

FORMULARIO ÚNICO DE OPOSICIÓN

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OPOSICIÓN A:

☒ ☐ ☐ ☐ ☐

Patente de Invención.
Patente de Modelo de Utilidad.
Diseño Industrial.
Esquema de Trazado para Circuitos Integrados.
Marcas de Productos o Servicios.

☐ Marca Colectiva.
☐ Marca de Certificación.
☐ Lema Comercial.

②

SOLICITUD
PUBLICADA

Numero del expediente: 03-107810
Solicitante: Warner Lambert Company LLC
Apoderado: _____
Título de la nueva creación o denominación del signo: Forma de la línea
de la caja de calcio del ácido ER-(R*, R*) 2-4
Gaceta: N° 538

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: <u>Procaps S.A</u> Dirección: <u>Calle 80 N° 78B-201</u> <u>Barranquilla.</u> Nacionalidad o Domicilio: <u>Colombia.</u> Lugar de Constitución: <u>B/guilla.</u> Teléfono: <u>3789000</u> Fax: <u>3533949</u> E-mail: _____	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>890106527-5</u>
REPRESENTANTE O APODERADO	Nombre: <u>Luis Fernando Pincon</u> Dirección: <u>Calle 115 A N° 53-99</u> <u>BOGOTÁ</u> Teléfono: <u>6133418</u> Fax: <u>6133374</u> E-mail: _____	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>79532197 P 113438</u>

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: FALTA DE REQUISITOS DE POTABILIDAD
Signo opositor: _____
Justificación: EXPUESTO EN EL DESARROLLO DE LA
PRESENTE OPOSICION

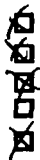
⑤ Comprobante de pago No.

50621

Fecha

11/06/2007

⑥ ANEXOS



Comprobante de pago de la tasa.

Poderes, si fuere el caso.

Pruebas de los fundamentos de la oposición.

Documentos que acrediten el legítimo interés, si fuere el caso.

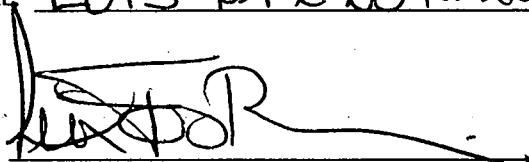
Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE:

Luis Fernando Rincón

FIRMA:



C.C. 79532181 TP. 113438

Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia: Expediente N° 03-107810
Asunto: Oposición a la solicitud de patente de
Invención titulada "**FORMAS**
CRISTALINAS DE LA SAL DE
CALCIO DEL ACIDO [R-(R*,R*)]-
2-(4-FLUOROFENIL)-β, O-
DIHIDROXI-5-(1-METILETIL)-3-
FENIL-4-[(FENILAMINO)
CARBONIL] - 1H- PIRROL-1-
HEPTANOICO(2:1)"
Solicitante: **WARNER-LAMBERT COMPANY**
LLC.
Opositora: **PROCAPS S.A.**

Publicada en la Gaceta de la Propiedad Industrial
N° 538 del 31 de marzo de 2004

Yo, Luis Fernando Rincón Cuellar, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad PROCAPS S.A. conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "FORMAS CRISTALINAS DE LA SAL DE CALCIO DEL ACIDO [R-(R*,R*)]-2-(4-FLUOROFENIL)-β, Õ-DIHIDROXI-5-(1-METILETIL)-3-FENIL-4-[(FENILAMINO)CARBONIL]-1H-PIRROL-1-HEPTANOICO(2:1)", solicitada por WARNER-LAMBERT COMPANY LLC., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

2. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de la sociedad que represento, radicado básicamente en la comercialización que mi representada efectúa de una presentación farmacéutica elaborada con base en la misma molécula de atorvastatina. La solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará

más adelante y de ser concedida atentaría directamente contra la comercialización realizada por mi representada.

Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

3. FUNDAMENTOS DE HECHOS

3.1. La solicitud objeto de la presente oposición fue presentada el 9 de diciembre de 2003, reivindicando prioridad bajo el N° US60/302.049, de fecha 29 de junio de 2001 y cuya fecha de inicio en la fase nacional fue el 29 de enero de 2004, con publicación internacional N° WO 03/004470 del 16 de enero del 2003 y fue publicada en Colombia, en la Gaceta de la propiedad industrial N° 538, del 31 de marzo de 2004, bajo el N° de publicación NP. 12 (página 282).

3.2. La solicitud colombiana 03-107810 objeto de la presente oposición, comprende las cristalina formas V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX de atorvastatina o un hidrato de la misma, que tiene un patrón de difracción de

rayos X en polvo que contiene los valores 2θ usando radiación de CuK_α , según lo definido en las reivindicaciones 1 a 15.

3.3. Con anterioridad a la fecha de prioridad de esta solicitud, la molécula de la atorvastatina ya era parte del estado de la técnica tal y como lo referencia el mismo solicitante en su texto descriptivo cuando hace referencia al estado del arte anterior. Adicionalmente, a la fecha de prioridad de la solicitud colombiana el estado de la técnica ya revelaba los siguientes documentos en los cuales se ha estudiado la conformación de la molécula de atorvastatina amorfa en atorvastatina cristalina:

- D1: WO 9703959, del 6 de febrero de 1997.
- D2: WO 9703958, del 6 de febrero de 1997.
- D3: WO 0136384, del 25 de mayo de 2001.

3.4. La solicitud D1 y D2, del mismo solicitante, se refieren a formas cristalinas de atorvastatina conocida con el nombre de hemisal de calcio de ácido $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorofenil})-$ beta , delta -dihidroxi-5-(1-metiletil)-3-fenil-4-[(fenilamino)carbonil]-1H-pirrol-1-heptanoico designado como una Forma I, Forma II y Forma IV en el D1 y la Forma III en el D2, caracterizados por tener un patrón de difracción de rayos X en polvo y/o en

estado sólido, así como los métodos para la preparación y la composición farmacéutica del mismo, que es útil como agentes para tratar la hiperlipidemia y la hipercolesterolemia.

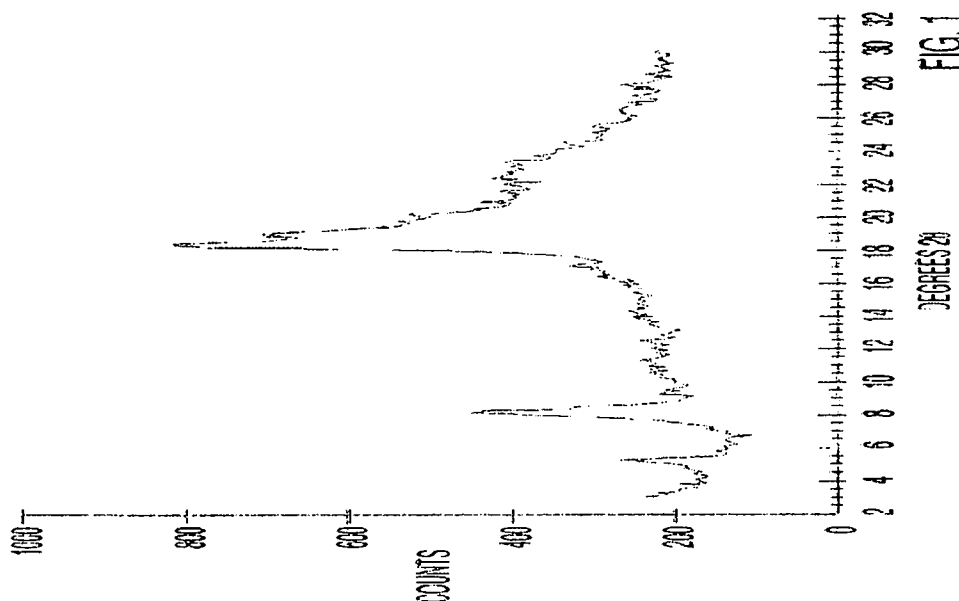
3.5. Como se puede apreciar a simple vista, el arte anterior descrito en estas solicitudes D1 y D2, ya revelaba un compuesto farmacéutico que comprendía unas formas cristalinas de atorvastatina.

3.6. Adicionalmente y como es de conocimiento general en la técnica, una forma cristalina representa un ordenamiento en el espacio o red cristalina de una estructura química (fenómeno denominado "Poliformismo"), de tal suerte, que sólo se requiere conjugar apropiadamente las condiciones de cristalización de un compuesto conocido para obtener un polimorfo derivado. Por lo tanto, aún alterando la forma de la molécula de atorvastatina, los componentes de dicha molécula se mantienen iguales, alterándose únicamente algunas propiedades fisicoquímicas del producto. El poliformismo es una técnica conocida desde 1788 (Martin Klaproth) para hacer pasar la molécula de una forma a otra.

3.7. Ahora bien, si combinamos el conocimiento indicado en estas solicitudes D1 y D2, y el conocimiento general de la técnica que dicta que las modificaciones polimórficas de un compuesto, en general pueden alterar algunas propiedades de las moléculas tales como su forma cristalina, velocidad de disolución, punto de fusión, densidad verdadera, dureza y/o fragilidad cristalina, el espectro de absorción infrarrojo o el difractograma de rayos X entre otros, indudablemente es posible derivar Formas Cristalinas V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX de atorvastatina o un hidrato de la misma, que tiene un patrón de difracción de rayos X en polvo. Es obvio, pues es de general conocimiento que algunas de estas modificaciones, en especial la alteración en la velocidad de disolución, causan diferencias en la absorción y por supuesto en los niveles de Biodisponibilidad de un medicamento presentado en forma sólida, sin implicar que exista una diferencia sustancial frente al mismo medicamento presentado en forma de solución. Así las cosas, lo expuesto en la solicitud colombiana 03-107810 en las reivindicaciones 1 a 15, se deriva evidentemente del arte anterior y es obvio para cualquier persona versada en la materia. Por lo tanto, la combinación del

conocimiento revelado en las solicitudes D1 y D2 en conjunto con el conocimiento general de la técnica, afecta de manera directa el requisito de altura inventiva de la solicitud colombiana que se pretenden proteger.

3.8. Ahora bien, la solicitud D3 de Teva, también se refiere a formas cristalinas de atorvastatina designado como una Forma V, caracterizado por tener un patrón de difracción de rayos X en polvo y/o en estado sólido. Según se describe en este documento D1, se revela una forma cristalina de atorvastatina que tiene un patrón de difracción de rayos X en polvo que contiene los valores según la figura 1.



3.9. Como se nota, la solicitud colombiana hace referencia a la misma molécula del documento D3, demostrando que alterando la forma de la molécula de atorvastatina, los componentes de dicha molécula se mantienen iguales, alterándose únicamente algunas propiedades fisicoquímicas del producto. Así las cosas, la solicitud colombiana objeto de la presente oposición no es novedosa desde ningún punto de vista, pues a todas luces lo que allí se describe ya se revelaba con anterioridad en la solicitud previa D3; por lo tanto consideramos que la concesión de esta solicitud colombiana atentaría abiertamente contra la normatividad colombiana, que explícitamente consagra a la NOVEDAD como uno de los tres elementos esenciales para que de a lugar la concesión de una patente.

3.10. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 03-107810 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los requisitos necesarios para su protección.

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

3.11.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 29 de junio de 2001, ya era conocido, pues como se demostró, era parte del arte anterior la materia sobre la cual busca protección en el capítulo reivindicatorio con base en el documento D3.

3.11.2. **CARENCIA DE ALTURA INVENTIVA**. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de presentación, 29 de junio de

FORMULARIO ÚNICO DE OPOSICIÓN

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OPOSICIÓN A:

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Patente de Invención.
Patente de Modelo de Utilidad.
Diseño Industrial.
Esquema de Trazado para Circuitos Integrados.
Marcas de Productos o Servicios.

☐ Marca Colectiva.
☐ Marca de Certificación.
☐ Lema Comercial.

②

SOLICITUD
PUBLICADA

Numero del expediente: 03-107810
Solicitante: Warner Lambert Company LLC
Apoderado: _____
Titulo de la nueva creación o denominación del signo: Formon 015K Inca
de la zona de calcio del acido ER-(R*,R*)-2-4
Gaceta: N° 538

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: <u>Procaps S.A</u> Direccion: <u>Calle 80 N° 78B-201</u> <u>Barranquilla.</u> Nacionalidad o Domicilio: <u>Colombia.</u> Lugar de Constitución: <u>B/guilla.</u>	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>890106577-5</u>
	Telefono: <u>3789000</u> Fax: <u>3533549</u> E-mail: _____	
REPRESENTANTE O APODERADO	Nombre: <u>Luis Fernando Pinco</u> Direccion: <u>Calle 119 A N° 53-99</u> <u>BOGOTA</u> Telefono: <u>6133418</u> Fax: <u>6133374</u> E-mail: _____	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>79532197P113438</u>

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: FALTA DE REQUISITOS DE POTENCIALIDAD
Signo opositor: _____
Justificación: EXPUESTO EN EL DESARROLLO DE LA
PRESENTE OPOSICION

⑤ Comprobante de pago No.

50621

Fecha

207
15/06/2007

⑥ ANEXOS



Comprobante de pago de la tasa.



Poderes, si fuere el caso.



Pruebas de los fundamentos de la oposición.



Documentos que acrediten el legítimo interés, si fuere el caso.



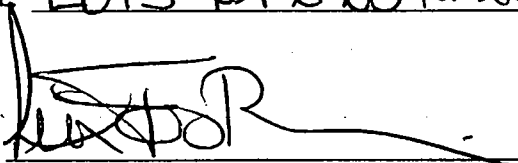
Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE:

Luis Fernando Rincón

FIRMA:



C.C. 79532181 TP. 113438

Señora Jefe,
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Superintendencia de Industria y Comercio
E. S. D.

Referencia: Expediente N° 03-107810
Asunto: Oposición a la solicitud de patente de
Invención titulada "**FORMAS**
CRISTALINAS DE LA SAL DE
CALCIO DEL ACIDO [R-(R*,R*)]-
2-(4-FLUOROFENIL)- β , O-
DIHIDROXI-5-(1-METILETIL)-3-
FENIL-4-[(FENILAMINO)
CARBONIL] - 1H- PIRROL-1-
HEPTANOICO(2:1)"
Solicitante: **WARNER-LAMBERT COMPANY**
LLC.
Opositora: **PROCAPS S.A.**

Publicada en la Gaceta de la Propiedad Industrial
N° 538 del 31 de marzo de 2004

Yo, Luis Fernando Rincón Cuellar, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad PROCAPS S.A. conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "FORMAS CRISTALINAS DE LA SAL DE CALCIO DEL ACIDO [R-(R*,R*)]-2-(4-FLUOROFENIL)-β, Õ-DIHIDROXI-5-(1-METILETIL)-3-FENIL-4-[(FENILAMINO)CARBONIL]-1H-PIRROL-1-HEPTANOICO(2:1)", solicitada por WARNER-LAMBERT COMPANY LLC., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

2. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de la sociedad que represento, radicado básicamente en la comercialización que mi representada efectúa de una presentación farmacéutica elaborada con base en la misma molécula de atorvastatina. La solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará

más adelante y de ser concedida atentaría directamente contra la comercialización realizada por mi representada.

Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

3. FUNDAMENTOS DE HECHOS

3.1. La solicitud objeto de la presente oposición fue presentada el 9 de diciembre de 2003, reivindicando prioridad bajo el N° US60/302.049, de fecha 29 de junio de 2001 y cuya fecha de inicio en la fase nacional fue el 29 de enero de 2004, con publicación internacional N° WO 03/004470 del 16 de enero del 2003 y fue publicada en Colombia, en la Gaceta de la propiedad industrial N° 538, del 31 de marzo de 2004, bajo el N° de publicación NP. 12 (página 282).

3.2. La solicitud colombiana 03-107810 objeto de la presente oposición, comprende las cristalina formas V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX de atorvastatina o un hidrato de la misma, que tiene un patrón de difracción de

rayos X en polvo que contiene los valores 2θ usando radiación de CuK_α , según lo definido en las reivindicaciones 1 a 15.

3.3. Con anterioridad a la fecha de prioridad de esta solicitud, la molécula de la atorvastatina ya era parte del estado de la técnica tal y como lo referencia el mismo solicitante en su texto descriptivo cuando hace referencia al estado del arte anterior. Adicionalmente, a la fecha de prioridad de la solicitud colombiana el estado de la técnica ya revelaba los siguientes documentos en los cuales se ha estudiado la conformación de la molécula de atorvastatina amorfa en atorvastatina cristalina:

- D1: WO 9703959, del 6 de febrero de 1997.
- D2: WO 9703958, del 6 de febrero de 1997.
- D3: WO 0136384, del 25 de mayo de 2001.

3.4. La solicitud D1 y D2, del mismo solicitante, se refieren a formas cristalinas de atorvastatina conocida con el nombre de hemisal de calcio de ácido $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorofenil})-$ beta , delta -dihidroxi-5-(1-metiletil)-3-fenil-4-[(fenilamino)carbonil]-1H-pirrol-1-heptanoico designado como una Forma I, Forma II y Forma IV en el D1 y la Forma III en el D2, caracterizados por tener un patrón de difracción de rayos X en polvo y/o en

estado sólido, así como los métodos para la preparación y la composición farmacéutica del mismo, que es útil como agentes para tratar la hiperlipidemia y la hipercolesterolemia.

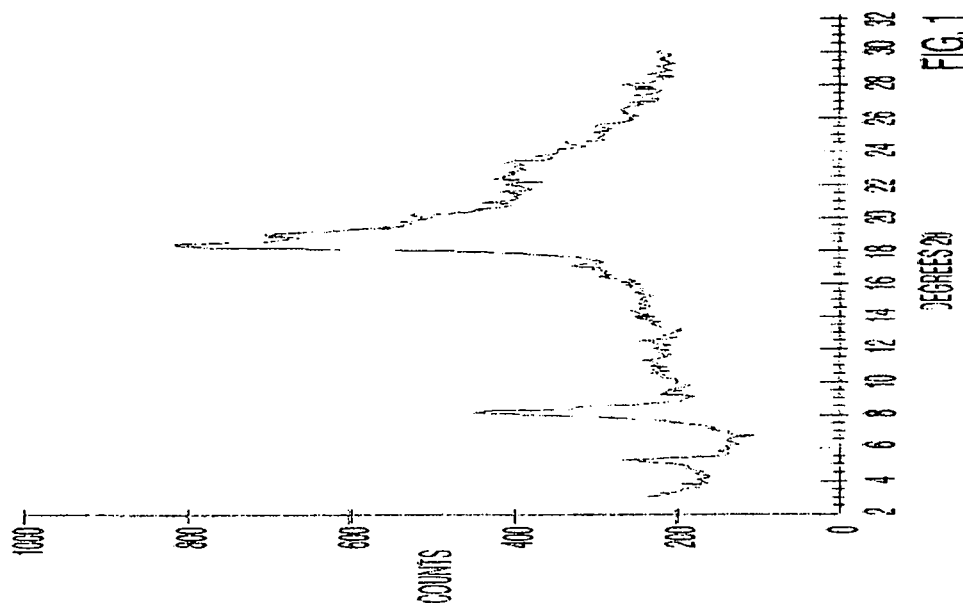
3.5. Como se puede apreciar a simple vista, el arte anterior descrito en estas solicitudes D1 y D2, ya revelaba un compuesto farmacéutico que comprendía unas formas cristalinas de atorvastatina.

3.6. Adicionalmente y como es de conocimiento general en la técnica, una forma cristalina representa un ordenamiento en el espacio o red cristalina de una estructura química (fenómeno denominado "Poliformismo"), de tal suerte, que sólo se requiere conjugar apropiadamente las condiciones de cristalización de un compuesto conocido para obtener un polimorfo derivado. Por lo tanto, aún alterando la forma de la molécula de atorvastatina, los componentes de dicha molécula se mantienen iguales, alterándose únicamente algunas propiedades fisicoquímicas del producto. El poliformismo es una técnica conocida desde 1788 (Martin Klaproth) para hacer pasar la molécula de una forma a otra.

2.7. Ahora bien, si combinamos el conocimiento indicado en estas solicitudes D1 y D2, y el conocimiento general de la técnica que dicta que las modificaciones polimórficas de un compuesto, en general pueden alterar algunas propiedades de las moléculas tales como su forma cristalina, velocidad de disolución, punto de fusión, densidad verdadera, dureza y/o fragilidad cristalina, el espectro de absorción infrarrojo o el difractograma de rayos X entre otros, indudablemente es posible derivar Formas Cristalinas V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX de atorvastatina o un hidrato de la misma, que tiene un patrón de difracción de rayos X en polvo. Es obvio, pues es de general conocimiento que algunas de estas modificaciones, en especial la alteración en la velocidad de disolución, causan diferencias en la absorción y por supuesto en los niveles de Biodisponibilidad de un medicamento presentado en forma sólida, sin implicar que exista una diferencia sustancial frente al mismo medicamento presentado en forma de solución. Así las cosas, lo expuesto en la solicitud colombiana 03-107810 en las reivindicaciones 1 a 15, se deriva evidentemente del arte anterior y es obvio para cualquier persona versada en la materia. Por lo tanto, la combinación del

conocimiento revelado en las solicitudes D1 y D2 en conjunto con el conocimiento general de la técnica, afecta de manera directa el requisito de altura inventiva de la solicitud colombiana que se pretenden proteger.

3.8. Ahora bien, la solicitud D3 de Teva, también se refiere a formas cristalinas de atorvastatina designado como una Forma V, caracterizado por tener un patrón de difracción de rayos X en polvo y/o en estado sólido. Según se describe en este documento D1, se revela una forma cristalina de atorvastatina que tiene un patrón de difracción de rayos X en polvo que contiene los valores según la figura 1.



3.9. Como se nota, la solicitud colombiana hace referencia a la misma molécula del documento D3, demostrando que alterando la forma de la molécula de atorvastatina, los componentes de dicha molécula se mantienen iguales, alterándose únicamente algunas propiedades fisicoquímicas del producto. Así las cosas, la solicitud colombiana objeto de la presente oposición no es novedosa desde ningún punto de vista, pues a todas luces lo que allí se describe ya se revelaba con anterioridad en la solicitud previa D3; por lo tanto consideramos que la concesión de esta solicitud colombiana atentaría abiertamente contra la normatividad colombiana, que explícitamente consagra a la NOVEDAD como uno de los tres elementos esenciales para que de a lugar la concesión de una patente.

3.10. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 03-107810 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los requisitos necesarios para su protección.

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

3.11.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 29 de junio de 2001, ya era conocido, pues como se demostró, era parte del arte anterior la materia sobre la cual busca protección en el capítulo reivindicatorio con base en el documento D3.

3.11.2. **CARENCIA DE ALTURA INVENTIVA**. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de presentación, 29 de junio de

2001, el documento D1 en combinación con el documento D2, es posible deducir las formas cristalinas de atorvastatina reivindicadas.

3.12. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."* La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

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

3.14. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"FORMAS CRISTALINAS DE LA SAL DE CALCIO DEL ACIDO [R-**

(R*,R*)]-2-(4-FLUOROFENIL)-β, Õ-DIHIDROXI-5-(1-METILETIL)-3-FENIL-4-[(FENILAMINO)CARBONIL]-1H-PIRROL-1-HEPTANOICO(2:1)”, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 538 del 31 de marzo de 2004, en la página 282, bajo el NP 12.

4. PRUEBAS

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

- Documento 1: WO 9703959, del 6 de febrero de 1997.
- Documento 2: WO 9703958, del 6 de febrero de 1997.
- Documento 3: WO 0136384, del 25 de mayo de 2001.

5. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

5.1. Numeral 1 del artículo 586 del Código de Comercio.

5.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

5.3. En las demás normas concordantes.

6. ANEXOS

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

6.1. ANEXO 1: WO 9703959, del 6 de febrero de 1997.

6.2. ANEXO 2: WO 9703958, del 6 de febrero de 1997.

6.3. ANEXO 3: WO 0136384, del 25 de mayo de 2001.

6.4. Recibo de pago expedido por el Fondo Especial de esa Superintendencia, en el cual consta que se ha pagado el valor correspondiente a la tasa por tramitación de esta oposición.

6.5. Copia de la oposición para el traslado al solicitante.

6.6. Poder para actuar a nombre de mi representada.

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7. NOTIFICACIONES

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

De la señora Jefe,



LUIS FERNANDO RINCÓN CUELLAR

C.C. No. 79.532.186 de Bogotá D.C.

T.P. No. 113438

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Santafé de Bogotá, 25 JUN. 2004

Presentado personalmente por

Fernando Rincón Cuellar

C.C. 79532186 st.

T.P. 11438

Notificador Secretaría General

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SECRETARIA GENERAL

NOTIFICADOR



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PODER ESPECIAL

Yo, **RUBÉN MINSKI GONTOVNIK**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a **LUIS FERNANDO RINCON CUELLAR**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 113438 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 03-107810, de título: "FORMAS CRISTALINAS DE LA SAL DE CALCIO DEL ACIDO [R-(R*,R*)]-2-(4-FLUOROFENIL)-B, Ñ-DIHIDROXI-5-(1-METILETIL)-3-FENIL-4-[(FENILAMINO)CARBONIL] - 1H - PIRROL-1-HEPTANOICO(2:1)", publicada en la gaceta No. 538 del 31 marzo de 2004, numero de publicación 12, y cuyo solicitante es la sociedad WARNER-LAMBERT COMPANY LLC.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 9 días del mes de junio de 2004.

PROCAPS S.A.
RUBÉN MINSKI GONTOVNIK
C.C. N° 7.468.982 de Barranquilla
Representante Legal

Acepto

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Santate de Bogotá. 25 JUN. 2004

Presentado personalmente por

C.C. 79532186 de 88.

T.P. 113438

Notificador Secretario General al dorso
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SECRETARIA GENERAL

NOTIFICADOR

DILIGENCIA DE PRESENTACION PERSONAL

DECRETO 960 DE 1970 - ART. 68

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

CERTIFICA

En Barranquilla a los 16 días del mes de junio de 2004 Firmaron esta

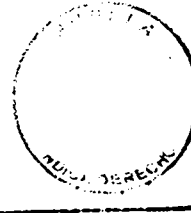
diligencia en su presencia: Ruben elinski

Gowtownik

Portadores de las cédulas: 7463982



Expedidas en E/C.
y en virtud de lo ordenado por el Gobierno
que antecede y en conformidad con sus firmas



Comparecientes

LA NOTARIA
REPUBLICA DE COLOMBIA
NOTARIA SEGUNDA DEL CIRCULO
DE BARRANQUILLA
2
Arteta
Maria del S. Roman de Arteta

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CAMARA DE COMERCIO
DE BARRANQUILLA

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

PROCAPS S.A. -----

EN JUNIO DE ESTE A/O SE ELEGIRA JUNTA DIRECTIVA DE LA CAMARA DE COMER-
CIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA
QUINCENA DE MAYO. PARA INFORMACION DETALLADA DIRIGIRSE A LA SEDE
PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO 3303911

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

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

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

PROCAPS S.A.

C E R T I F I C A

Que por Escritura Publica Nro. 3615 del 6 de Dic/bre de 1,996, otorgada en la Notaria 2a. de Barranquilla inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 bajo el No. 67,218 del libro respectivo, la sociedad antes mencionada cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A.

C E R T I F I C A

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

C E R T I F I C A

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

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

C E R T I F I C A

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

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.

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

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CAMARA DE COMERCIO
DE BARRANQUILLA

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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PROCAPS S.A. -----
Sigla: PROCAPS -----
DOMICILIO PRINCIPAL: BARRANQUILLA -----
Nit No. 890,106,527-5 -----
MATRICULA MERCANTIL: 24,802 -----

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) -La fabri-
cacion de capsulas y otros productos similares a partir de materia-
les tales como gelatinas u otros de distinta naturaleza, que puedan
ser utilizados como envases o recipientes de productos y sustancias
quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y
veterinario; b) -La investigacion, desarrollo y fabricacion de toda
clase de productos y sustancias quimicas, farmaceuticas y cosmeticas
para uso y consumo humano, animal y vegetal; c) -La compra y venta de
materias primas, insumos y productos intermedios necesarios para los
procesos de fabricacion de sustancias quimicas, farmaceuticas, alimen-
ticias y cosmeticas, asi como la comercializacion interna y externa
de los productos terminados, d) La compra, venta, importacion, ex-
portacion y distribucion de toda clase de elementos instru-
mentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios
para la salud humana y animal. e) La compra, venta, exportacion y dis-
tribucion de dulces, confites, galletas y todo tipo de
golosinas o alimentos para el consumo humano. f) Actuar como re-
presentante o agente de personas naturales y juridicas, nacio-
nacionales y extranjeras en la realizacion de operaciones o tran-
sacciones relacionadas con la industria farmaceutica y en especial

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

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

con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h) -Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.

