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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: **Expediente 01-011-529**

TÍTULO SOLICITADO: **"DERIVADOS DE PIRIMIDINA".**

PUBLICACIÓN: **Gaceta 528 de 30-05-2003, número de publicación 213**

SOLICITANTE: **Astra Zeneca UK Limited**
Shionogi & Co. Ltd

APODERADO: **Ramiro Castro Duque**

TRÁMITE: **Sustentación de Oposición**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LAFRANCOL S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, y estando dentro de los términos de la prórroga solicitada, por medio del presente escrito, me permito ratificar y sustentar los argumentos del escrito principal de oposición, también radicado dentro del plazo de ley ante esa entidad.

I. RATIFICACIÓN

Reitero a su Despacho la solicitud de negar el beneficio patentario para la totalidad de las reivindicaciones contenidas en el expediente en referencia, por los argumentos que se describen a continuación:

- El principio activo (E) -7- [4- (4-fluorofenil) -6- isopropil-2 [metil (metilsulfonil) amino] pirimidin-5-il] - (3R,5S) -3, 5-dihidroxihept -6-ácido enoico conocido por el nombre genérico de ROSUVASTATINA, incluyendo la forma amorfa de la sal cálcica, la sal sódica en forma de cristales, sus sales no-tóxicas farmacéuticamente aceptables, ciertos procesos de obtención, al igual que su

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utilidad y empleo como inhibidores de la HMG-CoA reductasa, han sido revelados al menos desde la publicación de la aplicación europea EP 521.471 en 07-01-1993, razón por la cual su conocimiento afectaría la **novedad** de la solicitud en curso.

- Es importante resaltar que el objeto último de la presente solicitud de patente es proteger la forma cálcica amorfa del compuesto (E) -7- [4- (4-fluorofenil) -6-isopropil-2 [metil (metilsulfonil) amino] pirimidin-5-il] - (3R,5S) -3, 5-dihidroxihept -6-ácido enoico, cuando se obtiene a partir de una sal cristalina –en este caso de metilamonio- del compuesto (E) -7- [4- (4-fluorofenil) -6- isopropil-2 [metil (metilsulfonil) amino] pirimidin-5-il] - (3R,5S) -3, 5-dihidroxihept -6-ácido enoico. Esta pretensión carece por completo de novedad y de nivel inventivo, pues en la patente Europea EP 0521471, mencionada tantas veces, se revela la forma de obtención de la misma sal cálcica amorfa a partir de una sal cristalina –con la única diferencia de que en aquella se parte también de una sal cristalina, pero en este caso, sódica.

- En cuanto a la caracterización de las sales hecha por el solicitante en función de sus patrones de difracción de RX, cabe anotar que este método de identificación – que no de creación -, permite a cualquier persona versada en la materia identificar y caracterizar diversas variaciones en la estructura cristalina de una molécula, por lo tanto, la metodología analítica para caracterizar una sustancia no es un proceso inventivo sino el reporte de un descubrimiento, pues proviene de herramientas tecnológicas conocidas y útiles en muchos otros campos de la ciencia, que están al alcance de la industria farmacéutica en el mundo.

- Las Resoluciones No. 59 de 14 de enero de 2003 y en la No. 60 de la misma fecha y emitidas por esa entidad, reiteran que "(...) la difracción de rayos X, además de ser importante, ha llegado a ser **absolutamente rutinaria** para los profesionales químicos (...)". Al ser la difracción de rayos X una labor "totalmente rutinaria", no puede por ningún motivo pensarse en que es un resultado del arduo trabajo del inventor, sino que consiste, por el contrario, en un simple proceso de identificación rutinario en la industria farmacéutica internacional.

- Por último, es obvio para una persona dedicada a la síntesis de compuestos, que un compuesto determinado llamado "compuesto final", (para el caso Rosuvastatina Cálcica Amorfa) pueda obtenerse el uso de diferentes materiales de partida, sin que una sustitución menor como la que se propone

respecto de uno de sus iones, suponga modificaciones en el producto final obtenido, y aún en el proceso de síntesis, que lo hagan merecedor de privilegio de patente.

II. COMPLEMENTACIÓN DE LA INFORMACIÓN

El Informe Internacional de Búsqueda practicado por la Oficina Europea de Patentes a la aplicación internacional PCT/WO01/60804A1, publicada el 23 de agosto de 2001, y equivalente a la solicitud en trámite, en tanto invocan la misma prioridad, señala la existencia de cinco (5) anterioridades que afectan el nivel inventivo de dicha solicitud y por ende, los de la solicitud colombiana, de las cuales nos referimos a tres (3):

- La aplicación europea EP 0521471 A1 (presentada el 30-06-1992), tantas veces mencionada, se refiere a compuestos derivados de pirimidina como inhibidores de la HMG-CoA reductasa y a su uso en el tratamiento de la hipercolesterolemia, hiperlipoproteinemia y aterosclerosis. Este documento revela el compuesto (E) -7- [4- (4-fluorofenil) -6- isopropil-2 [metil (metilsulfonil) amino] pirimidin-5-il] - (3R,5S) -3, 5-dihidroxihept -6-ácido enoico y sus sales no tóxicas farmacéuticamente aceptables.

