0 de: 16,619, 20,294 y 24,405.

3. Forma cristalina III del hidrato de atorvastatina segün la reivindicación 2, donide el anterior espec-
tro de difracción de polvo de rayos X contiene ademÆslos siguientes valores 20, inedidos mediante una radiación CuK0: 4,123, 17,731 y 18,267.
15

4. Forma cristalina III del hidrato de atorvastatina que tiene un espectro de difracción de polvo de rayos X que contiene adernÆs lossiguientes valores 20 medidos mediante la radiación CuK de: 4,123; 4,993; 5,768; 71670; 81451; 15,962; 16,619; 17,731; 18,267; 18,870; 19,480; 19,984; 20,294; 21,105; 21,670; 23,318; 21,405; 24,967 y 25,397.
20

5. forma cristalina III del hidrato de atorvastatina que tiene un espectro de difraccióii de polvo dc rayos X que contiene al nienos uno de los siguientes valores 20, medidos utilizando la radiación CUKa de: 16,6196 19,984.

25 6. Forma cristalina III del hidrato de atorvastatina caracterizado por una resonancia inagiiØt.ica nuclear 13C en estado sOlido que posee los siguientes cairibios quIrriicos expresados en partes por rnillOn:

19,9; 22,1; 24,1; 27.0; 35,4; 40,4; 44,1; 65,6; 67,3; 69,8 114,9; 117,2; 122,2; 124,3; 128,9; 131,8; 135,2; 140,1; 161,0; 166,7; y 184,9.
30

7. (oinposición faniriacØtitica que c()nI.Iene la forma cristalina. 111 (lei lii(IraI() (Id aiorvasl.atiiia. segliii (Ilalqilidra (le las rd vindicaciones aiil eriores. irle’/(lada (oh al irienios III eX(-Ip;f-TIte, 1111 (Iii iiyeuite o un soporte farii iaceuticanieiite acept able.

35 8. Corn posición farrnacØutica seg6n la reiviridicación 7, on forma de eomprimidos, pIldoras, grÆniilos dispersables, sellos para medicamentos, cÆpsulas, polvos, pastillas, supositorios o enemas de retención.

9. 1so dc la forma cristalina 111 del hidrato de atorvastatina, scgün cualquicra de las rcivindicaciones
1 a 7 en medicina.
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NOTA INFORMATIVA: Conforme a la reserva del art. 167.2 del Convenio de Paterites Europeas (CPE)
y a la Disposicidn Transitoria del RD 2424/1986, de 10 de octubre, relativo a la
55 aplicación del Conveiiio de Patente Earopea, las patentes europeas que desigiieii a
Espaæa y solicitadas antes del 7-10-1992, no producirIn ningu’ln cfeet,o en Espaæa en
la medida en que confieran protección a productos quImicos y farmacØuticos como
tales.

60 Est,a iniformacidn no prejusga que la patente estØ o no incluIda en la mencionada
reserva.

10