C E R T I F I C A

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

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde a la Asamblea General de Accionistas, a la Junta Directiva,

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

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PROCAPS S.A. -----

al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la

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

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

PROCAPS S.A.

sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantía sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dólares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la aprobación o celebración del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de intereses inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demás funciones que le corresponda como Representante legal por disposición de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendrá (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con idénticas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendrá un Gerente General designado por la Junta Directiva, quien también ejercerá la representación legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente y el Vicepresidente. El Gerente General tendrá las siguientes facultades entre otras: Ejecutar las decisiones de la Junta Directiva, del Presidente y del Vicepresidente. Ejercer la representación legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantía sea igual o inferior al equivalente en pesos colombianos a cincuenta mil dólares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la aprobación o celebración del acto, siempre que no se trate de enajenar a cualquier título bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de intereses, inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los

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

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

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

PROCAPS S.A. -----

anteriores o facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que les correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva.-----

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, y por Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

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

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

Principales

1. Minski Gontovnik Ruben
2. Minski Gontovnik Meyer
3. Minski Gontovnik Jose

Suplentes

- Minski Zilberblum Elliot
Minski Deitel Daniel
Minski Sharon

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:-----

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

C E R T I F I C A

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

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

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

PROCAPS S.A. -----

PROCAPS S.A. -----

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

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

C E R T I F I C A

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

PROCAPS S.A. -----

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

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

C E R T I F I C A

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

PROCAPS S.A. -----

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

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

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1. Se confiere Poder Especial Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nom-

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



***** Pag.05

CAMARA DE COMERCIO
DE BARRANQUILLA

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

PROCAPS S.A. -----

bre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, comparecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad, desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

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

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

PROCAPS S.A. -----

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

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

NO CAUSA IMPUESTO DE TIMBRE

EL SECRETARIO
MARIBEL REYES OVIEDO

mreyes

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ANEXO 1

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PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 207/34, A61K 31/40	A1	(11) International Publication Number: WO 97/03959 (43) International Publication Date: 6 February 1997 (06.02.97)
(21) International Application Number: PCT/US96/11368 (22) International Filing Date: 8 July 1996 (08.07.96) (30) Priority Data: 60/001,452 17 July 1995 (17.07.95) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRIGGS, Christopher, A. [US/US]; 643 East 12th Street, Holland, MI 49423 (US). JENNINGS, Rex, Allen [US/US]; 405 Lincoln Avenue, Holland, MI 49423 (US). WADE, Robert, A. [US/US]; 3882 62nd Street, Holland, MI 49423 (US). HARASAWA, Kikuko [JP/JP]; 202 Liberty Palace Odakyusagami-hara, 18-15, Minamidai 6-chome, Sagami-hara-shi, Kanagawa 228 (JP). ICHIKAWA, Shigeru [JP/JP]; D-403 CI-Heights, 1356 Yamasaki-cho, Machida-shi, Tokyo 195 (JP). MINOHARA, Kazuo [JP/JP]; 702 Park-Heights Sagami-hara, 4-4, Sagami-hara 5-chome, Sagami-hara-shi, Kanagawa 229 (JP). NAKAGAWA, Shinsuke [JP/JP]; 303 Seishin-Hills, 14-30, Seishin 7-chome, Sagami-hara-shi, Kanagawa 229 (JP).		(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al. (81) Designated States: AU, BG, BR, CA, CN, CZ, EE, GE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, UZ, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: CRYSTALLINE [R-(R*,R*)]-2-(4-FLUOROPHENYL)-BETA,DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN) (57) Abstract Novel crystalline forms of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt designated Form I, Form II, and Form IV are characterized by their X-ray powder diffraction and/or solid state NMR are described, as well as methods for the preparation and pharmaceutical composition of the same, which are useful as agents for treating hyperlipidemia and hypercholesterolemia.		

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CRYSTALLINE [R-(R*,R*)]-2-(4-FLUOROPHENYL)-BETA,DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)

10

BACKGROUND OF THE INVENTION

The present invention relates to novel crystalline forms of atorvastatin which is known by the chemical name [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt useful as pharmaceutical agents, to methods for their production and isolation, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel crystalline compounds of the present invention are useful as inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and are thus useful hypolipidemic and hypocholesterolemic agents.

25

United States Patent Number 4,681,893, which is herein incorporated by reference, discloses certain trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1-yl)alkyl]-4-hydroxy-pyran-2-ones including trans ($\pm$)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

30

United States Patent Number 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-

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methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

United States Patent Numbers 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; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

Atorvastatin is prepared as its calcium salt, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The calcium salt is desirable since it enables atorvastatin to be conveniently formulated in, for example, tablets, capsules, lozenges, powders, and the like for oral administration. Additionally, there is a need to produce atorvastatin in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

Furthermore, the process by which atorvastatin is produced needs to be one which is amenable to large-scale production. Additionally, it is desirable that the product should be in a form that is readily filterable and easily dried. Finally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

The processes in the above United States Patents disclose amorphous atorvastatin which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture.

We have now surprisingly and unexpectedly found that atorvastatin can be prepared in crystalline form. Thus, the present invention provides atorvastatin in new crystalline forms designated Form I, Form II, and

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Form IV. Form I atorvastatin consists of smaller particles and a more uniform size distribution than the previous amorphous product and exhibits more favorable filtration and drying characteristics. Additionally, Form I atorvastatin is purer and more stable than the amorphous product.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to crystalline Form I atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of $>20\%$ measured after 2 minutes of grinding and measured on a Siemens D-500 diffractometer with $\text{CuK}\alpha$ radiation:

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	2 θ	d	Relative Intensity (>20%) Ground 2 Minutes
	9.150	9.6565	42.60
	9.470	9.3311	41.94
	10.266	8.6098	55.67
5	10.560	8.3705	29.33
	11.853	7.4601	41.74
	12.195	7.2518	24.62
	17.075	5.1887	60.12
	19.485	4.5520	73.59
10	21.626	4.1059	100.00
	21.960	4.0442	49.44
	22.748	3.9059	45.85
	23.335	3.8088	44.72
	23.734	3.7457	63.04
15	24.438	3.6394	21.10
	28.915	3.0853	23.42
	29.234	3.0524	23.36

20 Further, the present invention is directed to
 crystalline Form I atorvastatin and hydrates thereof
 characterized by the following solid-state ^{13}C nuclear
 magnetic resonance spectrum wherein chemical shift is
 expressed in parts per million measured on a Bruker
 25 AX-250 spectrometer:

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Assignment (7 kHz)		Chemical Shift
5	C12 or C25	182.8
	C12 or C25	178.4
	C16	166.7 (broad)
		and 159.3
	Aromatic Carbons	
10	C2-C5, C13-C18, C19-C24, C27-C32	137.0
		134.9
		131.1
		129.5
		127.6
15		123.5
		120.9
		118.2
		113.8
	C8, C10	73.1
20		70.5
		68.1
		64.9
	Methylene Carbons	
	C6, C7, C9, C11	47.4
25		41.9
		40.2
	C33	26.4
		25.2
	C34	21.3

30 In a preferred embodiment of the first aspect of the invention, crystalline Form I atorvastatin is a trihydrate.

In a second aspect, the present invention is directed to crystalline Form II atorvastatin and hydrates thereof characterized by the following X-ray

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powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding and measured on a Siemens D-500 diffractometer with $\text{CuK}\alpha$ radiation:

	2θ	d	Relative Intensity (>20%) Ground 2 Minutes
	5.582	15.8180	42.00
	7.384	11.9620	38.63
10	8.533	10.3534	100.00
	9.040	9.7741	92.06
	12.440 (broad)	7.1094	30.69
	15.771 (broad)	5.6146	38.78
	17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
15	19.490	4.5507	56.64
	20.502	4.3283	67.20
	22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
	25.697 (broad)	3.4639	38.93
	29.504	3.0250	37.86
20			

Further, the second aspect of the present invention is directed to crystalline Form II atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million measured on a Bruker AX-250 spectrometer:

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Assignment		Chemical Shift
5	Spinning Side Band	209.1
	Spinning Side Band	206.8
	C12 or C25	181 (broad)
	C12 or C25	163 (broad)
	C16	161 (broad)
Aromatic Carbons		
10	C2-C5, C13-C18, C19-C24, C27-C32	140.5
		134.8
		133.3
		129.0
		122.9
15		121.4
		120.3
		119.0
		117.1
		115.7
20		114.7
	C8, C10	70.6
		69.0
		68.0
		67.3
25	Spinning Side Band	49.4
	Spinning Side Band	48.9
	Methylene Carbons	
	C6, C7, C9, C11	43.4
		42.3
30		41.7
		40.2
	C33	27.5
	C34	22.8 (broad)

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In a third aspect, the present invention is directed to crystalline Form IV atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2 θ , d-spacings, and relative intensities with a relative intensity of >15% measured on a Siemens D-500 diffractometer with CuK α radiation:

	2 θ	d	Relative Intensity (>15%)
10	4.889	18.605	38.45
	5.424	16.2804	20.12
	5.940	14.8660	17.29
	7.997	11.0465	100.00
	9.680	9.1295	67.31
15	10.416	8.4859	20.00
	12.355	7.1584	19.15
	17.662	5.0175	18.57
	18.367	4.8265	23.50
	19.200	4.6189	18.14
20	19.569	4.5327	54.79
	21.723	4.0879	17.99
	23.021	3.8602	28.89
	23.651	3.7587	33.39
	24.143	3.6832	17.23

Further, the fourth aspect of the present invention is directed to Form IV atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed as parts per million measured on a Bruker AX-250 spectrometer:

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	Assignment	Chemical Shift
	C12 or C25	186.4
		184.9
	C12 or C25	181.4
		179.3
	C16	166.1 (broad)
		and
		159.0 (broad)
5	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
		134.7
		129.2
		127.1
		122.7
		119.8
		115.7
10	C8, C10	71.5
		67.9
		66.3
		63.5
	Methylene Carbons	
	C6, C7, C9, C11	46.1
		43.4
		42.1
		40.0
	C33	25.9
	C34	20.3
		19.4
		17.9
15		

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As inhibitors of HMG-CoA, the novel crystalline forms of atorvastatin are useful hypolipidemic and hypocholesterolemic agents.

5 A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of crystalline Form I, Form II, or Form IV atorvastatin in unit dosage form in the treatment methods mentioned above. Finally, the present invention is directed to methods
10 for production of Form I, Form II, or Form IV atorvastatin.

BRIEF DESCRIPTION OF THE DRAWINGS

15 The invention is further described by the following nonlimiting examples which refer to the accompanying Figures 1 to 6, short particulars of which are given below.

20

Figure 1

Diffractiongram of Form I atorvastatin ground for 2 minutes (Y-axis = 0 to maximum intensity of 3767.50 counts per second (cps))

25

Figure 2

Diffractiongram of Form II atorvastatin ground for 2 minutes (Y-axis = 0 to maximum intensity of 1500 cps)

30

Figure 3

Diffractiongram of Form IV atorvastatin (Y-axis = 0 to maximum intensity of 8212.5 cps).

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Figure 4

Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form I atorvastatin.

Figure 5

Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form II atorvastatin.

Figure 6

Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form IV atorvastatin.

DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form I, Form II, or Form IV atorvastatin may be characterized by their X-ray powder diffraction patterns and/or by their solid state nuclear magnetic resonance spectra (NMR).

X-RAY POWDER DIFFRACTION

Forms I, II, and IV Atorvastatin

Forms I, II, or Form IV atorvastatin were characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of Forms I, II, and Form IV atorvastatin were measured on a Siemens D-500 diffractometer with CuK_α radiation.

Equipment

Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software = DIFFRAC AT (SOCABIM 1986, 1992).

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CuK_α radiation (20 mA, 40 kV, $\lambda = 1.5406 \text{ \AA}$) Slits I and II at 1°) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)] Detector (Slits: III at 1° and IV at 0.15°).

5

Methodology

The silicon standard is run each day to check the X-ray tube alignment.

Continuous $\theta/2\theta$ coupled scan: 4.00° to 40.00° in 2θ , scan rate of 6°/min: 0.4 sec/0.04° step.

10

Sample tapped out of vial and pressed onto zero-background quartz in aluminum holder. Sample width 13-15 mm.

Samples are stored and run at room temperature.

15

Grinding/Sieving

Grinding is used to minimize intensity variations for the diffractogram disclosed herein. However, if grinding significantly altered the diffractogram or increased the amorphous content of the sample, then the diffractogram of the unground sample was used. Grinding was done in a small agate mortar and pestle. The mortar was held during the grinding and light pressure was applied to the pestle.

20

25

Ground Form II atorvastatin was sieved through a 230 mesh screen before analysis by x-ray diffraction.

30

Table 1 lists the 2θ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >20% for crystalline Form I atorvastatin. Table 1 also lists the relative intensities of the same lines in a diffractogram measured after 2 minutes of grinding. The intensities of the sample ground for 2 minutes are more

35

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representative of the diffraction pattern without preferred orientation. It should also be noted that the computer-generated, unrounded numbers are listed in this table.

5

TABLE 1. Intensities and Peak Locations of all Diffraction Lines With Relative Intensity Greater Than 20% for Form I Atorvastatin

	2 θ	d	Relative Intensity (>20%) No Grinding	Relative Intensity (>20%)* Ground 2 Minutes
10	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
15	11.853	7.4601	55.16	41.74
	12.195	7.2518	20.03	24.62
	17.075	5.1887	25.95	60.12
	19.485	4.5520	89.93	73.59
	21.626	4.1059	100.00	100.00
20	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
25	28.915	3.0853	21.59	23.42
	29.234	3.0524	20.45	23.36

* The second relative intensity column gives the relative intensities of the diffraction lines on the original diffractogram after 2 minutes of grinding.

30

Table 2 lists the 2 θ , d-spacings, and relative intensities of all lines in the ground/sieved sample

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with a relative intensity of >20% for crystalline Form II atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

5

TABLE 2. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 20% for Form II Atorvastatin

	2 θ	d	Relative Intensity (>20%)
10	5.582	15.8180	42.00
	7.384	11.9620	38.63
	8.533	10.3534	100.00
	9.040	9.7741	92.06
15	12.440 (broad)	7.1094	30.69
	15.771 (broad)	5.6146	38.78
	17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
	19.490	4.5507	56.64
	20.502	4.3283	67.20
20	22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
	25.697 (broad)	3.4639	38.93
	29.504	3.0250	37.86

25

Table 3 lists the 2 θ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >15% for crystalline Form IV atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

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TABLE 3. Intensities and Peak Locations of All
Diffraction Lines With Relative Intensity
Greater Than 15% for Form IV Atorvastatin

	2 θ	d	Relative Intensity (>15%)
5	4.889	18.605	38.45
	5.424	16.2804	20.12
	5.940	14.8660	17.29
	7.997	11.0465	100.00
	9.680	9.1295	67.31
10	10.416	8.4859	20.00
	12.355	7.1584	19.15
	17.662	5.0175	18.57
	18.367	4.8265	23.50
	19.200	4.6189	18.14
15	19.569	4.5327	54.79
	21.723	4.0879	17.99
	23.021	3.8602	28.89
	23.651	3.7587	33.39
	24.143	3.6832	17.23
20			

SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

25 Methodology

All solid-state ^{13}C NMR measurements were made with a Bruker AX-250, 250 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and cross-polarization (CP) with magic-angle spinning (MAS) at approximately 5 kHz. The magic-angle was adjusted using the Br signal of KBr by detecting the side bands as described by Frye and Maciel (Frye J.S. and Maciel G.E., J. Mag. Res., 30

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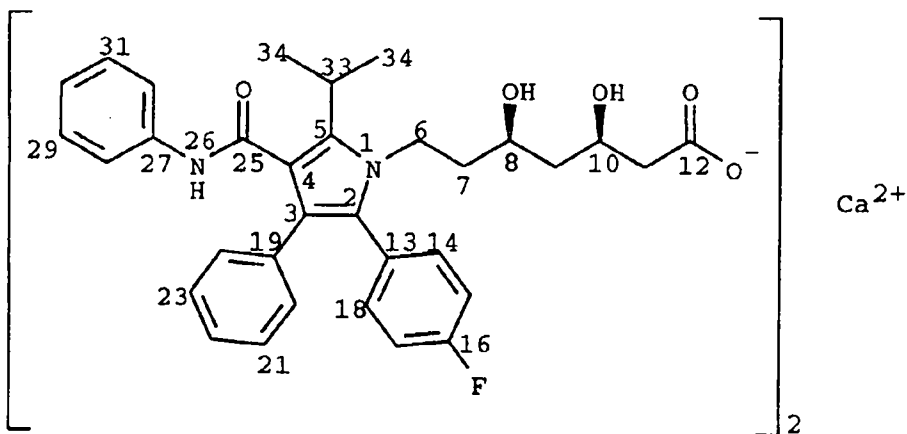
1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J.V. and Stock L.M., J. Mag. Res., 1988;76:54).