- La publicación WO 0042024 A de categoría "P" y "Y"(publicada antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada), revela la sal cálcica cristalina del compuesto bis (E) -7- [4- (4-fluorofenil) -6- isopropil-2 [metil (metilsulfonil) amino] pirimidin-5-il] - (3R,5S) -3, 5-dihidroxihept -6-ácido enoico y el proceso de obtención de la misma. Este proceso consiste en la formación de los cristales a partir de una mezcla del compuesto mencionado, agua y uno o más solventes orgánicos, siendo este último acetonitrilo, acetona o una mezcla de metanol y metil tert-butil ester.

  La comparación de la publicación WO 0042024 (Ejemplo 1 y reivindicaciones 4-5) y la presente solicitud de patente permite concluir que, el proceso revelado en la reivindicación 12 de la CO-01-011-529, carece de novedad y de nivel inventivo, ya que no sólo pretenden la obtención de una sal **cristalina** mediante la adición de una sal o una **base apropiada** a una solución de (E) -7- [4- (4-fluorofenil) -6- isopropil-2 [metil (metilsulfonil) amino] pirimidin-5-il] - (3R,5S) -3, 5-dihidroxihept -6-ácido enoico sino que también usa un solvente orgánico como el **acetonitrilo**.

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- La publicación WO 01/54668A1, equivalente a la publicación FR 2795324 de categoría "P" y "Y"(publicada antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada), revela una composición farmacéutica que comprende un inhibidor de la HMG-CoA reductasa (E) -7- [4- (4-fluorofenil) -6- isopropil-2 [metil (metilsulfonil) amino] pirimidin-5-il] - (3R,5S) -3, 5-dihidroxihept -6-ácido enoico o una sal farmacéuticamente aceptable de la misma, por tal razón, es obvio pensar que puede tratarse de cualquiera de las sales mencionadas dada la generalidad de las reivindicaciones, en consecuencia la presente solicitud de patente carece de novedad y de nivel inventivo.

Ahora bien, si se tiene en cuenta lo contenido en el capítulo descriptivo de la publicación internacional WO 01/54668A1, en donde se hace mención tanto de la sal sódica como la **cálcica** del compuesto en cuestión, podemos de la misma manera decir que afecta la novedad y el nivel inventivo de la solicitud colombiana puesto que, la finalidad particular de ésta es obtener la sal **cálcica** *amorfa* de (E) -7- [4- (4-fluorofenil) -6- isopropil-2 [metil (metilsulfonil) amino] pirimidin-5-il] - (3R,5S) -3, 5- dihidroxihept -6-ácido enoico .

EN CONCLUSIÓN

Es claro que la presente solicitud de patente CO 01-011-529 se encuentra afectada tanto en novedad como en nivel inventivo, teniendo en cuenta los argumentos expuestos en el escrito de oposición presentada ante ese Despacho el 29 de agosto de 2003 y lo contenido en ésta sustentación de oposición.

III PRUEBAS

Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, la siguiente:

3.1. Informe Internacional de Búsqueda practicado por la Oficina Europea de Patentes a la aplicación internacional PCT/WO01/60804 A1.

3.2. Copia íntegra de aplicación internacional PCT WO00/42024.

3.3. Primera página de la publicación FR 2795324.

3.4. Apartes de la publicación internacional WO 01/54668 A1.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 August 2001 (23.08.2001)

PCT

(10) International Publication Number
WO 01/60804 A1

(51) International Patent Classification[7]: C07D 239/42, A61K 31/505, A61P 3/06

(21) International Application Number: PCT/GB01/00574

(22) International Filing Date: 12 February 2001 (12.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0003305.0 15 February 2000 (15.02.2000) GB

(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Sodertalje (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(71) Applicant *(for all designated States except MG, US)*: **SHIONOGI & CO., LTD.** [JP/JP]; 1-8, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TAYLOR, Nigel, Philip** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **OKADA, Tetsuo** [JP/JP]; 12-4, Sagisu 5-chome, Fukushima-ku, Osaka-shi, Osaka 553-0002 (JP).

(74) Agent: **BRYANT, Tracey**; AstraZeneca, Global Intellectual Property, Alderley Park, P.O. Box 272, Mereside, Macclesfield, Cheshire SK10 4GR (GB).

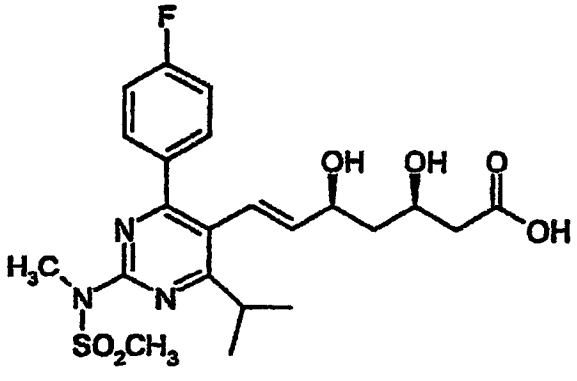
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, 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).