Table 4 shows the solid-state NMR spectrum for crystalline Form I atorvastatin.

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TABLE 4. Carbon Atom Assignment and Chemical Shift for Form I Atorvastatin

	Assignment (7 kHz)	Chemical Shift
5	C12 or C25	182.8
	C12 or C25	178.4
	C16	166.7 (broad) and 159.3
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	137.0
10		134.9
		131.1
		129.5
		127.6
		123.5
15		120.9
		118.2
		113.8
	C8, C10	73.1
		70.5
20		68.1
		64.9
	Methylene Carbons	
	C6, C7, C9, C11	47.4
		41.9
25		40.2
	C33	26.4
		25.2
	C34	21.3

30

Table 5 shows the solid-state NMR spectrum for crystalline Form II atorvastatin.

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TABLE 5. Carbon Atom Assignment and Chemical Shift for Form II Atorvastatin

	Assignment	Chemical Shift
	Spinning Side Band	209.1
5	Spinning Side Band	206.8
	C12 or C25	181 (broad)
	C12 or C25	163 (broad)
	C16	161 (broad)
	Aromatic Carbons	
10	C2-C5, C13-C18, C19-C24, C27-C32	140.5
		134.8
		133.3
		129.0
		122.9
15		121.4
		120.3
		119.0
		117.1
		115.7
20		114.7
		70.6
		69.0
	C8, C10	68.0
		67.3
25	Spinning Side Band	49.4
	Spinning Side Band	48.9
	Methylene Carbons	
	C6, C7, C9, C11	43.4
		42.3
30		41.7
		40.2
	C33	27.5
	C34	22.8 (broad)

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Table 6 shows the solid-state NMR spectrum for crystalline Form IV atorvastatin.

5 TABLE 6. Carbon Atom Assignment and Chemical Shift
for Form IV Atorvastatin

Assignment	Chemical Shift
C12 or C25	186.4
	184.9
C12 or C25	181.4
	179.3
C16	166.1 (broad) and 159.0 (broad)
10 Aromatic Carbons	
C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
	134.7
	129.2
	127.1
	122.7
	119.8
	115.7
15 C8, C10	71.5
	67.9
	66.3
	63.5
Methylene Carbons	
C6, C7, C9, C11	46.1
	43.4
	42.1
	40.0
C33	25.9
C34	20.3
	19.4
	17.9
20	

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Crystalline Form I, Form II, and Form IV atorvastatin of the present invention may exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms, are equivalent to unhydrated forms and are intended to be encompassed within the scope of the present invention. Crystalline Form I atorvastatin contains about 1 to 8 mol of water. Preferably, Form I atorvastatin contains 3 mol of water.

The present invention provides a process for the preparation of crystalline Form I atorvastatin which comprises crystallizing atorvastatin from a solution in solvents under conditions which yield crystalline Form I atorvastatin.

The precise conditions under which crystalline Form I atorvastatin is formed may be empirically determined and it is only possible to give a number of methods which have been found to be suitable in practice.

Thus, for example, crystalline Form I atorvastatin may be prepared by crystallization under controlled conditions. In particular, it can be prepared either from an aqueous solution of the corresponding basic salt such as, an alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending amorphous atorvastatin in water. In general, the use of a hydroxylic co-solvent such as, for example, a lower alkanol, for example methanol and the like, is preferred.

When the starting material for the preparation of the desired crystalline Form I atorvastatin is a solution of the corresponding sodium salt, one preferred preparation involves treating a solution of the sodium salt in water containing not less than about 5% v/v methanol, preferably about 5% to 33% v/v

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methanol, particularly preferred about 10% to 15% v/v methanol, with an aqueous solution of calcium acetate, preferably at an elevated temperature at up to about 70°C such as, for example, about 45-60°C, particularly preferred about 47-52°C. It is preferable to use calcium acetate and, in general, 1 mole of calcium acetate to 2 moles of the sodium salt of atorvastatin. Under these conditions, calcium salt formation as well as crystallization should preferably be carried out at an elevated temperature, for example within the above-mentioned temperature ranges. It has been found that it may be advantageous to include in the starting solution a small amount of methyl ~~tert~~-butyl ether (MTBE) such as, for example, about 7% w/w. It has frequently been found desirable to add "seeds" of crystalline Form I atorvastatin to the crystallization solution in order to consistently produce crystalline Form I atorvastatin.

When the starting material is amorphous atorvastatin or a combination of amorphous and crystalline Form I Atorvastatin, the desired crystalline Form I atorvastatin may be obtained by suspending the solid in water containing up to about 40% v/v, such as, for example, about 0% to 20% v/v, particularly preferred about 5% to 15% v/v co-solvent such as, for example, methanol, ethanol, 2-propanol, acetone, and the like until conversion to the required form is complete, followed by filtration. It has frequently been found desirable to add "seeds" of crystalline Form I atorvastatin to the suspension in order to ensure complete conversion to crystalline Form I atorvastatin. Alternatively, a water-wet cake consisting principally of amorphous atorvastatin can be heated at elevated temperatures such as, for example, up to about 75°C, particularly preferred about 65-70°C, until a significant amount of crystalline Form I

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atorvastatin is present, whereupon the amorphous/
crystalline Form I mixture can be slurried as described
above.

Crystalline Form I atorvastatin is significantly
5 easier to isolate than amorphous atorvastatin and can
be filtered from the crystallization medium after
cooling, and washed and dried. For example, filtration
of a 50 mL slurry of crystalline Form I atorvastatin
was complete within 10 seconds. A similarly sized
10 sample of amorphous atorvastatin took more than an hour
to filter.

The present invention also provides a process for
the preparation of crystalline Form II atorvastatin
which comprises suspending atorvastatin in solvents
15 under conditions which yield crystalline Form II
atorvastatin.

The precise conditions under which Form II of
crystalline atorvastatin is formed may be empirically
determined and it is only possible to give a method
20 which has been found to be suitable in practice.

Thus, for example, when the starting material is
amorphous, a combination of amorphous and Form I, or
crystalline Form I atorvastatin, the desired Form II of
crystalline atorvastatin may be obtained by suspending
25 the solid in methanol containing about 40% to about 50%
water until conversion to the required form is
complete, followed by filtration.

The present invention also provides a process for
the preparation of crystalline Form IV atorvastatin
30 which comprises crystallizing atorvastatin from a
solution thereof in solvents under conditions which
yield crystalline Form IV atorvastatin.

The precise conditions under which Form IV of
crystalline atorvastatin is formed may be empirically
35 determined and it is only possible to give a method
which has been found to be suitable in practice.

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Thus, for example, when the starting material is Form I of crystalline atorvastatin, the desired Form IV of crystalline atorvastatin may be obtained by dissolving the solid in methanol whereupon crystalline Form IV precipitates.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either compounds or a corresponding pharmaceutically acceptable salt of a compound of the present invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in

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suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from two or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

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

Liquid form preparations include solutions, suspensions, retention enemas, and emulsions, for example water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component

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in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

5 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition
10 to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

 The pharmaceutical preparation is preferably in
15 unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as
20 packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

 The quantity of active component in a unit dose
25 preparation may be varied or adjusted from 0.5 mg to 100 mg, preferably 2.5 mg to 80 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

30 In therapeutic use as hypolipidemic and/or hypocholesterolemic agents, the crystalline Forms I, II, and Form IV atorvastatin utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 2.5 mg to
35 about 80 mg daily. A daily dose range of about 2.5 mg to about 20 mg is preferred. The dosages, however, may

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be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

[R-(R*,R*)]-2-(4-Fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form I Atorvastatin)

Method A

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48-58°C for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25-35°C, the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47-52°C. To this solution is added a solution of calcium acetate hemihydrate (11.94 kg) dissolved in water (410 L), over at least

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30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to 51-57°C for at least 10 minutes and then cooled to 15-40°C. The mixture is filtered, washed with a solution of water (300 L) and methanol (150 L) followed by water (450 L). The solid is dried at 60-70°C under vacuum for 3 to 4 days to give crystalline Form I atorvastatin (72.2 kg).

Method B

Amorphous atorvastatin (9 g) and crystalline Form I atorvastatin (1 g) are stirred at about 40°C in a mixture of water (170 mL) and methanol (30 mL) for a total of 17 hours. The mixture is filtered, rinsed with water, and dried at 70°C under reduced pressure to give crystalline Form I atorvastatin (9.7 g).

20

EXAMPLE 2

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form II Atorvastatin)

25

A mixture of amorphous and crystalline Form I atorvastatin (100 g) was suspended in a mixture of methanol (1200 mL) and water (800 mL) and stirred for 3 days. The material was filtered, dried at 70°C under reduced pressure to give crystalline Form II atorvastatin.

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EXAMPLE 3

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form IV Atorvastatin)

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number 5,273,995) (12 kg), MTBE (50 kg), methanol (30 L) is reacted with an aqueous solution of sodium hydroxide (1.83 kg in 150 L) at 50-55°C for 30-45 minutes to form the ring-opened sodium salt. After cooling to 20-25°C, the organic layer is discarded and the aqueous layer is again extracted with MTBE (37 kg). The organic layer is discarded and the aqueous solution of the sodium salt is heated to 70-80°C and the residual MTBE is removed by distillation. The solution is then cooled to 60-70°C. To this solution is added a solution of calcium acetate hemihydrate (1.91 kg) dissolved in water/methanol (72 L water + 16 L methanol). The mixture is seeded with crystalline Form I atorvastatin (180 g) shortly after addition of the calcium acetate solution. The mixture is heated at 65-75°C for at least 5 minutes and then cooled to 50-55°C. The mixture is filtered and slurried in methanol (about 200 L) at 55-65°C and then cooled to 25-30°C and filtered. The solid is dried at 66-70°C under vacuum to give Form IV of crystalline atorvastatin (about 3 kg isolated).

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CLAIMS

1. Crystalline Form I atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding using $\text{CuK}\alpha$ radiation:

	2θ	d	Relative Intensity (>20%) Ground 2 Minutes
10	9.150	9.6565	42.60
	9.470	9.3311	41.94
	10.266	8.6098	55.67
	10.560	8.3705	29.33
15	11.853	7.4601	41.74
	12.195	7.2518	24.62
	17.075	5.1887	60.12
	19.485	4.5520	73.59
	21.626	4.1059	100.00
20	21.960	4.0442	49.44
	22.748	3.9059	45.85
	23.335	3.8088	44.72
	23.734	3.7457	63.04
	24.438	3.6394	21.10
25	28.915	3.0853	23.42
	29.234	3.0524	23.36

2. Crystalline Form I atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

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	Assignment (7 kHz)	Chemical Shift
5	C12 or C25	182.8
	C12 or C25	178.4
	C16	166.7 (broad) and 159.3
	Aromatic Carbons	
10	C2-C5, C13-C18, C19-C24, C27-C32	137.0
		134.9
		131.1
		129.5
		127.6
15		123.5
		120.9
		118.2
		113.8
	C8,C10	73.1
20		70.5
		68.1
		64.9
	Methylene Carbons	
	C6, C7, C9, C11	47.4
25		41.9
		40.2
	C33	26.4
		25.2
	C34	21.3

3. Crystalline Form I atorvastatin of Claim 1 in which the hydrate is a trihydrate.
4. Crystalline Form II atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of

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the 2 θ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding using CuK α radiation:

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2 θ	d	Relative Intensity (>20%) Ground 2 Minutes
5.582	15.8180	42.00
7.384	11.9620	38.63
8.533	10.3534	100.00
9.040	9.7741	92.06
12.440 (broad)	7.1094	30.69
15.771 (broad)	5.6146	38.78
17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
19.490	4.5507	56.64
20.502	4.3283	67.20
22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
25.697 (broad)	3.4639	38.93
29.504	3.0250	37.86

5. Crystalline Form II atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

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5	Assignment	Chemical Shift
	Spinning Side Band	209.1
	Spinning Side Band	206.8
	C12 or C25	181 (broad)
	C12 or C25	163 (broad)
10	C16	161 (broad)
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	140.5
		134.8
		133.3
15		129.0
		122.9
		121.4
		120.3
		119.0
20		117.1
		115.7
		114.7
	C8, C10	70.6
		69.0
25		68.0
		67.3
	Spinning Side Band	49.4
	Spinning Side Band	48.9
	Methylene Carbons	
30	C6, C7, C9, C11	43.4
		42.3
		41.7
		40.2
	C33	27.5
35	C34	22.8 (broad)

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6. Crystalline Form IV atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >15% measured using $\text{CuK}\alpha$ radiation:

5

	2θ	d	Relative Intensity (>15%)
	4.889	18.605	38.45
10	5.424	16.2804	20.12
	5.940	14.8660	17.29
	7.997	11.0465	100.00
	9.680	9.1295	67.31
	10.416	8.4859	20.00
15	12.355	7.1584	19.15
	17.662	5.0175	18.57
	18.367	4.8265	23.50
	19.200	4.6189	18.14
	19.569	4.5327	54.79
20	21.723	4.0879	17.99
	23.021	3.8602	28.89
	23.651	3.7587	33.39
	24.143	3.6832	17.23

7. Crystalline Form IV atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

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	Assignment	Chemical Shift
5	C12 or C25	186.4
		184.9
	C12 or C25	181.4
		179.3
	C16	166.1 (broad) and 159.0 (broad)
	Aromatic Carbons	
10	C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
		134.7
		129.2
		127.1
		122.7
		119.8
		115.7
	C8, C10	
		71.5
		67.9
		66.3
		63.5
	Methylene Carbons	
15	C6, C7, C9, C11	46.1
		43.4
		42.1
		40.0
	C33	25.9
	C34	20.3
		19.4
		17.9

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8. A pharmaceutical composition in the form of tablets comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one pharmaceutically acceptable excipient, diluent, or carrier.
- 5
9. A pharmaceutical composition in the form of capsules comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
- 5
10. A pharmaceutical composition in the form of a powder comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
- 5
11. A pharmaceutical composition in the form of lozenges comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
- 5
12. A pharmaceutical composition in the form of suppositories comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
- 5
13. A pharmaceutical composition in the form of retention enemas comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
- 5

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14. A method of treating hyperlipidemia and hypercholesterolemia comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 5
15. A process for the preparation of crystalline Form I atorvastatin comprising:
Step (a) treating an aqueous solution of a basic salt of [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-
5 [(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid with a calcium salt; and
Step (b) isolating crystalline Form I atorvastatin.
16. A process according to Claim 15 wherein in Step (a) seeds of crystalline Form I atorvastatin are added during or after treating the aqueous solution of a basic salt of [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid with a calcium salt.
- 5
17. A process according to Claim 15 wherein in Step (a) the aqueous solution contains a hydroxylic co-solvent and methyl tert-butyl ether.
18. A process according to Claim 17 wherein in Step (a) the hydroxylic co-solvent is methanol.
19. A process according to Claim 15 wherein in Step (a) the calcium salt is calcium acetate.