Published:
— *with international search report*

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

(54) Title: CRYSTALLINE SALTS OF 7-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL(METHYLSULFONYL)AMINO]PYRIMIDIN-5-YL]-(3R,5S)-3,5-DIHYDROXYHEPT-6-ENOIC ACID



(I)

(57) Abstract: The invention relates to crystalline salts of the compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid of formula (I), as well as processes for their manufacture, pharmaceutical compositions containing them, and their uses.

WO 01/60804 A1

INTERNATIONAL SEARCH REPORT

Inter··tional Application No
PC1/GB 01/00574

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/42 A61K31/505 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 521 471 A (SHIONOGI & CO) 7 January 1993 (1993-01-07) cited in the application claims; examples 1,2	1-15
P,Y	WO 00 42024 A (ASTRAZENECA UK LTD ;TAYLOR NIGEL PHILLIP (GB)) 20 July 2000 (2000-07-20) example 1	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 May 2001	23/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Menegaki, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter "tional Application No
PC1/GB 01/00574

1A+ 137

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WATANABE M ET AL: "SYNTHESIS AND BIOLOGICAL ANTIVITY OF METHANESULFONAMIDE PYRIMIDINE-AND N-METHANESULFONYL PYRROLE-SUBSTITUTED 3,5-DIHYDROXY-6-HEPTENOATES, A NOVEL SERIES OF HMG-COA REDUCTASE INHIBITORS" BIOORGANIC & MEDICINAL CHEMISTRY,GB,ELSEVIER SCIENCE LTD, vol. 5, no. 2, 1997, pages 437-444, XP000882043 ISSN: 0968-0896 page 439 -page 442; table 1	1-15
P,Y	FR 2 795 324 A (ASTRAZENECA AB) 29 December 2000 (2000-12-29) claims; examples	1-15
P,Y	WO 01 04100 A (LONZA AG ;VEITH ULRICH (CH)) 18 January 2001 (2001-01-18) claims; examples	1-15

Form PCT /SA/210 (continuation of second sheet) (July 1992)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 239/42, A61K 31/505, A61P 3/06	A1	(11) International Publication Number: WO 00/42024
		(43) International Publication Date: 20 July 2000 (20.07.00)

(21) International Application Number: PCT/GB99/04439

(22) International Filing Date: 23 December 1999 (23.12.99)

(30) Priority Data:
9900339.4 9 January 1999 (09.01.99) GB

(71) Applicant *(for all designated States except US)*: ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: TAYLOR, Nigel, Phillip [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: BRYANT, Tracey; Global Intellectual Property, Patents, AstraZeneca UK Limited, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, 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, 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, ARIPO patent (GH, GM, KE, LS, MW, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: CRYSTALLINE BIS[(E)-7- [4-(4- FLUOROPHENYL)- 6-ISOPROPYL-2- [METHYL (METHYLSULFONYL) AMINO] PYRIMIDIN -5-YL] (3R,5S)-3, 5-DIHYDROXYHEPT -6-ENOIC ACID]CALCIUM SALT

(57) Abstract

The present invention relates to a crystalline form of the compound bis[(E)-7-[4-(4- fluorophenyl)- 6-isopropyl-2- [methyl (methylsulfonyl) amino] pyrimidin-5-yl] (3R, 5S)-3, 5-dihydroxyhept -6-enoic acid]calcium salt, as well as processes for its manufacture and pharmaceutical compositions comprising the crystalline form, which is useful as an agent for treating hyperlipidemia, hypercholesterolemia and atherosclerosis.

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CRYSTALLINE BIS[(E)-7- [4-(4- FLUOROPHENYL)- 6-ISOPROPYL-2- [METHYL (METHYLSULFONYL) AMINO] PYRIMIDIN -5-YL] (3R,5S)-3, 5-DIHYDROXYHEPT -6-ENOIC ACID]CALCIUM SALT

The present invention relates to a novel crystalline chemical compound and more particularly to a novel crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt, hereinafter referred to as "the Agent", and illustrated in Formula I hereinafter, which compound is an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase) and is useful as a pharmaceutical agent, for example in the treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis, as well as other diseases or conditions in which HMG CoA reductase is implicated. The invention also relates to processes for the manufacture of the crystalline form, pharmaceutical compositions comprising the crystalline form and the use of the crystalline form in medical treatment.

European Patent Application, Publication No. 521471 (hereinafter EPA 521471), which is herein incorporated by reference, discloses an amorphous (powder) form of the Agent, prepared by dissolving the corresponding sodium salt in water, adding calcium chloride and collecting the resultant precipitate by filtration.

An amorphous form of a compound intended for pharmaceutical use may give rise to manufacturing problems and there is a need to identify crystalline forms of such compounds which have different physical characteristics compared to the amorphous form which may assist in the manufacture of the compound, or formulation of the compound, to the purity levels and uniformity required for regulatory approval. Crystalline forms of such compounds may also possess improved pharmacological characteristics, for example, improved bioavailability.

We have now surprisingly and unexpectedly discovered that the Agent can be prepared in a crystalline form.

According to the present invention there is provided a crystalline form of the Agent and hydrates thereof having an X-ray powder diffraction pattern with specific peaks at 2-theta = 4.92, 11.50, 6.93, 9.35, 23.12 and 18.76° (hereinafter referred to as Form A).

The X-ray powder diffraction spectra was determined by mounting a sample of the crystalline form on Siemans single silicon crystal (SSC) wafer mounts and spreading out the sample into a thin layer with the aid of a microscope slide. The sample was spun at 30

revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40kV and 40mA with a wavelength of 1.5406 angstroms. The collimated x-ray source was passed through an automatic variable divergence slit set at V20 (20mm path length) and the reflected radiation directed through a 2mm antiscatter slit and a 0.2mm detector slit. The sample was exposed for 4 seconds per 0.02 degree 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in theta-theta mode. The running time was 2 hours 6 minutes and 40 seconds. The instrument was equipped with a scintillation counter as detector. Control and data capture was by means of a DECpc LPv 433sx personal computer running with Diffrac AT (Socabim) software.

The X-ray powder diffraction spectra of a typical sample of Form A is shown in Figure 1 hereinafter. It will be understood that the 2-theta values of the X-ray powder diffraction pattern may vary slightly from one machine to another or from one sample of Form A to another, and so the values quoted are not to be construed as absolute.

Typically Form A is obtained in a hydrated form with, for example, a water content of about 7% w/w.

A further aspect of the present invention comprises a process for the preparation of Form A wherein Form A is caused to crystallise from a mixture of the Agent, water and one or more organic solvents. The optimum ratio of organic solvents and water in the mixture to obtain Form A is dependent on the characteristics of the organic solvents used and the process conditions employed. The precise conditions may be empirically determined. For example, Form A may be obtained by suspending the amorphous form of the Agent in water containing a co-solvent, such as acetonitrile, acetone or a mixture of methanol and methyl tert-butyl ether (MTBE), warming the mixture to obtain complete solution and then allowing the solution to cool, followed by isolation of Form A, such as by filtration. Suitable mixtures of water and co-solvent include, for example, 1:1 water/acetonitrile, 1:1 water/acetone and 1:1:1 water/methanol/MTBE, the ratios given being by volume. The amorphous form of the Agent to be used as starting material for the manufacture of Form A may be obtained, for example, as described in EPA 521471.

The utility of the compound of the invention may be demonstrated by standard tests and clinical studies, including those described in EPA 521471.

According to a further feature of the invention is a method of treating a disease condition wherein inhibition of HMG CoA reductase is beneficial which comprises administering to a warm-blooded mammal an effective amount of the Agent. The invention also relates to the use of Form A in the manufacture of a medicament for use in a disease condition.

The compound of the invention may be administered to a warm-blooded animal, particularly a human, in need thereof for treatment of a disease in which HMG CoA reductase is implicated, in the form of a conventional pharmaceutical composition. Therefore in another aspect of the invention, there is provided a pharmaceutical composition comprising Form A in admixture with a pharmaceutically acceptable carrier.

Such compositions may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the Agent may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solution or suspensions or sterile emulsions. A preferred route of administration is oral. The Agent will be administered to humans at a daily dose in, for example, the ranges set out in EPA 521471. The daily doses may be given in divided doses as necessary, the precise amount of the Agent received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

According to a further feature of the invention, there is provided a process for the manufacture of a pharmaceutical composition containing Form A as active ingredient, which comprises admixing Form A together with a pharmaceutically acceptable carrier.

The invention will now be illustrated by the following non-limiting Example.

Example 1

Amorphous form of the Agent (465 mg) was added to a mixture of water (5 ml) and acetonitrile (5 ml) at 15°C. The mixture was warmed to 40°C to obtain complete solution.

The mixture was then cooled slowly to ambient temperature and stirred for 16 hours. The crystalline product was separated by filtration at ambient temperature and dried at 50° under vacuum to give Form A (337 mg) as white crystals.