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20. A process according to Claim 15 wherein in Step (b) crystalline Form I atorvastatin is further dried.
21. A process according to Claim 20 wherein in Step (b) crystalline Form I atorvastatin is further dried under reduced pressure.
22. A process according to Claim 15 wherein in Step (a) the basic salt is selected from the group consisting of an alkali metal salt, ammonia, and an amine salt.
23. A process according to Claim 22 wherein in Step (a) the basic salt is the sodium salt.
24. A process according to Claim 15 wherein two moles of the basic salt to one mole of the calcium salt is used.
25. A process for the preparation of crystalline Form I atorvastatin comprising:
Step (a) suspending a mixture of amorphous atorvastatin and crystalline Form I atorvastatin in water containing a co-solvent; and
Step (b) isolating crystalline Form I atorvastatin.
26. A process according to Claim 25 wherein in Step (a) the co-solvent is selected from the group consisting of methanol, ethanol, 2-propanol, and acetone.
27. A process according to Claim 26 wherein in Step (a) the co-solvent is methanol.

5

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28. A process according to Claim 25 wherein in Step (b) crystalline Form I atorvastatin is further dried.
29. A process according to Claim 28 wherein in Step (b) crystalline Form I atorvastatin is further dried under reduced pressure.

ANEXO 2

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 207/34, A61K 31/40	A1	(11) International Publication Number: WO 97/03958 (43) International Publication Date: 6 February 1997 (06.02.97)
(21) International Application Number: PCT/US96/11367 (22) International Filing Date: 8 July 1996 (08.07.96) (30) Priority Data: 60/001,454 17 July 1995 (17.07.95) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): MCKENZIE, Ann, T. [US/US]; 1932 Happy Hollow Road, West Lafayette, IN 47906 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		(81) Designated States: AU, BG, BR, CA, CN, CZ, EE, GE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, UZ, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: FORM III CRYSTALLINE (R-(R*,R*)-2-(4-FLUOROPHENYL)-BETA-DELTA-DIHYDROXY-5-(1-METHYL-ETHYL)-3-PHENYL-4-((PHENYLAMINO)CARBONYL)-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN) (57) Abstract A novel crystalline form of [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt designated Form III is characterized by its X-ray powder diffraction and/or solid state NMR is described, as well as methods for the preparation and pharmaceutical composition of the same, which is useful as an agent for treating hyperlipidemia and hypercholesterolemia.		

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5 **FORM III CRYSTALLINE (R-(R*,R*)-2-(4-FLUOROPHENYL)-BETA-DELTA-DIHYDROXY-5-(1-METHYL-ETHYL)-3-PHENYL-4-((PHENYLAMINO)CARBONYL)-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)**

10 BACKGROUND OF THE INVENTION

 The present invention relates to a novel
crystalline form of atorvastatin which is known by the
chemical name [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -
15 dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)
carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt
useful as a pharmaceutical agent, to methods for its
production and isolation, to pharmaceutical
compositions which include this compound and a
20 pharmaceutically acceptable carrier, and to
pharmaceutical methods of treatment. The novel
crystalline compound of the present invention is useful
as an inhibitor of the enzyme 3-hydroxy-3-
methylglutaryl-coenzyme A reductase (HMG-CoA reductase)
25 and is thus useful as a hypolipidemic and
hypocholesterolemic agent.

 United States Patent Number 4,681,893, which is
herein incorporated by reference, discloses certain
trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1-
30 yl)alkyl]-4-hydroxy-pyran-2-ones including trans ($\pm$)-5-
(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-
[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-
pyrrole-3-carboxamide.

 United States Patent Number 5,273,995, which is
35 herein incorporated by reference, discloses the
enantiomer having the R form of the ring-opened acid of
trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-
diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-
2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e.,

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

United States Patent Numbers 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; and
5,342,952, which are herein incorporated by reference,
disclose various processes and key intermediates for
preparing atorvastatin.

Atorvastatin is prepared as its calcium salt,
i.e., [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The
calcium salt is desirable since it enables atorvastatin
to be conveniently formulated in, for example, tablets,
capsules, lozenges, powders, and the like for oral
administration. Additionally, there is a need to
produce atorvastatin in a pure and crystalline form to
enable formulations to meet exacting pharmaceutical
requirements and specifications.

Furthermore, the process by which atorvastatin is
produced needs to be one which is amenable to large-
scale production. Additionally, it is desirable that
the product should be in a form that is readily
filterable and easily dried. Finally, it is
economically desirable that the product be stable for
extended periods of time without the need for
specialized storage conditions.

The processes in the above United States Patents
disclose amorphous atorvastatin which has unsuitable
filtration and drying characteristics for large-scale
production and must be protected from heat, light,
oxygen, and moisture.

We have now surprisingly and unexpectedly found
that atorvastatin can be prepared in crystalline form.
Thus, the present invention provides atorvastatin in a

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new crystalline form designated Form III. Form III atorvastatin has different physical characteristics compared to the previous amorphous product.

5

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to crystalline Form III atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >25% measured on a Siemens D-500 diffractometer with $\text{CuK}\alpha$ radiation:

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	2 θ	d	Relative Intensity (>25%)
	4.123	21.4140	49.20
	4.993	17.6832	30.82
	5.768	15.3099	28.69
5	7.670	11.5173	25.49
	8.451	10.4538	100.00
	15.962	5.5478	32.59
	16.619	5.3298	62.34
	17.731	4.9981	49.29
10	18.267	4.8526	45.12
	18.870	4.6989	39.52
	19.480	4.5531	36.59
	19.984	4.4393	70.34
	20.294	4.3722	69.54
15	21.105	4.2061	37.39
	21.670	4.0976	36.50
	23.318	3.8117	38.63
	24.405	3.6442	65.54
	24.967	3.5635	27.20
20	25.397	3.5041	33.75

Further, the present invention is directed to crystalline Form III atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million measured on a Bruker AX-250 spectrometer:

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		Assignment	Chemical Shift
		Spinning Side Band	214.8
			209.3
			202.3
5		C12 or C25	184.9
		C12 or C25	166.7
		C16	161.0(weak, broad)
		Aromatic Carbons	
		C2-C5, C13-C18, C19-C24, C27-C32	140.1
10			135.2
			131.8
			128.9
			124.3
			122.2
15			117.2
			114.9
		C8, C10	69.8
			67.3
			65.6
20		Methylene Carbons	
		C6, C7, C9, C11	44.1
			40.4
			35.4
		C33	27.0
25			24.1
		C34	22.1
			19.9

30 As an inhibitor of HMG-CoA, the novel crystalline form of atorvastatin is useful as a hypolipidemic and hypocholesterolemic agent.

A still further embodiment of the present invention is a pharmaceutical composition for

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administering an effective amount of crystalline
Form III atorvastatin in unit dosage form in the
treatment methods mentioned above. Finally, the
present invention is directed to methods for production
5 of Form III atorvastatin.

BRIEF DESCRIPTION OF THE DRAWINGS

10 The invention is further described by the
following nonlimiting examples which refer to the
accompanying Figures 1 to 2, short particulars of which
are given below.

15 Figure 1

Diffractiongram of Form III atorvastatin (Y-axis = 0
to maximum intensity of 2815 counts per seconds (cps)).

Figure 2

20 Solid-state ^{13}C nuclear magnetic resonance
spectrum with spinning side bands identified by an
asterisk of Form III atorvastatin.

25 DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form III atorvastatin may be
characterized by its X-ray powder diffraction pattern
and/or by its solid state nuclear magnetic resonance
30 spectra (NMR).

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X-RAY POWDER DIFFRACTION

Form III Atorvastatin

5 Form III atorvastatin was characterized by its X-ray powder diffraction pattern. Thus, the X-ray diffraction pattern of Form III atorvastatin was measured on a Siemens D-500 diffractometer with CuK_α radiation.

10 Equipment

Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software = DIFFRAC AT (SOCABIM 1986, 1992).

15 CuK_α radiation (20 mA, 40 kV, $\lambda = 1.5406 \text{ \AA}$) slits I and II at 1°) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)] Detector (Slits: III at 1° and IV at 0.15°).

Methodology

20 The silicon standard is run each day to check the X-ray tube alignment.

Continuous $\theta/2\theta$ coupled scan: 4.00° to 40.00° in 2θ , scan rate of $6^\circ/\text{min}$: 0.4 sec/ 0.04° step.

25 Sample tapped out of vial and pressed onto zero-background quartz in Al holder. Sample width 13-15 mm.

Samples are stored and run at room temperature.

30 Table 1 lists the 2θ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of $>25\%$ for crystalline Form III atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

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TABLE 1. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 25% for Form III Atorvastatin

	2θ	d	Relative Intensity (>25%)
5	4.123	21.4140	49.20
	4.993	17.6832	30.82
	5.768	15.3099	28.69
	7.670	11.5173	25.49
10	8.451	10.4538	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
15	18.870	4.6989	39.52
	19.480	4.5531	36.59
	19.984	4.4393	70.34
	20.294	4.3722	69.54
	21.105	4.2061	37.39
20	21.670	4.0976	36.50
	23.318	3.8117	38.63
	24.405	3.6442	65.54
	24.967	3.5635	27.20
	25.397	3.5041	33.75
25			

SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

Methodology

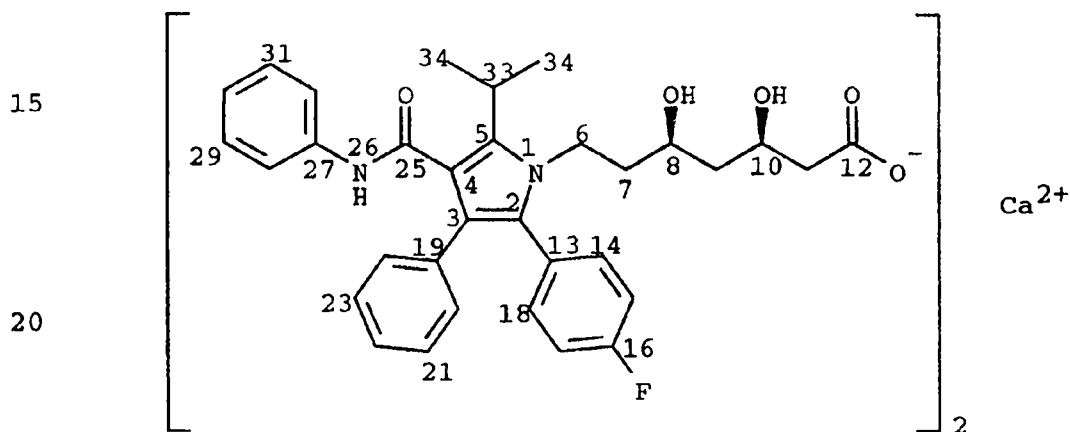
30 All solid-state ^{13}C NMR measurements were made with a Bruker AX-250, 250 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and cross-polarization (CP) with magic-angle spinning (MAS) at approximately 5 kHz. The
35 magic-angle was adjusted using the Br signal of KBr by

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detecting the side bands as described by Frye and Maciel (Frye J.S. and Maciel G.E., J. Mag. Res., 1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J.V. and Stock L.M., J. Mag. Res., 1988;76:54).

Table 2 shows the solid-state NMR spectrum for crystalline Form III atorvastatin.



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TABLE 2. Carbon Atom Assignment and Chemical Shift for Form III Atorvastatin

Assignment	Chemical Shift
Spinning Side Band	214.8
5	209.3
	202.3
C12 or C25	184.9
C12 or C25	166.7
C16	161.0 (weak, broad)
10 Aromatic Carbons	
C2-C5, C13-C18, C19-C24, C27-C32	140.1
	135.2
	131.8
	128.9
15	124.3
	122.2
	117.2
	114.9
C8, C10	69.8
20	67.3
	65.6
Methylene Carbons	
C6, C7, C9, C11	44.1
	40.4
25	35.4
C33	27.0
	24.1
C34	22.1
	19.9
30	

Crystalline Form III atorvastatin of the present invention can exist in anhydrous form as well as hydrated forms. In general, the hydrated forms, are equivalent to unhydrated forms and are intended to be

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encompassed within the scope of the present invention.

The present invention also provides a process for the preparation of crystalline Form III atorvastatin which comprises exposing atorvastatin to a high
5 relative humidity under conditions which yield crystalline Form III atorvastatin.

The precise conditions under which Form III of crystalline atorvastatin is formed may be empirically determined and it is only possible to give a method
10 which has been found to be suitable in practice.

Thus, for example, when the starting material is Form II of crystalline atorvastatin disclosed in concurrently filed United States Patent Application titled "Crystalline [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -
15 dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1)" commonly owned, attorney's Case Number PD-5250-01-FJT, Serial Number _____ (Crystalline Form I and Form IV atorvastatin are also disclosed in this
20 application), the desired Form III of crystalline atorvastatin may be obtained by exposing the solid to a relative humidity of 95% for 11 days.

Crystalline Form II atorvastatin may be prepared from amorphous, a combination of amorphous and
25 crystalline Form I atorvastatin or crystalline Form I atorvastatin. Thus, for example, when the starting material is amorphous, a combination of amorphous and Form I, or crystalline Form I atorvastatin, the desired Form II of crystalline atorvastatin may be obtained by
30 suspending the solid in methanol containing about 40% to about 50% water until conversion to the required form is complete, followed by filtration.

Crystalline Form I atorvastatin may be prepared by crystallization under controlled conditions. In
35 particular, it can be prepared either from an aqueous solution of the corresponding basic salt such as, an

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alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending amorphous atorvastatin in water. In general, the use of a hydroxylic co-solvent such as, for example, a lower alkanol, for example methanol and the like, is preferred.

The compound of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compound of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compound of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compound of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either compounds or a corresponding pharmaceutically acceptable salt of the compound of the present invention.