X-ray powder diffraction (XRD):

Peak Number	2θ	d-Spacing	Counts/sec	Relative Intensity (>20%)
1	4.92	17.945	820.25	100
2	11.50	7.686	258.75	31.55
3	6.93	12.750	230.25	28.07
4	9.35	9.455	213.75	26.06
5	23.12	3.843	212.75	25.94
6	18.76	4.726	177.5	21.64

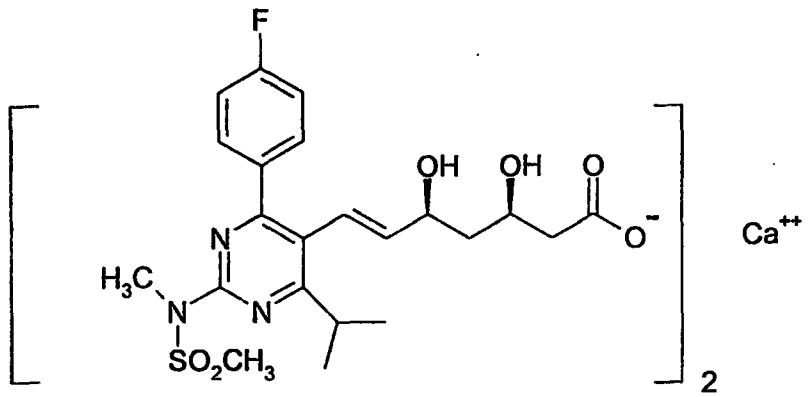
Water content 7.1% w/w

^{1}H NMR (d^6-DMSO) δ : 7.7 (2H, t), 7.3 (2H, t), 6.5 (1H, d), 5.5 (1H,dd), 4.2 (1H, m), 3.8 (1H, m), 3.5 (3H, s), 1.9 - 2.1 (2H, dd), 1.3 - 1.5 (2H, m), 1.2 (6H, d)

Mass Spectrum: MH+ 482.3

CLAIMS

1. A crystalline form of the compound bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt of the formula I



I

or a hydrate thereof having an X-ray powder diffraction pattern with specific peaks at 2-theta (2θ) = 4.92, 11.50, 6.93, 9.35, 23.12 and 18.76°.

2. A crystalline form as claimed in claim 1 which is a crystalline hydrated form.

3. A pharmaceutical composition comprising a crystalline form as claimed in claim 1 or 2, together with a pharmaceutically acceptable carrier.

4. A process for the manufacture of a crystalline form or hydrated form as claimed in claim 1 which comprises forming crystals from a mixture of the compound of formula I, water and one or more organic solvents.

5. A process as claimed in claim 4 wherein the organic solvent is selected from acetonitrile, acetone or a mixture of methanol and methyl tert-butyl ester.

6. A process for the manufacture of a pharmaceutical composition as claimed in claim 3 which comprises admixing a crystalline form as claimed in claim 1 together with a pharmaceutically acceptable carrier.

7. The use of a crystalline form as claimed in claim 1 in the manufacture of a medicament.

8. A method of treating a disease condition wherein inhibition of HMG CoA reductase is beneficial which comprises administering to a warm-blooded mammal an effective amount of a crystalline form as claimed in claim 1.

(19) RÉPUBLIQUE FRANÇAISE

INSTITUT NATIONAL
DE LA PROPRIÉTÉ INDUSTRIELLE

PARIS

(11) N° de publication : **2 795 324**
(à n'utiliser que pour les commandes de reproduction)

(21) N° d'enregistrement national : **00 10334**

(51) Int Cl[7] : **A 61 K 31/435**, A 61 P 3/00, 19/00

(12) DEMANDE DE BREVET D'INVENTION A1

(22) **Date de dépôt :** 04.08.00.

(30) **Priorité :** 26.01.00 GB 00001621.

(43) **Date de mise à la disposition du public de la demande :** 29.12.00 Bulletin 00/52.

(56) **Liste des documents cités dans le rapport de recherche préliminaire :** *Ce dernier n'a pas été établi à la date de publication de la demande.*

(60) **Références à d'autres documents nationaux apparentés :**

(71) **Demandeur(s) :** *ASTRAZENECA AB* — SE.

(72) **Inventeur(s) :** CREEKMORE JOSEPH RICHARD et WIGGINS NORMAN ALFRED.

(73) **Titulaire(s) :**

(74) **Mandataire(s) :** CABINET ORES.

(54) COMPOSITIONS PHARMACEUTIQUES STABILISEES.

(57) L'invention est relative à une composition pharmaceutique comprenant l'inhibiteur de la HMG CoA réductase, à savoir l'acide (E) -7-[4- (4fluorophényl) - 6-iso-propyl-2 [méthyl (méthylsulfonyl) amino] pyrimidin-5-yl] - (3R, 5S) -3, 5-dihydroxyhept-6-ènoïque ou un sel pharmaceutiquement acceptable de celui-ci, en tant qu'ingrédient actif, ainsi qu'un sel phosphate tribasique dans lequel le cation est multivalent, ladite composition restant stable sur une période de temps prolongée.

FR 2 795 324 - A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 August 2001 (02.08.2001)

PCT

(10) International Publication Number
WO 01/54668 A1

(51) International Patent Classification[7]: A61K 9/20, 31/505

(21) International Application Number: PCT/GB00/03014

(22) International Filing Date: 4 August 2000 (04.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0001621.1 26 January 2000 (26.01.2000) GB

(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Sodertalje (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CREEKMORE, Joseph, Richard** [US/US]; 1800 Concord Pike, Wilmington, DE 19850-5437 (US). **WIGGINS, Norman, Alfred** [US/US]; 1800 Concord Pike, Wilmington, DE 19850-5437 (US).

(74) Agent: **BROWN, Andrew, Stephen**; AstraZeneca UK Limited, Global Intellectual Property: Patents, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, 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, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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

WO 01/54668 A1

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING A HMG REDUCTASE INHIBITOR

(57) Abstract: The invention concerns a pharmaceutical composition comprising the HMG CoA reductase inhibitor (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof as the active ingredient, which remains stable over a prolonged period.

PHARMACEUTICAL COMPOSITIONS COMPRISING A HMG REDUCTASE INHIBITOR

The present invention relates to pharmaceutical compositions and more particularly to a pharmaceutical composition containing (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (and referred to hereinafter as "the Agent"), in particular the sodium and calcium salts, and especially the calcium salt, bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt (of the formula I hereinafter).

The Agent is disclosed as an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMG CoA reductase) in European Patent Application , Publication No. 0521471 and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 and is useful in the treatment of hypercholesterolemia, hyperlipidproteinemia and atherosclerosis.

A problem associated with the Agent is that it undergoes degradation under certain conditions. This makes it difficult to formulate the product and provide a pharmaceutical composition with adequate storage life. The major degradation products formed are the corresponding (3R, 5S) lactone (hereinafter referred to as "the lactone") and an oxidation product (hereinafter referred to as "B2") in which the hydroxy group adjacent to the carbon-carbon double bond is oxidised to a ketone functionality.

It is therefore important to find a pharmaceutical composition of the Agent which remains stable over a prolonged period. It is also preferable that such a composition has a good flow rate to assist processing into unit dosage forms for oral administration, for example into tablets, and good disintegration and dissolution characteristics when processed into tablets for oral administration, which tablets can be in different dosage strengths. It is also desirable that such tablets are of a convenient size for ease of administration.

Pharmaceutical formulations of certain 7-substituted-3,5-dihydroxy-6-heptenoic acid salts, which are HMG CoA reductase inhibitors, are disclosed in UK Patent 2262229. These formulations require the presence of an alkaline medium (such as a carbonate or bicarbonate) capable of imparting a pH of at least 8 to an aqueous solution or dispersion of the composition.

Suitable lubricants include, for example, magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, carnauba wax, hydrogenated vegetable oils, mineral oil, polyethylene glycols and sodium stearyl fumarate.

Additional conventional excipients which may be added include preservatives, stabilisers, anti-oxidants, silica flow conditioners, antiadherents or glidants.

Other suitable fillers, binders, disintegrants, lubricants and additional excipients which may be used are described in *Handbook of Pharmaceutical Excipients*, 2nd Edition, American Pharmaceutical Association; *The Theory and Practice of Industrial Pharmacy*, 2nd Edition, Lachman, Leon, 1976; *Pharmaceutical Dosage Forms: Tablets Volume 1*, 2nd Edition, Lieberman, Hebert A., et al, 1989; *Modern Pharmaceutics*, Banker, Gilbert and Rhodes, Christopher T, 1979; and *Remington's Pharmaceutical Sciences*, 15th Edition, 1975.

Typically the Agent will be present in an amount within the range of 1 to 50%, and preferably from 1 to 20% (especially 2 to 15%) by weight of the composition.

Typically the tribasic phosphate salt, such as tribasic calcium phosphate, will be present in an amount within the range of 1 to 50%, for example 1 to 25%, such as 1 to 20%, and particularly 5 to 18% by weight.

Typically one or more fillers will be present in an amount 30 to 90% by weight.

Typically one or more binders will be present in an amount 2 to 90% by weight.

Typically one or more disintegrants will be present in an amount 2 to 10%, and especially 4 to 6% by weight.

It will be appreciated that a particular excipient may act as both a binder and a filler, or as a binder, a filler and a disintegrant. Typically the combined amount of filler, binder and disintegrant comprises, for example, 70 to 90% by weight of the composition.

Typically one or more lubricants will be present in an amount 0.5 to 3%, and especially 1 to 2% by weight.

Preferred compositions of the invention include, for example, those comprising the Agent, tribasic calcium phosphate and excipients selected from lactose, mannitol, microcrystalline cellulose, povidone, crospovidone, sodium starch glycollate and magnesium stearate. Preferred independent compositions of the invention include, for example, compositions comprising the Agent, tribasic calcium phosphate, microcrystalline cellulose, lactose, sodium starch glycollate, butylated hydroxytoluene and magnesium stearate;

We have now discovered a novel pharmaceutical composition of the Agent which has advantageous properties and which solves one or more of the problems associated with formulation of the Agent.

Accordingly, a first aspect of the invention comprises a pharmaceutical composition comprising the Agent and a tribasic phosphate salt in which the cation is multivalent.

A second aspect of the invention comprises the use of a tribasic phosphate salt in which the cation is multivalent to stabilise the Agent.