For preparing pharmaceutical compositions from the compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 83107810 00000001 Folios: 189
Fecha (AMD): 2004-06-25 16:52:50
Tramite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

HIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 50,621
FECHA : JUNIO 25 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	8408474	31/05/2004	224,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	224,000.00
		TOTAL :	\$ 224,000.00

SON: DOSCIENTOS VEINTICUATRO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

109

282

COPIA PARA EL MASLADO

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03107810 00000001

Folios: 109

Fecha (AND): 2004-06-25 16:52:50

Tramite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia: Expediente N° 03-107810

Asunto: Oposición a la solicitud de patente de
Invención titulada "**FORMAS
CRISTALINAS DE LA SAL DE
CALCIO DEL ACIDO [R-(R*,R*)]-
2-(4-FLUOROFENIL)- β , O-
DIHIDROXI-5-(1-METILETIL)-3-
FENIL-4-[(FENILAMINO)
CARBONIL] - 1H-PIRROL-1-
HEPTANOICO(2:1)"**

Solicitante: WARNER-LAMBERT COMPANY
LLC.

Opositora: PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 538 del 31 de marzo de 2004

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Yo, Luis Fernando Rincón Cuellar, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad PROCAPS S.A. conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "FORMAS CRISTALINAS DE LA SAL DE CALCIO DEL ACIDO [R-(R*,R*)]-2-(4-FLUOROFENIL)-β, Õ-DIHIDROXI-5-(1-METILETIL)-3-FENIL-4-[(FENILAMINO)CARBONIL]-1H-PIRROL-1-HEPTANOICO(2:1)", solicitada por WARNER-LAMBERT COMPANY LLC., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

2. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de la sociedad que represento, radicado básicamente en la comercialización que mi representada efectúa de una presentación farmacéutica elaborada con base en la misma molécula de atorvastatina. La solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará

más adelante y de ser concedida atentaría directamente contra la comercialización realizada por mi representada.

Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

3. FUNDAMENTOS DE HECHOS

3.1. La solicitud objeto de la presente oposición fue presentada el 9 de diciembre de 2003, reivindicando prioridad bajo el N° US60/302.049, de fecha 29 de junio de 2001 y cuya fecha de inicio en la fase nacional fue el 29 de enero de 2004, con publicación internacional N° WO 03/004470 del 16 de enero del 2003 y fue publicada en Colombia, en la Gaceta de la propiedad industrial N° 538, del 31 de marzo de 2004, bajo el N° de publicación NP. 12 (página 282).

3.2. La solicitud colombiana 03-107810 objeto de la presente oposición, comprende las cristalina formas V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX de atorvastatina o un hidrato de la misma, que tiene un patrón de difracción de

rayos X en polvo que contiene los valores 2θ usando radiación de CuK_α , según lo definido en las reivindicaciones 1 a 15.

3.3. Con anterioridad a la fecha de prioridad de esta solicitud, la molécula de la atorvastatina ya era parte del estado de la técnica tal y como lo referencia el mismo solicitante en su texto descriptivo cuando hace referencia al estado del arte anterior. Adicionalmente, a la fecha de prioridad de la solicitud colombiana el estado de la técnica ya revelaba los siguientes documentos en los cuales se ha estudiado la conformación de la molécula de atorvastatina amorfa en atorvastatina cristalina:

- D1: WO 9703959, del 6 de febrero de 1997.
- D2: WO 9703958, del 6 de febrero de 1997.
- D3: WO 0136384, del 25 de mayo de 2001.

3.4. La solicitud D1 y D2, del mismo solicitante, se refieren a formas cristalinas de atorvastatina conocida con el nombre de hemisal de calcio de ácido $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorofenil})-$ beta , delta -dihidroxi-5-(1-metiletil)-3-fenil-4-[(fenilamino)carbonil]-1H-pirrol-1-heptanoico designado como una Forma I, Forma II y Forma IV en el D1 y la Forma III en el D2, caracterizados por tener un patrón de difracción de rayos X en polvo y/o en

estado sólido, así como los métodos para la preparación y la composición farmacéutica del mismo, que es útil como agentes para tratar la hiperlipidemia y la hipercolesterolemia.

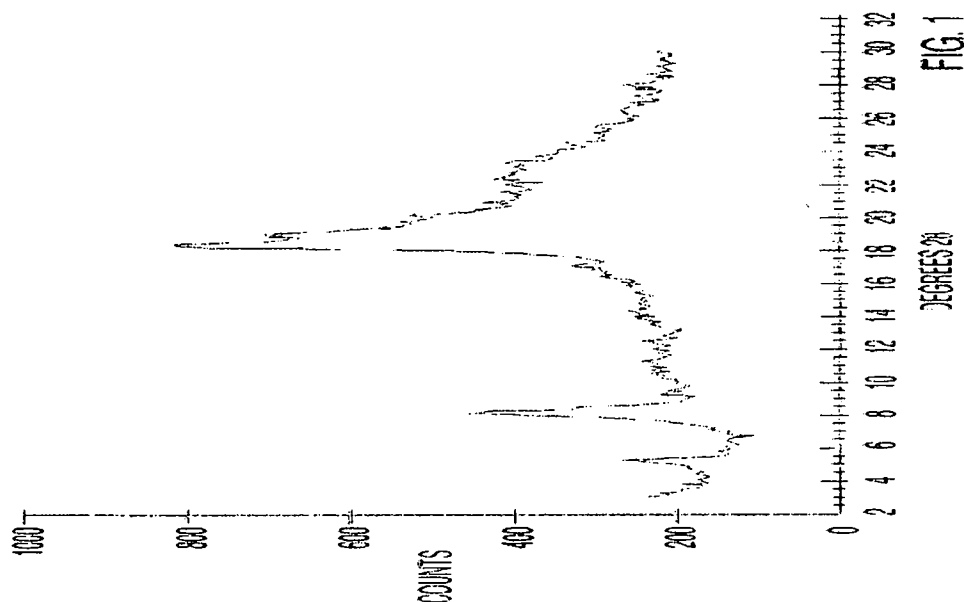
3.5. Como se puede apreciar a simple vista, el arte anterior descrito en estas solicitudes D1 y D2, ya revelaba un compuesto farmacéutico que comprendía unas formas cristalinas de atorvastatina.

3.6. Adicionalmente y como es de conocimiento general en la técnica, una forma cristalina representa un ordenamiento en el espacio o red cristalina de una estructura química (fenómeno denominado "Poliformismo"), de tal suerte, que sólo se requiere conjugar apropiadamente las condiciones de cristalización de un compuesto conocido para obtener un polimorfo derivado. Por lo tanto, aún alterando la forma de la molécula de atorvastatina, los componentes de dicha molécula se mantienen iguales, alterándose únicamente algunas propiedades fisicoquímicas del producto. El poliformismo es una técnica conocida desde 1788 (Martin Klaproth) para hacer pasar la molécula de una forma a otra.

3.7. Ahora bien, si combinamos el conocimiento indicado en estas solicitudes D1 y D2, y el conocimiento general de la técnica que dicta que las modificaciones polimórficas de un compuesto, en general pueden alterar algunas propiedades de las moléculas tales como su forma cristalina, velocidad de disolución, punto de fusión, densidad verdadera, dureza y/o fragilidad cristalina, el espectro de absorción infrarrojo o el difractograma de rayos X entre otros, indudablemente es posible derivar Formas Cristalinas V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX de atorvastatina o un hidrato de la misma, que tiene un patrón de difracción de rayos X en polvo. Es obvio, pues es de general conocimiento que algunas de estas modificaciones, en especial la alteración en la velocidad de disolución, causan diferencias en la absorción y por supuesto en los niveles de Biodisponibilidad de un medicamento presentado en forma sólida, sin implicar que exista una diferencia sustancial frente al mismo medicamento presentado en forma de solución. Así las cosas, lo expuesto en la solicitud colombiana 03-107810 en las reivindicaciones 1 a 15, se deriva evidentemente del arte anterior y es obvio para cualquier persona versada en la materia. Por lo tanto, la combinación del

conocimiento revelado en las solicitudes D1 y D2 en conjunto con el conocimiento general de la técnica, afecta de manera directa el requisito de altura inventiva de la solicitud colombiana que se pretenden proteger.

3.8. Ahora bien, la solicitud D3 de Teva, también se refiere a formas cristalinas de atorvastatina designado como una Forma V, caracterizado por tener un patrón de difracción de rayos X en polvo y/o en estado sólido. Según se describe en este documento D1, se revela una forma cristalina de atorvastatina que tiene un patrón de difracción de rayos X en polvo que contiene los valores según la figura 1.



3.9. Como se nota, la solicitud colombiana hace referencia a la misma molécula del documento D3, demostrando que alterando la forma de la molécula de atorvastatina, los componentes de dicha molécula se mantienen iguales, alterándose únicamente algunas propiedades fisicoquímicas del producto. Así las cosas, la solicitud colombiana objeto de la presente oposición no es novedosa desde ningún punto de vista, pues a todas luces lo que allí se describe ya se revelaba con anterioridad en la solicitud previa D3; por lo tanto consideramos que la concesión de esta solicitud colombiana atentaría abiertamente contra la normatividad colombiana, que explícitamente consagra a la NOVEDAD como uno de los tres elementos esenciales para que de a lugar la concesión de una patente.

3.10. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 03-107810 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los requisitos necesarios para su protección.

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

3.11.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 29 de junio de 2001, ya era conocido, pues como se demostró, era parte del arte anterior la materia sobre la cual busca protección en el capítulo reivindicatorio con base en el documento D3.

3.11.2. **CARENCIA DE ALTURA INVENTIVA**. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de presentación, 29 de junio de

2001, el documento D1 en combinación con el documento D2, es posible deducir las formas cristalinas de atorvastatina reivindicadas.

3.12. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."* La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

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

3.14. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"FORMAS CRISTALINAS DE LA SAL DE CALCIO DEL ACIDO [R-**

(R*,R*)]-2-(4-FLUOROFENIL)-β, Õ-DIHIDROXI-5-(1-METILETIL)-3-FENIL-4-[(FENILAMINO)CARBONIL]-1H-PIRROL-1-HEPTANOICO(2:1)", solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 538 del 31 de marzo de 2004, en la página 282, bajo el NP 12.

4. PRUEBAS

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

- Documento 1: WO 9703959, del 6 de febrero de 1997.
- Documento 2: WO 9703958, del 6 de febrero de 1997.
- Documento 3: WO 0136384, del 25 de mayo de 2001.

5. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

5.1. Numeral 1 del artículo 586 del Código de Comercio.

5.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

5.3. En las demás normas concordantes.

6. ANEXOS

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

6.1. ANEXO 1: WO 9703959, del 6 de febrero de 1997.

6.2. ANEXO 2: WO 9703958, del 6 de febrero de 1997.

6.3. ANEXO 3: WO 0136384, del 25 de mayo de 2001.

6.4. Recibo de pago expedido por el Fondo Especial de esa Superintendencia, en el cual consta que se ha pagado el valor correspondiente a la tasa por tramitación de esta oposición.

6.5. Copia de la oposición para el traslado al solicitante.

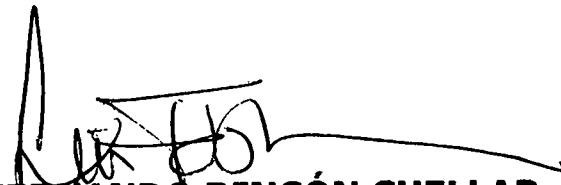
6.6. Poder para actuar a nombre de mi representada.

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7. NOTIFICACIONES

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

De la señora Jefe,



LUIS FERNANDO RINCÓN CUELLAR

C.C. No. 79.532.186 de Bogotá D.C.

T.P. No. 113438

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In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

5 The powders and tablets preferably contain from two or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, 10 sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with 15 or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

20 For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into 25 convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, retention enemas, and emulsions, for example water or water propylene glycol solutions. For 30 parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water 35 and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

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Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents..

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.5 mg to 100 mg, preferably 2.5 mg to 80 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as a hypolipidemic and/or hypocholesterolemic agent, crystalline Form III atorvastatin utilized in the pharmaceutical method of this invention is administered at the initial dosage of about 2.5 mg to about 80 mg daily. A daily dose range

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of about 2.5 mg to about 20 mg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

[R-(R*,R*)]-2-(4-Fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form I Atorvastatin)

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48-58°C for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25-35°C, the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47-52°C. To this solution is added a solution of calcium acetate hemihydrate

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(11.94 kg) dissolved in water (410 L), over at least 30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to 51-57°C for at least 10 minutes and then cooled to 15-40°C. The mixture is filtered, washed with a solution of water (300 L) and methanol (150 L) followed by water (450 L). The solid is dried at 60-70°C under vacuum for 3 to 4 days to give crystalline Form I atorvastatin (72.2 kg).

EXAMPLE 2

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form II Atorvastatin)

A mixture of amorphous and crystalline Form I atorvastatin (100 g) was suspended in a mixture of methanol (1200 mL) and water (800 mL) and stirred for 3 days. The material was filtered, dried at 70°C under reduced pressure to give crystalline Form II atorvastatin.

EXAMPLE 3

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form III Atorvastatin)

Form II atorvastatin (Example 2) is rotapped through a 50 mesh screen onto a 100 mesh screen and exposed in a humidity jar to 95% relative humidity for 11 days to afford crystalline Form III atorvastatin.

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CLAIMS

1. Crystalline Form III atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >25% measured using $\text{CuK}\alpha$ radiation:

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2θ	d	Relative Intensity (>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	10.4538	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
19.984	4.4393	70.34
20.294	4.3722	69.54
21.105	4.2061	37.39
21.670	4.0976	36.50
23.318	3.8117	38.63
24.405	3.6442	65.54
24.967	3.5635	27.20
25.397	3.5041	33.75

2. Crystalline Form III atorvastatin and hydrates thereof characterized by the following solid-state

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^{13}C nuclear magnetic resonance spectrum wherein
chemical shift is expressed in parts per million:

5	Assignment	Chemical Shift
	Spinning Side Band	214.8
		209.3
		202.3
	C12 or C25	184.9
10	C12 or C25	166.7
	C16	161.0 (weak, broad)
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	140.1
		135.2
15		131.8
		128.9
		124.3
		122.2
		117.2
20		114.9
	C8, C10	69.8
		67.3
		65.6
	Methylene Carbons	
25	C6, C7, C9, C11	44.1
		40.4
		35.4
	C33	27.0
		24.1
30	C34	22.1
		19.9

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3. A pharmaceutical composition in the form of tablets comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one pharmaceutically acceptable excipient, diluent, or carrier.
5
 4. A pharmaceutical composition in the form of capsules comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
5
 5. A pharmaceutical composition in the form of a powder comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
5
 6. A pharmaceutical composition in the form of lozenges comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
5
 7. A pharmaceutical composition in the form of suppositories comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
5
 8. A pharmaceutical composition in the form of retention enemas comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
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9. A method of treating hyperlipidemia and hypercholesterolemia comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
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ANEXO 3

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 May 2001 (25.05.2001)

PCT

(10) International Publication Number
WO 01/36384 A1

(51) International Patent Classification⁷: **C07D 207/335**,
A61K 31/40

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(21) International Application Number: **PCT/US00/31555**

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(22) International Filing Date:

16 November 2000 (16.11.2000)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/166,153 17 November 1999 (17.11.1999) US

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

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 01/36384 A1

(54) Title: **POLYMORPHIC FORM OF ATORVASTATIN CALCIUM**

(57) Abstract: The present invention relates to atorvastatin calcium, a useful agent for lowering serum cholesterol levels. New atorvastatin calcium Form V, processes for preparing the new form, and pharmaceutical compositions and dosage forms containing the new form are disclosed.

POLYMORPHIC FORM OF ATORVASTATIN CALCIUM

FIELD OF THE INVENTION

The present invention relates to a novel crystalline form of atorvastatin calcium, to
5 processes for preparing it and to pharmaceutical compositions and dosages containing it.

BACKGROUND OF THE INVENTION

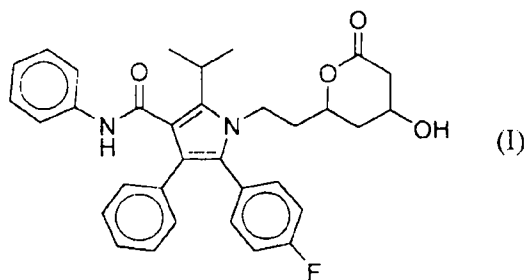
Atorvastatin is a member of the class of drugs called statins. Statin drugs are
currently the most therapeutically effective drugs available for reducing low density
10 lipoprotein (LDL) particle concentration in the blood stream of patients at risk for
cardiovascular disease. A high level of LDL in the bloodstream has been linked to the
formation of coronary lesions which obstruct the flow of blood and can rupture and
promote thrombosis. Goodman and Gilman, *The Pharmacological Basis of Therapeutics*
879 (9th ed. 1996). Reducing plasma LDL levels has been shown to reduce the risk of
15 clinical events in patients with cardiovascular disease and patients who are free of
cardiovascular disease but who have hypercholesterolemia. Scandinavian Simvastatin
Survival Study Group, 1994; Lipid Research Clinics Program, 1984a, 1984b.

The mechanism of action of statin drugs has been elucidated in some detail. They
interfere with the synthesis of cholesterol and other sterols in the liver by competitively
20 inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase enzyme ("HMG-CoA
reductase"). HMG-CoA reductase catalyzes the conversion HMG to mevalonate, which

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is the rate determining step in the biosynthesis of cholesterol, and so, its inhibition leads to a reduction in the concentration of cholesterol in the liver. Very low density lipoprotein (VLDL) is the biological vehicle for transporting cholesterol and triglycerides from the liver to peripheral cells. VLDL is catabolized in the peripheral cells which releases fatty acids which may be stored in adipocytes or oxidized by muscle. The VLDL is converted to intermediate density lipoprotein (IDL), which is either removed by an LDL receptor, or is converted to LDL. Decreased production of cholesterol leads to an increase in the number of LDL receptors and corresponding reduction in the production of LDL particles by metabolism of IDL.

Atorvastatin is the common chemical name of $[R-(R^*, R^*)]$ -2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid. The free acid is prone to lactonization. The molecular structure of the lactone is represented by formula (I).

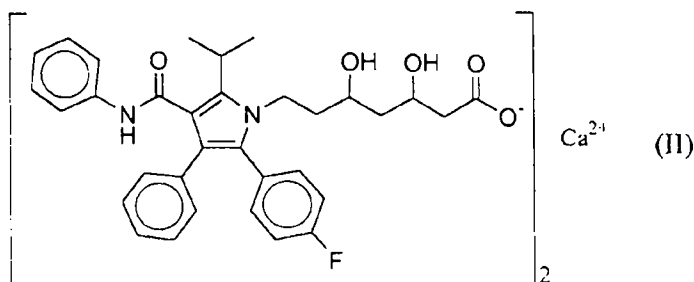


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Atorvastatin is marketed as the hemi calcium salt-trihydrate under the name LIPITOR by Warner-Lambert Co.

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Atorvastatin was first disclosed to the public and claimed in U.S. Patent No. 4,681,893. The hemi calcium salt depicted in formula (II) (hereafter "atorvastatin calcium") is disclosed in U.S. Patent No. 5,273,995. This patent teaches that the calcium salt is obtained by crystallization from a brine solution resulting from the transposition of the sodium salt with CaCl_2 and further purified by recrystallization from a 5:3 mixture of ethyl acetate and hexane. Both of these U.S. patents are hereby incorporated by reference.

The present invention includes a new crystal form of atorvastatin calcium in both hydrate and anhydrate states. Polymorphism is the property of some molecules and molecular complexes to assume more than one crystalline or amorphous form in the solid state. A single molecule, like the atorvastatin in formula (I) or the salt complex of formula (II), may give rise to a variety of solids having distinct physical properties like solubility, X-ray diffraction pattern and solid state ^{13}C NMR spectrum. The differences in the physical properties of polymorphs result from the orientation and intermolecular interactions of adjacent molecules (complexes) in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular formula, which may be thought

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of as analogous to a unit cell in metallurgy, yet having distinct advantageous and/or disadvantageous physical properties compared to other forms in the polymorph family.

One of the most important physical properties of pharmaceutical polymorphs is their solubility in aqueous solution, particularly their solubility in the gastric juices of a patient.

5 For example, where absorption through the gastrointestinal tract is slow, it is often desirable for a drug that is unstable to conditions in the patient's stomach or intestine to dissolve slowly so that it does not accumulate in a deleterious environment. On the other hand, where the effectiveness of a drug correlates with peak bloodstream levels of the drug, a property shared by statin drugs, and provided the drug is rapidly absorbed by the
10 GI system, then a more rapidly dissolving form is likely to exhibit increased effectiveness over a comparable amount of a more slowly dissolving form.

U.S. Patent No. 5,969,156 discloses three polymorphs of atorvastatin designated Forms I, II, and IV by the inventors of those forms. While the inventors of U.S. Patent No. 5,969,156 claim certain processing and therapeutic advantages of their forms over
15 amorphous atorvastatin calcium, advantages may yet be realized by other heretofore undiscovered forms of atorvastatin calcium.

SUMMARY OF THE INVENTION

The present invention provides new Form V of atorvastatin calcium in both
20 anhydrate and hydrate states, which possesses the advantage of higher solubility in water than atorvastatin Form I. The present invention further provides a process for preparing

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new Form V as well as pharmaceutical compositions and dosages containing the new form.

BRIEF DESCRIPTION OF THE DRAWINGS

- 5 FIG. 1 is an X-ray powder diffractogram of atorvastatin calcium Form V.
FIG. 2 is a solid state ^{13}C NMR spectrum of atorvastatin calcium Form V.

DETAILED DESCRIPTION OF THE INVENTION

The new crystalline form of atorvastatin calcium Form V is well distinguished
10 from the crystal modifications obtained by carrying out the procedures described in U.S. Patents Nos. 5,273,995 and 5,969,156 using X-ray powder diffraction and solid-state ^{13}C nuclear magnetic resonance techniques.

The X-ray powder diffractogram of Form V (Fig.1) has two medium peaks at
5.3 $\pm$ 0.2 and 8.3 $\pm$ 0.2 degrees 2θ and one large peak in the range 18-23 degrees 2θ with a
15 maximum at about 18.3 $\pm$ 0.2 degrees two-theta. This X-Ray pattern is well distinguished from that of known Forms I, II, III and IV and also is well distinguished from the X-Ray pattern of amorphous atorvastatin calcium which is characterized by two broad humps in the ranges 8-14 degrees 2θ and 15-26 degrees 2θ . The X-ray powder diffractogram of Fig. 1 was obtained by methods known in the art using a Philips X-ray powder
20 diffractometer with a curved graphite monochromator using goniometer model 1050/70. Copper radiation of $\lambda = 1.5418 \text{ \AA}$ was used. Measurement range: 3-30 degrees 2θ .

a3

The solid-state ^{13}C NMR spectrum of Form V is characterized by the following chemical shifts:

	δ (ppm)
	21.9
5	25.9
	40.4
	41.8
	42.3
	63-73 (two broad peaks)
10	115.6
	118.9
	122.5
	128.7 (strong)
	135.1
15	161.0
	167.1
	176-186 (broad peak)

This solid-state ^{13}C NMR spectrum (Fig. 2) is well distinguished from those of known Forms I, II, III and IV, and also is distinguished from that of the amorphous form which displays a different pattern with shifts significantly different from that of Form V at 21.0 ppm, 26.4 ppm, one broad peak in the range 60-75 ppm with a maximum at 69.7 ppm and 138.8 ppm. The spectrum of Fig. 2 was obtained on a Bruker DMX-500 digital F NMR spectrometer operating at 125.76 MHz. The instrument was equipped with a BL-4 cpmas probehead and a high resolution/high performance (HPHP) ^1H for solids. The magic angle and proton decoupling efficiency were optimized before acquisition. The sample was spun at 5.0 kHz spin rate on 4 mm zirconia rotors.

Atorvastatin calcium Form V may contain up to 12% water, which corresponds to the stoichiometric value of 9 water molecules per molecule of atorvastatin calcium. Thus, atorvastatin calcium Form V can be in various states of hydration, between 0 and 9 moles of water.

5 The present invention further provides a process for the preparation of atorvastatin calcium Form V. The process comprises the steps of dissolving a salt of atorvastatin in a solvent to form an atorvastatin salt solution, optionally removing impurities from the atorvastatin salt solution, contacting the atorvastatin salt solution with a calcium salt and isolating atorvastatin calcium in new Form V.

10 The atorvastatin salt of the present invention includes alkali metal salts, e.g. lithium, sodium, and potassium salts; alkaline-earth metal salts such as magnesium salts; as well as ammonium and alkyl, aryl or alkaryl ammonium salts. The preferred atorvastatin salts are alkali metal salts; most preferred is the sodium salt.

Any solvent capable of dissolving the atorvastatin salt and from which atorvastatin
15 calcium Form V may be isolated is a suitable solvent of the invention. The choice of solvent will therefore depend upon the selection of the atorvastatin salt and the calcium salt. The solvent should be selected from those in which the atorvastatin salt and calcium salt are at least sparingly soluble. By sparingly soluble is meant not substantially less
20 soluble than 0.02 g/ml at 50-60°C for the atorvastatin salt and not substantially less soluble than 0.0002 M at 10-15°C for the calcium salt.

Suitable solvents include but are not limited to hydroxylic solvents like water, alcohols and mixtures thereof, including hydroxylic solvents and hydroxylic solvent mixtures which have been made either acidic or basic by addition of a mineral acid or base. Preferred solvents are water, methanol, ethanol and mixtures thereof.

5 The calcium salt of the present invention includes organic and inorganic salts of calcium which are capable of dissociating into Ca^{2+} and an anionic component when added to the atorvastatin salt solution. Among the organic salts that may be used are carboxylates and sulfonates. Among the carboxylates are lower alkyl carboxylates like acetate, propionate, butyrate and tartrate and aryl carboxylates like benzoate and
10 phthalate as well as higher alkyl carboxylates like stearate, dodecanoate and the like. Also included are calcium ascorbate and succinate. Among the sulfonates that may be used are lower alkyl and aryl sulfonates like calcium methane sulfonate, calcium benzene sulfonate and calcium *p*-toluene sulfonate. The preferred organic calcium salts are lower carboxylate salts, the most preferred organic calcium salt is calcium acetate.

15 Depending upon solubility, inorganic salts which may be used include halide salts such as CaCl_2 , CaF_2 , CaBr_2 and CaI_2 , as well as calcium borate (B_4CaO_7), calcium tetrafluoroborate (CaBF_4), calcium carbonate (CaCO_3), monobasic calcium phosphate ($\text{Ca}(\text{H}_2\text{PO}_4)_2$), dibasic calcium phosphate (CaHPO_4) and tribasic calcium phosphate ($\text{Ca}(\text{PO}_4)_2$), calcium sulfate (CaSO_4) and calcium hydroxide ($\text{Ca}(\text{OH})_2$), and hydrates
20 thereof.

Whether organic or inorganic, the calcium salt is preferably added in an amount that provides one half mole of Ca^{2+} per mole of atorvastatin in the atorvastatin salt solution. For example, if the atorvastatin salt is atorvastatin sodium ($\text{atorvastatin}^- \text{Na}^+$), then about one half mole of calcium salt per mole of the atorvastatin salt is appropriate. If
5 the atorvastatin salt is atorvastatin magnesium ($[\text{atorvastatin}^-]_2 \text{Mg}^{2+}$), then about one mole of calcium salt per mole of atorvastatin salt is appropriate. Otherwise, mixed salts containing atorvastatin may form.

The calcium salt may be contacted with the atorvastatin salt solution by adding the calcium salt in substantially pure form, *i.e.* either as a solid or, if liquid, as a neat liquid, to
10 the atorvastatin salt solution or, preferably, by first forming a calcium salt solution and then contacting the atorvastatin salt solution and calcium salt solution. It is most preferred to contact the calcium salt and the atorvastatin salt solution by first dissolving the calcium salt in a solvent and then adding the calcium salt solution to the atorvastatin salt solution slowly. Suitable calcium salt solvents are solvents previously mentioned as being suitable
15 solvents for the atorvastatin salt, provided the calcium salt is at least sparingly soluble in the particular solvent.

In a particularly preferred embodiment, wherein the atorvastatin salt is an atorvastatin alkali metal salt and the atorvastatin salt solvent is a 1:2 methanol:water mixture, the preferred calcium salt is calcium acetate and the preferred calcium salt solvent
20 is water. When the calcium salt solvent is water, it is preferably used in an amount that

provides about a 20 to 30 millimolar solution of the calcium salt, more preferably about a 25 millimolar solution.

In addition, the atorvastatin and calcium salts are preferably combined at elevated temperature and at concentrations disclosed above and in the examples, which follow, in order that crystallization of Form V may be induced by cooling of the so-formed atorvastatin calcium solution. The elevated temperature is preferably above 40°C and below 80°C, more preferably above 50°C and below 70°C and most preferably about 60°C. One skilled in the art will appreciate that by adjusting temperature and concentration, the yield of atorvastatin calcium Form V may be optimized. Crystallization of atorvastatin calcium Form V may also be induced by addition of a seed crystal of atorvastatin calcium, preferably Form V although other forms also may be used.

Once crystals of atorvastatin Form V have crystallized, either spontaneously, upon cooling, upon seeding or by another inducement, the crystals may be isolated by filtration or other conventional means known to the art. The isolated crystals may also be dried by conventional means.

It has also been found that atorvastatin calcium can be crystallized in Form V by dissolving atorvastatin calcium in THF or alcohols like methanol or ethanol, and subsequently adding water as an antisolvent.

A further aspect of the present invention is a pharmaceutical composition and dosage form containing the novel form of atorvastatin calcium.

The compositions of the invention include powders, granulates, aggregates and other solid compositions comprising novel Form V of atorvastatin calcium. In addition, Form V solid compositions that are contemplated by the present invention may further included diluents, such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents like calcium carbonate and calcium diphosphate and other diluents known to the pharmaceutical industry. Yet other suitable diluents include waxes, sugars and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Further excipients that are within the contemplation of the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes. Excipients that may also be present in a solid composition of Form V atorvastatin calcium further include disintegrants like sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others. In addition, excipients may include tableting lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The

5 Dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

Dosage forms include solid dosage forms, like tablets, powders, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions and elixirs. While the description is not intended to be limiting, the invention is also not intended to

10 pertain to true solutions of atorvastatin calcium whereupon the properties that distinguish the solid forms of atorvastatin calcium are lost. However, the use of the novel forms to prepare such solutions (e.g. so as to deliver, in addition to atorvastatin, a solvate to said solution in a certain ratio with a solvate) is considered to be within the contemplated invention.

15 Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate,

20 carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be

employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

Preferred unit dosages of the pharmaceutical compositions of this invention typically contain from 0.5 to 100 mg of the novel atorvastatin calcium Form V, or mixtures thereof with other forms of atorvastatin calcium. More usually, the combined weight of the atorvastatin calcium forms of a unit dosage are from 2.5 mg. to 80 mg.

Having thus described the various aspects of the present invention, the following examples are provided to illustrate specific embodiments of the present invention. They are not intended to be limiting in any way.

EXAMPLES

EXAMPLE I

The sodium salt of atorvastatin (52.2 g) was dissolved in methanol (510 ml) and then diluted with water (1 L). The resulting solution was transferred to a separatory funnel containing 1:1 ethyl acetate/hexane (1 L). The phases were mixed by bubbling nitrogen gas through the separatory funnel. Upon cessation of nitrogen flow, the phases separated and the upper, organic, phase was removed. The lower, aqueous, phase was washed with 1:1 ethyl acetate/hexane (1 L) and then transferred to a round bottom flask. Active charcoal (10.2 g) was added. The flask was heated to 50 °C and the solution was stirred for two hours. The activated charcoal was then removed by filtration through celite, the

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charcoal and celite being rinsed with methanol (1540 ml), and the rinsate and filtrate then being combined into one atorvastatin sodium salt solution.

The quantity of atorvastatin obtained by purification was determined by calibrated HPLC analysis of the purified atorvastatin sodium salt solution. Based on this analysis, a
5 quantity of calcium acetate (8.38 g, 0.5 eq.) was dissolved in water (1.9 L) and heated to 60 °C. The atorvastatin sodium salt solution was heated to 63 °C and the solutions were combined by slow addition of the calcium acetate solution to the atorvastatin sodium salt solution. Upon completing the addition, the mixture was cooled. Crystallization of Form V began to occur at a temperature of 43 °C and cooling was continued until the flask
10 temperature reached 13 °C.

The crystals were isolated by slow vacuum filtration and then dried over anhydrous silica for 5 days to yield atorvastatin calcium salt Form V.

EXAMPLE 2

15 Atorvastatin calcium (10 g) was dissolved in methanol (400 ml) at room temperature. Water (300 ml) was added slowly to the methanolic solution with stirring and the resulting solution was heated to 60°C. The solution was then cooled to between 10 and 15 °C within 3 h. Precipitation started at about 40°C. The thick slurry was then dried at
20 50°C under reduced pressure for 48 h to yield atorvastatin calcium Form V.

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EXAMPLE 3

Atorvastatin calcium (5 g) was dissolved in methanol (100 ml) at room temperature. To this methanolic solution, water (100 ml) was added while stirring. Precipitation occurred instantly and after cooling the slurry to 15°C the precipitate was
5 filtered and dried at 50°C under reduced pressure for 48 h to yield atorvastatin calcium Form V.

EXAMPLE 4

Atorvastatin calcium (5 g) was dissolved in methanol (200 ml). The methanolic
10 solution was placed into a stirred reactor containing water (150 ml) at 45°C. The obtained slurry was cooled to 10°C, filtered and dried at 50°C under reduced pressure for 48 h to yield atorvastatin calcium Form V.

EXAMPLE 5

Atorvastatin calcium (1 g) was dissolved in ethanol (15 ml) after heating. To this
15 ethanolic solution, water (10 ml) was added while stirring. Precipitation occurred instantly. The gel-like precipitate was filtered without vacuum and dried at 50°C under reduced pressure for 24 h to yield atorvastatin calcium Form V.

EXAMPLE 6

Atorvastatin calcium (1 g) was dissolved in THF (25 ml) at room temperature. To this solution, water (60 ml) was added while stirring. The reaction mixture was stirred for 18 hours at room temperature and the precipitate (gel) was filtered without vacuum and
5 dried at 50°C under reduced pressure for 24 h to yield atorvastatin calcium Form V.

The invention has been described with reference to its preferred embodiments. From this description, those skilled in the art may appreciate changes that could be made in the invention which do not depart from the scope and spirit of the invention as described above and claimed hereafter.

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CLAIMS

We claim:

1. Atorvastatin calcium Form V or hydrate thereof.
2. The atorvastatin calcium Form V or hydrate thereof of claim 1 having an X-ray powder diffractogram substantially as depicted in Figure 1.
3. The atorvastatin calcium Form V or hydrate thereof of claim 1 having X-ray powder diffraction peaks at about 5.5 and 8.3 degrees at 2θ and a broad peak at about 18-23 degrees 2θ .
4. The atorvastatin calcium Form V or hydrate thereof of claim 1 having a solid state ^{13}C NMR spectrum substantially as depicted in Figure 2.
5. The atorvastatin calcium Form V or hydrate thereof of claim 1 having solid state ^{13}C NMR signals at about 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm.
6. Atorvastatin calcium Form V containing up to about 9 moles of water per mole of atorvastatin calcium.
7. A process for preparing atorvastatin calcium Form V, or hydrate thereof, comprising the steps of
 - a) dissolving a metal, ammonium or alkylammonium salt of atorvastatin in a solvent to form an atorvastatin salt solution
 - b) contacting the atorvastatin salt solution with a calcium salt, and
 - c) isolating atorvastatin calcium Form V or hydrates thereof.
8. The process of claim 7 wherein the salt of atorvastatin is a metal salt of

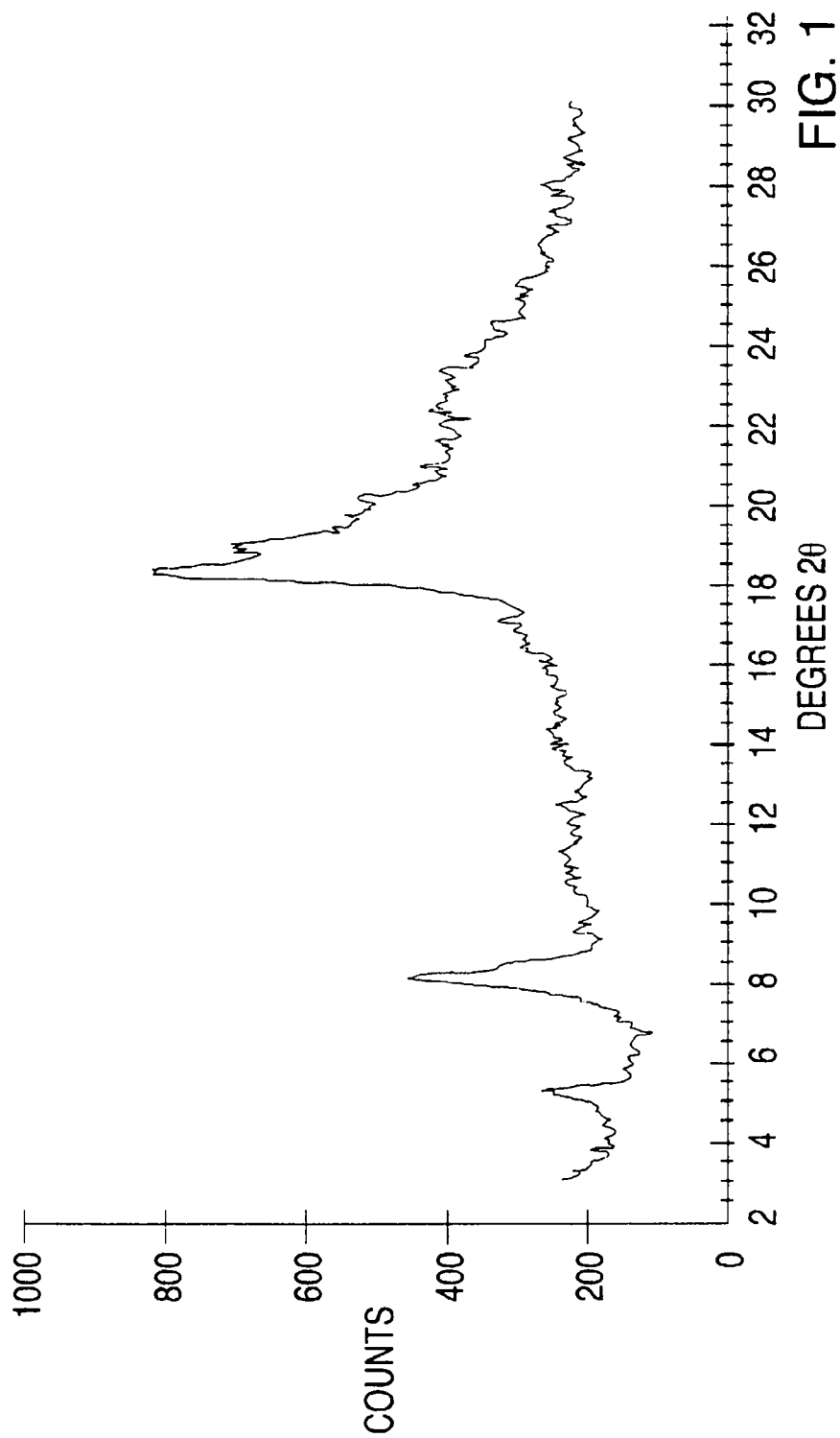
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atorvastatin.

9. The process of claim 8 wherein the metal salt of atorvastatin is a sodium salt of atorvastatin.
10. The process of claim 7 wherein the calcium salt is calcium acetate.
11. The process of claim 7 wherein the calcium salt is dissolved in a solvent and the atorvastatin salt solution is contacted with the calcium salt by adding the calcium salt solution to the atorvastatin salt solution.
12. A process for preparing atorvastatin calcium Form V or hydrates thereof comprising the steps of
 - a) dissolving atorvastatin calcium in a solvent selected from the group consisting of tetrahydrofuran and hydroxylic solvents to form an atorvastatin calcium salt solution,
 - b) adding water to the atorvastatin calcium salt solution, and
 - c) isolating atorvastatin calcium Form V or hydrates thereof.
13. The process of claim 12 wherein the solvent is methanol.
14. The process of claim 12 wherein the solvent is ethanol.
15. The process of claim 12 wherein the solvent is tetrahydrofuran.
16. A pharmaceutical composition comprising a therapeutic amount of atorvastatin Form V or hydrates thereof of claim 1.

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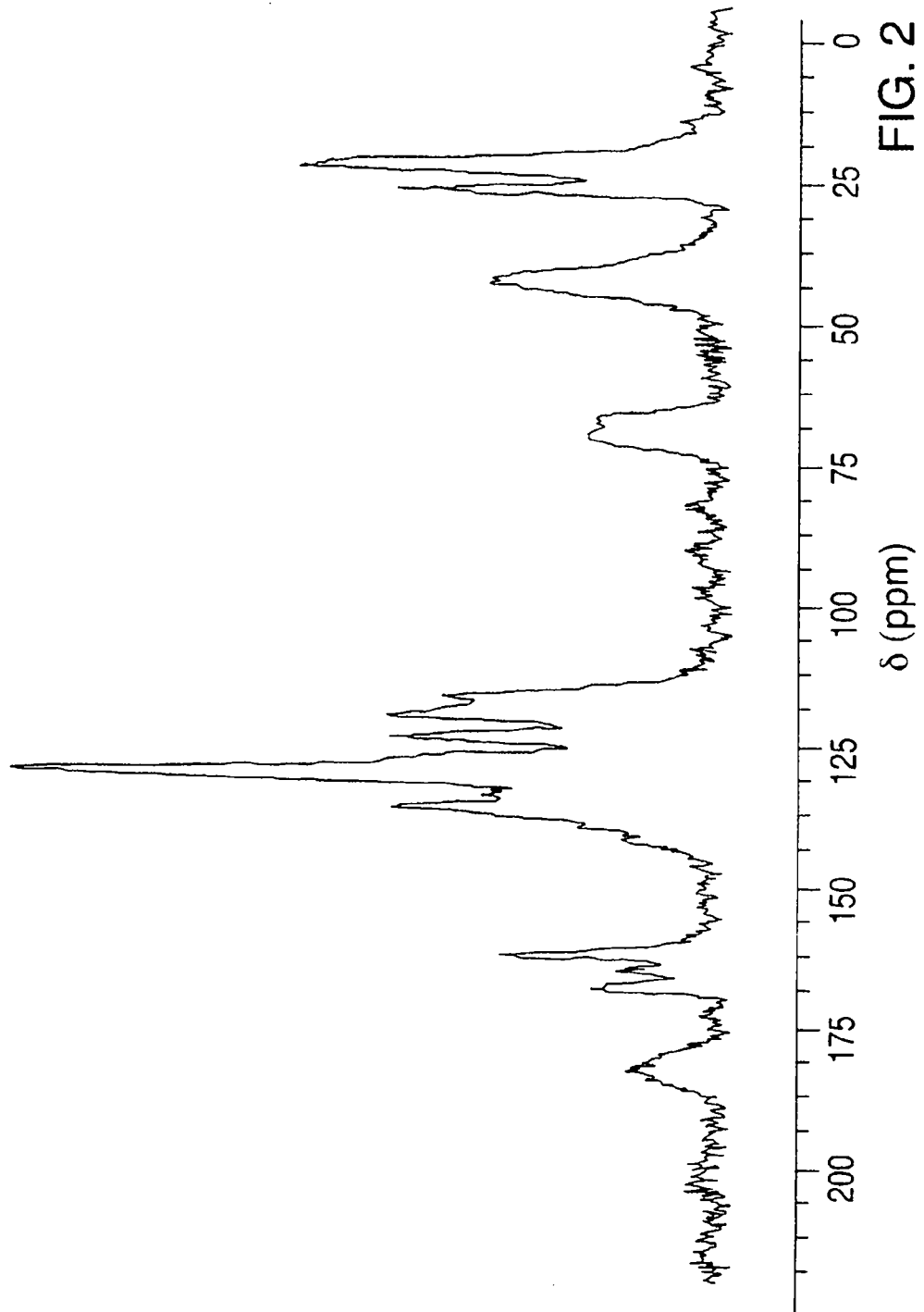


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