A tribasic phosphate salt in which the cation is multivalent includes, for example, tribasic calcium phosphate, tribasic magnesium phosphate and tribasic aluminium phosphate. Tribasic calcium phosphate is especially preferred.

The ratio of tribasic phosphate salt to Agent in the pharmaceutical composition is, for example, within the range of 1:80 to 50:1 by weight, for example 1:50 to 50:1 by weight, such as 1:10 to 10:1 by weight, and more particularly 1:5 to 10:1 by weight.

Preferably the pharmaceutical composition of the invention is formulated into an oral dosage form, such as a tablet. Accordingly a further aspect of the invention comprises a pharmaceutical composition comprising the Agent, a tribasic phosphate salt in which the cation is multivalent, and one or more fillers, binders, disintegrants or lubricants. A still further aspect of the invention relates to a pharmaceutical composition for oral administration comprising the Agent, one or more fillers, one or more binders, one or more disintegrants, one or more lubricants and a tribasic phosphate salt in which the cation is multivalent.

Suitable fillers include, for example, lactose, sugar, starches, modified starches, mannitol, sorbitol, inorganic salts, cellulose derivatives (e.g. microcrystalline cellulose, cellulose), calcium sulfate, xylitol and lactitol.

Suitable binders include, for example, polyvinylpyrrolidone, lactose, starches, modified starches, sugars, gum acacia, gum tragacanth, guar gum, pectin, wax binders, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, copolyvidone, gelatin and sodium alginate.

Suitable disintegrants include, for example, crosscarmellose sodium, crospovidone, polyvinylpyrrolidone, sodium starch glycollate, corn starch, microcrystalline cellulose, hydroxypropyl methylcellulose and hydroxypropyl cellulose.

The tablets were stored at 70°C/80% relative humidity for one week. After one week there was found to be only 0.11%w/w of the oxidation product B2 formed and only 0.50%w/w of the lactone. By comparison a similar formulation in which 20.0 mg of tribasic calcium phosphate was replaced by 20.0 mg of dibasic calcium phosphate, 0.23%w/w of B2 was formed and 15.61%w/w of the lactone.

Example 2

The Agent	2.50 mg
Povidone	2.50 mg
Tribasic calcium phosphate	20.0 mg
Microcrystalline cellulose	47.0 mg
Mannitol	47.0 mg
Sodium starch glycollate	3.00 mg
Butylated hydroxytoluene	0.05 mg
Magnesium stearate	1.00 mg

The Agent, povidone, mannitol, microcrystalline cellulose, butylated hydroxytoluene, tribasic calcium phosphate and sodium starch glycollate (in the amounts given above) were blended for 5 to 60 minutes. Magnesium stearate was screened through a #40 mesh (425 um) screen and added to the blend and blending continued for a further three minutes. The resulting homogeneous mixture was compressed into tablets. The compressed tablets were coated by spraying with a mixture of hydroxypropyl methylcellulose, polyethylene glycol 400, titanium dioxide and ferric oxide (sold as Spectrablend by Warner-Jenkinson) and water in a coating pan. The weight gain provided by the coating was 1 to 6%w/w, and preferably 2 to 3 %w/w.

The tablets were stored at 70°C/80% relative humidity for one week. After one week there was found to be only 0.06%w/w of the oxidation product B2 formed and only 2.22%w/w of the lactone.

Example 3

The Agent	2.60 mg
Crospovidone	3.75 mg
Tribasic calcium phosphate	5.66 mg
Microcrystalline cellulose	15.5 mg
Lactose monohydrate	46.5 mg
Magnesium stearate	0.94 mg

The Agent and crospovidone were blended together for 5 minutes and the blend then passed through a 400-700um screen. A small portion of the microcrystalline cellulose was passed through the screen afterwards. The screened material was blended with the other ingredients, excluding the lubricant, for 10 minutes. Magnesium stearate was passed through a #40 mesh (425 um) screen and added to the blend and the mixture was blended for a further 3 minutes. The resulting homogeneous mixture was compressed into tablets. The compressed tablets were coated by spraying with a mixture of lactose monohydrate, hydroxypropyl methylcellulose, triacetin and ferric oxide (sold as Opadry II by Colorcon) and water in a coating pan. The weight gain provided by the coating 1 to 6%w/w, and preferably 2 to 3%w/w.

The tablets were stored at 70°C/80% relative humidity for one week. After this time only 0.19%w/w of the oxidation product B2 had formed and only 2.71%w/w of the lactone.

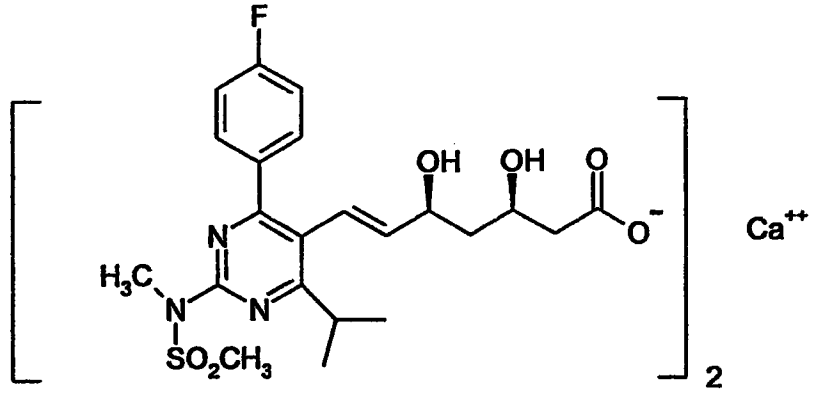
Example 4

The Agent	2.50 mg
Povidone	2.50 mg
Tribasic calcium phosphate	20.0 mg
Microcrystalline cellulose	34.5 mg
Lactose monohydrate	34.0 mg
Sodium starch glycollate	6.00 mg
Magnesium stearate	1.00 mg

Butylated hydroxytoluene 0.05 mg

A portion of the tribasic calcium phosphate and butylated hydroxytoluene were blended for 30 seconds in a bag. The Agent, povidone, remainder of the tribasic calcium phosphate, microcrystalline cellulose, lactose monohydrate, tribasic calcium phophate/butylated hydroxytoluene mixture and a portion of the sodium starch glycolate were blended in a granulator for 30 seconds. The powder blend was granulated with purified water for 1 minute at the addition rate of 70 mg/tablet/minute. The granulation is dried in a fluidized bed drier at 50°C until the loss on drying is less than 2% w/w. The dried granulation is passed through a mill (e.g. Comil). The milled granulation and the remainder of the sodium starch glycolate was blended for approximately 5 minutes. Magnesium stearate was screened through a #40 mesh (425 um) screen and added to the blend and blending continued for a further three minutes. The resulting homogeneous mixture was compressed into tablets.

The tablets were stored at 70°C/80% relative humidity for one week. After this time only 0.23 %w/w of the oxidation product B2 had formed and only 0.28%w/w of the lactone. By comparison a similar formulation in which 20.0 mg of tribasic calcium phosphate was replaced by 20.0 mg of dibasic calcium phosphate, 0.19 %w/w of B2 was formed and 28.15 %w/w of the lactone.



Formula I

8. A pharmaceutical composition as claimed in claim 6 or 7 wherein the tribasic phosphate salt is present in an amount 1 to 50% by weight of the composition.

9. A pharmaceutical composition as claimed in claim 6, 7 or 8 wherein the filler is present in an amount 30 to 90% by weight of the composition.

10. A pharmaceutical composition as claimed in any of claims 6 to 9 wherein the binder is present in an amount 2 to 90% by weight of the composition.

11. A pharmaceutical composition as claimed in any of claims 6 to 10 wherein the disintegrant is present in an amount 2 to 10% by weight of the composition.

12. A pharmaceutical composition as claimed in any of claims 6 to 11 wherein the lubricant is present in an amount 0.5 to 3% by weight.

13. A pharmaceutical composition as claimed in claim 6 comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof as the active ingredient, tribasic calcium phosphate, microcrystalline cellulose, lactose, sodium starch glycollate, butylated hydroxytoluene and magnesium stearate.

14. A pharmaceutical composition as claimed in claim 6 comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof as the active ingredient, tribasic calcium phosphate, povidone, microcrystalline cellulose, mannitol, sodium starch glycollate, butylated hydroxytoluene and magnesium stearate.

15. A pharmaceutical composition as claimed in claim 6 comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof as the active

ingredient, tribasic calcium phosphate, crospovidone, microcrystalline cellulose, lactose and magnesium stearate.

16. A pharmaceutical composition as claimed in claim 6 comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof as the active ingredient, tribasic calcium phosphate, povidone, microcrystalline cellulose, lactose, sodium starch glycollate, butylated hydroxytoluene and magnesium stearate.

17. A pharmaceutical composition as claimed in any preceding claim wherein the active ingredient is the calcium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid.

18. The use of a tribasic phosphate salt in which the cation is multivalent to stabilise the compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

19. The use as claimed in claim 18 wherein the the tribasic phosphate salt in which the cation is multivalent is selected from tribasic calcium phosphate, tribasic magnesium phosphate and tribasic aluminium phosphate.

20. The use as claimed in claim 18 or 19 wherein the the tribasic phosphate salt in which the cation is multivalent is tribasic calcium phosphate.

21. A method of producing a stabilised pharmaceutical composition which comprises incorporating a tribasic phosphate salt in which the cation is multivalent in a pharmaceutical composition containing the compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

Industria y Comercio
SUPERINTENDENCIA

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2020
Bogotá, D.C.,

Doctor:
Ramiro Castro Duque
Apoderado

Oficio N°: 11386

ASUNTO:

Radicación N°	01-11529
Trámite	002
Evento	001
Actuación	430
Folios	043

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorio Franco Colombiano Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 26 DIC. 2003.

202021

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia