

(56) Related Art

WO 2003/097614 A2 (Ranbaxy Laboratories Ltd) 27 November 2003.

WO 2005/092867 A2 (Avecia Pharmaceuticals Ltd) 6 October 2005.

WO 2005/042522 A1 (Astrazeneca UK Ltd et al) 12 May 2005.

WO 2005/077917 A1 (Ranbaxy Laboratories Ltd) 25 August 2005.

EP 0521471 A1 (Shionogi & Co.) 7 January 1993.

WO 2005/051921 A1 (Teva Pharmaceutical Industries Ltd) 9 June 2005.

WO2004/014872 A1 (Astrezeneca UK Ltd) 19 February 2004.

US 2003/0114685 A1 (NIDDAM-HILDESHEIM at al.) 19 June 2003.

WO 2005/040134 A1 (Ranbaxy Laboratories Ltd) 6 May 2005.

WO 2005/054207 A1 (Glen-Mark Pharmaceuticals) 16 June 2005.

WO 2004/052867 A (Ranbaxy Lab Ltd) 24 June 2004.

WO 2005/023778 A2 (Teva Pharmaceutical Industries Ltd) 17 March 2005.

WO 2005/077916 A1 (Ranbaxy Laboratories Ltd) 25 August 2005

WO 2001/060804 A1 (Astrazeneca AB) 23 August 2001.

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
28 December 2006 (28.12.2006)

PCT

(10) International Publication Number  
WO 2006/136407 A1(51) International Patent Classification:  
C07D 239/42 (2006.01) A61P 3/06 (2006.01)  
A61K 31/505 (2006.01)(21) International Application Number:  
PCT/JP2006/006007

(22) International Filing Date: 22 June 2006 (22.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
P200500188 24 June 2005 (24.06.2005) SI(71) Applicant (for all designated States except US): LEK  
PHARMACEUTICALS D.D. [SI/SI]; Verovskova 57,  
1526 Ljubljana (SI).(72) Inventor: CASAR, Zdenko; Nova vas 20, 1370 Logatec  
(SI).

(72) Inventor; and

(75) Inventor/Applicant (for US only): ZLICAR, Marko  
[SI/SI]; Ulica Frankolovskih zrtev 15, 3000 Celje (SI).(74) Agent: LIPHARDT, Bernd; Novartis AG, Corporate In-  
tellectual Property, CH-4002 Basel (CH).(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP,  
KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LI,  
LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA,  
NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC,  
SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ,  
UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.(84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,  
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,  
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a  
patent (Rule 4.17(ii))

## 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  
amendmentsFor 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.

(54) Title: PROCESS FOR PREPARING AMORPHOUS ROSUVASTATIN CALCIUM FREE OF IMPURITIES

(57) Abstract: A pure amorphous form of rosuvastatin calcium having purity of more than 99.5%, preferably a purity of more than 99.8%, more preferably a purity of more than 99.9% as determined by HPLC area percentage, and free from any traces of alkali metal impurities is disclosed. A process of preparing said pure amorphous form of rosuvastatin calcium is disclosed, which comprises hydrolysis of C<sub>1</sub>-C<sub>3</sub> alkyl esters of rosuvastatin, preferably tert-butyl ester of rosuvastatin, with an organic nitrogen base, e.g. guanidines, amidines, amines and quaternary ammonium hydroxides, in the presence of water, optionally containing aprotic solvent, following the conversion of thus obtained rosuvastatin salt with a source of calcium to desired rosuvastatin calcium, which is then isolated. An alternative process is disclosed, which comprises the conversion of numerous novel ammonium salts of rosuvastatin, preferably tert-octylammonium salt of rosuvastatin, with the source of calcium to desired commercial rosuvastatin calcium. Rosuvastatin calcium is HMG CoA reductase, useful in the treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis.

WO 2006/136407 A1

**Process for preparing amorphous rosuvastatin calcium free of impurities****Field of the invention**

The present invention relates to a process for the preparation of amorphous rosuvastatin calcium, substantially free of alkali metal impurities, *via* ammonium salts of rosuvastatin as intermediary compounds.

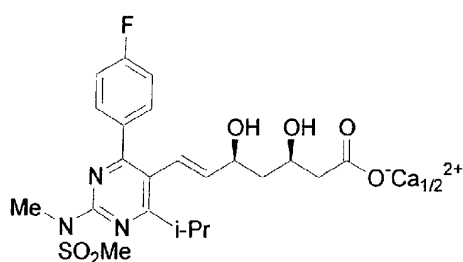
**Background of the invention**

Rosuvastatin is generic name for (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-heptenoic acid administered in the therapy as its calcium salt as commercial drug, and illustrated in Formula 1 hereinafter, which compound is an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase), useful in the treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis. Rosuvastatin and the synthesis of rosuvastatin calcium was first described in patent EP-B-521 471; in the last two steps of the whole synthesis provided by hydrolysis of methyl ester of rosuvastatin (methyl rosuvastatin) in polar solvent, e.g. ethanol, in the presence of a base, e.g. sodium hydroxide, following by isolation of sodium salt of rosuvastatin and converting said sodium salt of rosuvastatin with a water soluble calcium salt under aqueous conditions to calcium salt of rosuvastatin. The process for the preparation of the intermediates described in EP-B-521 471 patent is incorporate herein by reference.

WO 2005/023778 describes a process for the preparation of rosuvastatin calcium by conversion of C<sub>1</sub> to C<sub>4</sub> alkyl ester of rosuvastatin, preferably *tert*-butyl ester of rosuvastatin with a base, preferably sodium hydroxide, in the presence of a C<sub>1</sub> to C<sub>4</sub> alcohol, preferably ethanol, to a solution of rosuvastatin salt, e.g. its sodium salt and converted said salt into rosuvastatin calcium by adding a source of calcium to said solution.

A novel crystalline form of rosuvastatin calcium can be prepared by crystallization of amorphous form of rosuvastatin calcium from a mixture of: (i) water and acetonitrile in the ratio of 1 : 1 by volume; (ii) water and acetone in the ratio of 1 : 1 by volume; or water, methanol and methyl *tert*-butyl ether in the ratio of 1:1:1 by volume, what is described in WO 2000/042024.

WO 01/60804 discloses certain novel amine salt with rosuvastatin, which may be prepared by addition of an appropriate amine or base to a solution of rosuvastatin acid in acetonitrile or ethyl acetate. Certain novel amine salts of rosuvastatin, preferably its crystalline methylammonium salt, may be used in the preparation of amorphous calcium salt of rosuvastatin, which process comprises sequential reaction of the crystalline methylammonium salt of rosuvastatin with sodium hydroxide, followed by a water soluble calcium salt, such as calcium chloride, under aqueous conditions. An approach is disclosed in WO 2005/051921 where rosuvastatin calcium salt is purified by conversion into isopropylammonium or cyclohexylammonium salt and back to calcium salt.



Formula 1

It is well known that alkali metal salts of organic acids are often hygroscopic what may cause problems at isolation. Indeed the isolation of sodium salt of rosuvastatin, which can be an intermediate in preparing rosuvastatin calcium salt, might be unrepeatable in yield and physical state what depends on the reaction conditions and evaporation of solvents, which is difficult to control. International publication WO 2005/23778 tried to avoid said problems without isolating rosuvastatin sodium salt by extraction of impurities from its aqueous solution into water immiscible solvent, but by using C<sub>1</sub> to C<sub>4</sub> alcohols as reaction medium a risk of conversion into specific impurities still existed. Namely, it is known that  $\beta$ -hydroxy acids in alcoholic alkali solution are submitted to dehydration what may lead after realkoxylation into special side products (see Scheme 1, wherein R and R<sub>1</sub> independently denotes C<sub>1</sub> to C<sub>5</sub> alkyl group), O-alkyl derivatives of rosuvastatin, e.g. O-ethyl rosuvastatin.

Therefore a need for an efficient process for preparing pure amorphous rosuvastatin calcium, without any significant amounts of side products and in having the exact stoichiometric content without other alkali metal cation, still exists.

**Summary of the invention**

In a general aspect of the invention there is provided a pure amorphous form of rosuvastatin calcium of Formula 1 having a purity of more than 99.5%, preferably a purity of more than 99.8%, more preferably a purity of more than 99.9% as determined by HPLC area percentage, and free from any traces of alkali metal impurities.

In a first aspect the present invention provides a process for producing pure amorphous calcium salt of rosuvastatin, substantially free of alkali metal impurities, e.g. sodium cation impurity, which comprises:

- a) hydrolysis of C<sub>1</sub> to C<sub>6</sub> alkyl esters of rosuvastatin or rosuvastatin lactone with an organic nitrogen base in the presence of water, optionally containing aprotic solvent,
- b) converting thus obtained rosuvastatin salt of an organic nitrogen base with a source of calcium to obtain rosuvastatin calcium,
- c) isolating the pure amorphous calcium salt of rosuvastatin.

The starting ester may be methyl ester of rosuvastatin, preferably *tert*-butyl ester of rosuvastatin (*tert*-butyl rosuvastatin).

An organic nitrogen base is selected from the group consisting of guanidines, amidines, amines, quaternary ammonium hydroxides, unsubstituted or C<sub>1</sub> to C<sub>6</sub> alkyl substituted piperazines, morpholines, thiomorpholines, imidazolidines or adamantans.

Any aprotic solvent in step a) may be used, preferably tetrahydrofuran.

Any appropriate source of calcium may be used, preferably calcium chloride, calcium hydroxide, calcium acetate and calcium palmitate.

The process according to the invention may be performed in a solutions of an intermediary salts of rosuvastatin with organic nitrogen bases. Said salts are novel compounds, e.g. amine salts of rosuvastatin, not described in the prior art.

In another aspect of the invention rosuvastatin salts of an organic nitrogen bases may be isolated, optionally purified, e.g. by recrystallization, and used as intermediates in the preparation of the pure amorphous rosuvastatin calcium salt.

The desired pure amorphous rosuvastatin calcium salt is substantially free from any traces of alkali metal salt impurities, e.g. from sodium cation, containing in intermediary rosuvastatin sodium salt obtained according to prior art processes. Further is desired pure rosuvastatin calcium free of any O-alkyl derivatives of rosuvastatin, e.g. free of O-ethyl derivative of rosuvastatin, which may be obtained as side product according to prior art processes, performed in C<sub>1</sub> to C<sub>4</sub> alcoholic medium.

Amorphous rosuvastatin calcium prepared by the process according to the invention has at least 99.5% of chromatographic purity; moreover when using very pure starting C<sub>1</sub> to C<sub>5</sub> rosuvastatin ester more than 99.8% purity, even more, in some cases more than 99.9% of chromatographic purity of desired rosuvastatin calcium may be obtained.

The term "chromatographic purity" means purity as determined by area percentage HPLC ("High Pressure Liquid Chromatography").

In another aspect of the invention the amorphous rosuvastatin calcium may be prepared by conversion of the novel intermediary ammonium salts of rosuvastatin with the source of calcium. Intermediary ammonium salts of rosuvastatin may be obtained by contacting rosuvastatin free acid with an appropriate amine according to the procedure which comprises:

- a) hydrolysis of C<sub>1</sub> to C<sub>5</sub> alkyl ester of rosuvastatin or rosuvastatin lactone with an alkali metal hydroxide in a mixture of an aprotic solvent and water,
- b) washing the reaction mixture with water immiscible solvent,
- c) acidifying aqueous solution of rosuvastatin alkali salt with an acid,
- d) extraction of the resulted aqueous solution of rosuvastatinic acid into a water immiscible organic solvent,
- e) adding an appropriate amine to the obtained extract containing rosuvastatinic acid to convert said rosuvastatinic acid into ammonium salt of rosuvastatin,
- f) converting ammonium salt of rosuvastatin with a source of calcium to obtain rosuvastatin calcium,
- g) isolation of amorphous rosuvastatin calcium.

The water immiscible solvent used in above steps b) and d) is selected from the group consisting of C<sub>2</sub> to C<sub>5</sub> alkyl esters, e.g. acetate esters, preferably ethyl acetate (AcOEt), *iso*-

propyl acetate (i-Pr acetate) and *iso*-butyl acetate, ethers, chlorinated hydrocarbons and cyclic hydrocarbons.

As acid for acidifying aqueous solution of rosuvastatin alkali salt in step c) of above process e.g. hydrochloric acid or phosphoric acid may be used.

The term "rosuvastatinic acid" ("rosuvastatin free acid") means (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid.

By using sodium hydroxide in step a) for cleavage of starting rosuvastatin esters according to above procedure purification and isolation of various isolable intermediary rosuvastatin salts with an appropriate amine may be performed after which the content of sodium cation impurity may be lowered, e.g. by washing the reaction mixture of step b) by water immiscible solvents, in the desired rosuvastatin calcium salt to less than 0.1% of sodium by weight.

Some of the novel ammonium salts of rosuvastatin were prepared in well defined forms, preferably as *tert*-octylammonium salt of rosuvastatin, which may be isolated in highly pure crystalline form and may be valuable as analytical standard for HPLC and other analyses.

The above described process of the first aspect of the invention by means of organic nitrogen bases cleavage of rosuvastatin C<sub>1</sub> to C<sub>5</sub> esters or lactone can be successfully applied for the preparation of other in the art known statins, preferably atorvastatin.

In another aspect the invention provides for a pharmaceutical formulation comprising rosuvastatin calcium prepared according to above described process and a method of treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis, comprising the step of administering said pharmaceutical formulation to the mammal in need thereof.

Another aspect of the invention provides for a process for producing pure amorphous rosuvastatin calcium which comprises:

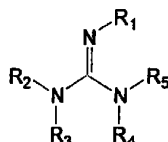
- a) hydrolysis of C<sub>1</sub>-C<sub>5</sub> alkyl esters of rosuvastatin with an organic nitrogen base in the presence of water, optionally containing an aprotic solvent,
- b) converting thus obtained rosuvastatin salt of organic nitrogen base with a source of calcium to obtain rosuvastatin calcium,
- c) isolating pure amorphous rosuvastatin calcium.

2006261087 01 Feb 2010

- 5A -

In one embodiment, the organic nitrogen base in the process of the invention is selected from the group consisting of:

5 a) guanidines of the formula:

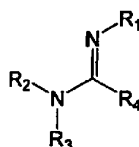


10

wherein each of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$  independently denotes a hydrogen atom or a chained, branched or cyclic  $\text{C}_1$ - $\text{C}_6$  alkyl group or each pair of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$  independently denotes a  $\text{C}_1$ - $\text{C}_6$  alkylene group connection which forms a ring,

15

b) amidines of the formula:

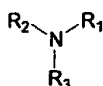


20

wherein each of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$  independently denotes a hydrogen atom or a chained, branched or cyclic  $\text{C}_1$ - $\text{C}_6$  alkyl group or each pair of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ , and  $\text{R}_4$  independently denotes a  $\text{C}_1$ - $\text{C}_6$  alkylene group connection which forms a ring;

25

c) amines of the formula



30

35



2006261087 01 Feb 2010

- 5B -

wherein each of  $R_1$ ,  $R_2$  and  $R_3$  independently denotes a hydrogen atom or a chained, branched or cyclic  $C_1$ - $C_{12}$  alkyl group, unsubstituted or substituted on one or more C-members of the alkyl chain with a radical selected from the group consisting of hydroxy,  $C_1$ - $C_6$  alkoxy, amino,  $C_1$ - $C_6$  alkylamino, di- $C_1$ - $C_6$  alkylamino, phenyl, pyridinyl,  $C_1$ - $C_6$  alkylamino or each pair of  $R_1$ ,  $R_2$  and  $R_3$  independently denotes  $C_1$ - $C_6$  alkylene group connection which forms a ring;

d) quaternary ammonium hydroxides of formula:



wherein each of  $R_1$ ,  $R_2$  and  $R_3$  independently denotes a hydrogen atom or a chained, branched or cyclic  $C_1$ - $C_6$  alkyl group or each pair of  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  independently denotes  $C_1$ - $C_6$  alkylene connection which forms a ring.

A further aspect of the invention provides for a process for preparing pure amorphous rosuvastatin calcium, which comprises:

- a) hydrolysis of  $C_1$ - $C_5$  alkyl ester of rosuvastatin with an alkali metal hydroxide in a mixture of an aprotic solvent and water,
- b) washing the reaction mixture with water immiscible organic solvent,
- c) acidifying the aqueous solution of rosuvastatin alkali salt with an acid,
- d) extraction of the resulted aqueous solution of rosuvastatinic acid into a water immiscible organic solvent,
- e) adding an amine selected from the group consisting of pyrrolidine, piperidine, morpholine, 1-adamantane, cyclohexylamine, N,N-dicyclohexylamine, *iso*-propylamine and *tert*-octylamine to the obtained extract containing rosuvastatinic acid to convert said rosuvastatinic acid into ammonium salt of rosuvastatin,
- f) converting ammonium salt of rosuvastatin with a source of calcium to obtain rosuvastatin calcium,
- g) isolation of amorphous rosuvastatin calcium.

In further aspects, the invention provides:

2006261087 01 Feb 2010

- 5C -

- 5 solid pyrrolidinium salt of rosuvastatin  
solid piperidinium salt of rosuvastatin  
solid morpholinium salt of rosuvastatin  
solid 1-adamantylammonium salt of rosuvastatin  
solid cyclohexylammonium salt of rosuvastatin  
solid N-methylcyclohexylammonium salt of rosuvastatin  
solid isopropylammonium salt of rosuvastatin and  
solid *tert*-octylammonium salt of rosuvastatin.

- 10 In another aspect the invention provides crystalline *tert*-octylammonium salt of rosuvastatin having X-Ray powder diffraction pattern with peaks:

	Angle (° 2θ)	Relative intensity ( % )
	7.13	14.45
15	8.00	39.04
	9.18	19.37
	10.40	19.55
	12.47	39.04
	14.42	33.65
	14.97	42.00
	15.48	28.38
	15.78	34.00
20	15.95	33.65
	17.68	100.00
	18.44	83.35
	18.77	39.87
	19.68	33.53
	20.27	44.55
	23.35	45.85
25	24.24	30.27
	29.31	28.79

- 30 In a further aspect the invention provides crystalline *tert*-octylammonium salt of rosuvastatin as monohydrate having X-Ray powder diffraction pattern with peaks:

	Angle (° 2θ)	Relative intensity ( % )
	4.68	19.36
	8.63	51.97
35	9.36	21.74
	10.15	21.58
	10.42	10.28
	14.10	34.45
	14.37	29.04

2006261087 01 Feb 2010

- 5D -

16.54	41.32
16.98	34.51
18.59	100.00
19.14	65.60
19.72	81.83
27.31	20.01

5

In another aspect the invention provides a use of crystalline *tert*-octylammonium salt of rosuvastatin monohydrate as analytical standard.

Detailed description of the invention

10

In one aspect, the present invention advantageously provides a novel process for the preparation of pure amorphous rosuvastatin calcium, substantially free of sodium cation impurities or other alkali metal cation impurities and other impurities as well, which would avoid the use of alcohols, e.g. C<sub>1</sub>-C<sub>4</sub> alcohols as a reaction medium and the use of alkali metal

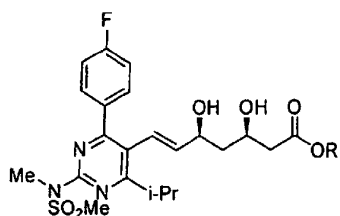
15 hydroxides, e.g. sodium hydroxide, thus eliminating O-alkyl rosuvastatin impurities (see Scheme 1), e.g. O-

ethyl rosuvastatin derivative and obtaining rosuvastatin calcium free of any traces of sodium cation impurity or alkaline metal cation impurities, which may be present as impurities in rosuvastatin calcium, prepared according to the prior art processes.

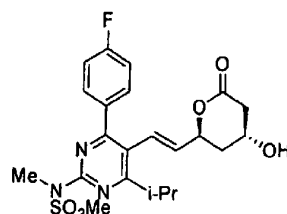
Thus, the term "substantially free" means that the desired obtained amorphous rosuvastatin calcium is free of any traces of alkali metal impurities, e.g. sodium metal impurity.

In another aspect, the present invention advantageously provides a novel process which would enable easy and simple preparation and optionally isolation of intermediary novel rosuvastatin salt with organic nitrogen bases, e.g. novel ammonium salts of rosuvastatin, in good quality, and which would enable simple and easy conversion of said novel intermediary compounds to desired commercial amorphous rosuvastatin calcium.

We have unexpectedly and surprisingly found that hydrolysis of starting C<sub>1</sub>-C<sub>5</sub> alkyl esters of rosuvastatin (Formula 2) or rosuvastatin lactone (Formula 3), may be effected in an aqueous solution of organic nitrogen bases instead of using C<sub>1</sub>-C<sub>4</sub> alcohols as protic solvent medium and strong inorganic alkali bases, e.g. sodium hydroxide, as known in the prior art processes. Namely, hydrolysis of starting C<sub>1</sub> to C<sub>5</sub> rosuvastatin esters in the presence of strong inorganic base, e.g. sodium hydroxide, according to the prior art processes, may result to incomplete conversion to desired rosuvastatin calcium. The consequence of incomplete conversion usually manifests in the presence of residual alkali metals, e.g. sodium cation, in the desired product. After using sodium hydroxide as a strong inorganic base, various amounts of residual sodium are found in the desired rosuvastatin calcium.



Formula 2



Formula 3

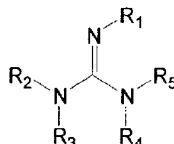
Residual sodium cation may be removed from rosuvastatin calcium by specific method, for instance the rosuvastatin calcium salt can be retreated by vigorous stirring in aqueous suspension, preferably by ultraturrax (Ultra-Turrax® is brand name of IKA Werke GmbH & Co., Staufen, Germany for dispersion making device with high speed rotation unit). Such methods eliminate sodium in a great extent, but none of the methods completely removes sodium from the desired rosuvastatin calcium.

The present invention provides the use of aqueous solution of organic nitrogen bases for cleavage of starting C<sub>1</sub> to C<sub>5</sub> alkyl ester of rosuvastatin or rosuvastatin lactone. Strong organic nitrogen bases selected from the group consisting of guanidines and amidines can be a method of choice. We have surprisingly found that also weak bases such as numerous amines if dissolved in water or in the mixtures of water and aprotic solvents, successfully cleft starting rosuvastatin esters if higher temperature is used. Moreover, we found out that by elevating temperature to 100 °C desired product did not neither degrade in considerable extent nor lead to appearance of corresponding amides of rosuvastatin.

According to the first aspect of the invention C<sub>1</sub>-C<sub>5</sub> alkyl esters of rosuvastatin or rosuvastatin lactone, where alkyl denotes methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl, *tert*-butyl, amyl or *tert*-amyl group, more preferably *tert*-alkyl esters, most preferably *tert*-butyl ester of rosuvastatin, are cleft in the solutions of organic nitrogen bases and water, optionally containing organic aprotic solvent, e.g. tetrahydrofuran.

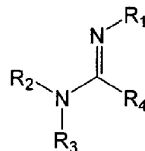
The organic nitrogen base used according to the process of the invention is selected from the group consisting of:

a) guanidines of the formula:



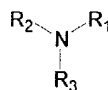
wherein each of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> independently denotes a hydrogen atom, a straight chain or branched chain C<sub>1</sub>-C<sub>8</sub> alkyl group or cyclic C<sub>1</sub>-C<sub>6</sub> alkyl group or each pair of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> independently denotes a C<sub>1</sub>-C<sub>8</sub> alkylene group connection which forms a ring;

b) amidines of the formula:



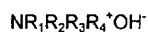
wherein each of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ , and  $\text{R}_4$  independently denotes a hydrogen atom, a straight chain or branched chain  $\text{C}_1\text{-C}_6$  alkyl group or cyclic  $\text{C}_1\text{-C}_6$  alkyl group or each pair of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ , and  $\text{R}_4$  independently denotes a  $\text{C}_1\text{-C}_6$  alkylene group connection which forms a ring;

c) amines of the formula:



wherein each of  $\text{R}_1$ ,  $\text{R}_2$  and  $\text{R}_3$  independently denotes a hydrogen atom, a straight chain or branched chain  $\text{C}_1\text{-C}_6$  alkyl group or cyclic  $\text{C}_1\text{-C}_{12}$  alkyl group, unsubstituted or substituted on one or more C-members of the alkyl chain with a radical selected from the group consisting of hydroxy,  $\text{C}_1\text{-C}_6$  alkoxy, amino,  $\text{C}_1\text{-C}_6$  alkylamino, di- $\text{C}_1\text{-C}_6$  alkylamino, phenyl, pyridinyl,  $\text{C}_1\text{-C}_6$  alkylamino or each pair of  $\text{R}_1$ ,  $\text{R}_2$  and  $\text{R}_3$  independently denotes  $\text{C}_1\text{-C}_6$  alkylene connection which forms a ring;

d) quaternary ammonium hydroxides of formula

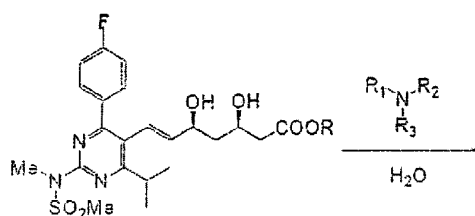


wherein each of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $\text{R}_4$  independently denotes a hydrogen atom, a straight chain or branched chain  $\text{C}_1\text{-C}_6$  alkyl group or cyclic  $\text{C}_1\text{-C}_6$  alkyl group or each pair of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $\text{R}_4$  independently denotes  $\text{C}_1\text{-C}_6$  alkylene group connection which forms a ring;

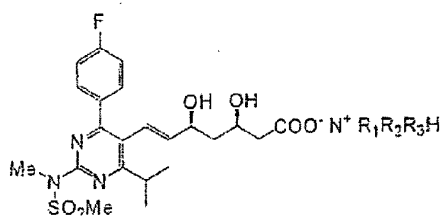
e) unsubstituted or  $\text{C}_1\text{-C}_6$  alkyl N-substituted piperazines, morpholines,

thiomorpholines, imidazolidines or adamantans.

A process for preparing ammonium salts of rosuvastatin by hydrolysis of C<sub>1</sub> to C<sub>5</sub> alkyl esters of rosuvastatin or rosuvastatin lactone with amines of above formula in the presence of water is shown on the following Scheme 2.



Formula 2  
(or Formula 3 - lactone)



Formula 4

Scheme 2

wherein in Formula 2 R denotes C<sub>1</sub> to C<sub>5</sub> alkyl group and R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> denotes radicals as denoted in above formula of amines.

According to the process of the invention a preferred organic nitrogen base used from the guanidine group is N,N,N',N'-tetramethylguanidine, from the amidine group 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), from the amine group n-propylamine *iso*-propylamine, N-methylcyclohexylamine, dicyclohexylamine, N-methyl-*iso*-propylamine, N,N-di-*iso*-propylamine, *tert*-butylamine, *tert*-octylamine (2,4,4-trimethylpent-2-ylamine), *sec*-butylamine and diethylamine.

According to the first aspect of the invention are starting C<sub>1</sub> to C<sub>5</sub> esters of rosuvastatin or rosuvastatin lactone, hydrolysed with organic nitrogen bases in the presence of water, optionally containing aprotic organic solvent (water content is more than 50 % by volume, preferably more than 75 % by volume). The hydrolysis is carried out at temperatures from 0° to 120 °C. By said hydrolysis using strong organic nitrogen bases, e.g. guanidines and amidines is preferred temperature from 20° to 70 °C, more preferred from 40° to 60°. By said hydrolysis using weak bases, e.g. amines, is the preferred temperature from 80° to 110 °C, more preferred from 95° to 105 °C, most preferred from 98° to 100 °C. The hydrolysis of starting rosuvastatin esters according to the invention by applying volatile amines (boiling point below 120 °C) is carried out in tightly closed vessels at increased pressures.

In another aspect of the invention a novel intermediary ammonium salts of rosuvastatin may be isolated directly from the hydrolysis mixture by evaporation to dryness, optionally following by treatment with suitable solvent to induce solidification of the corresponding salt, which is further collected, e.g. by filtration. The choice of a solvent for solidification depends on physico-chemical properties of particular salt and can be selected but not limited from nitriles, esters, ethers or hydrocarbons. For example, solid isopropylammonium salt of rosuvastatin from acetonitrile and N-methylcyclohexylammonium salt of rosuvastatin from tert-butyl methyl ether are isolated by this manner.

In another aspect of the invention ammonium salts of rosuvastatin may be converted into rosuvastatin calcium salt without previous isolation of intermediary ammonium salt of rosuvastatin from the solution. Aqueous solution of rosuvastatin salt with an appropriate amine obtained after hydrolysis step is optionally washed by water immiscible solvents and further converted with calcium source to precipitate the desired pure amorphous rosuvastatin calcium.

The water immiscible solvents are selected from the group consisting of esters, ethers, chlorinated hydrocarbons or cyclic hydrocarbons, preferably more user-friendly solvents, e.g. C<sub>2</sub>-C<sub>5</sub> acetate esters, e.g. ethyl acetate or cyclic hydrocarbons.

The source of calcium ion is selected from the group consisting of calcium halogenide, preferably calcium chloride, and another calcium source, e.g. calcium nitrate or calcium hydroxide, calcium salt of C<sub>1</sub>-C<sub>20</sub> alkanic acid, preferably calcium palmitate, calcium pivalate or calcium acetate.



In another aspect of the invention the novel intermediary ammonium salts of rosuvastatin may be prepared from rosuvastatin free acid by the reaction with an appropriate amine.

The rosuvastatin free acid is prepared from a starting C<sub>1</sub> to C<sub>5</sub> ester of rosuvastatin or rosuvastatin lactone by reacting it with a suitable base, e.g. sodium hydroxide, in the presence of an aprotic solvent, optionally diluted with water, and subsequent addition of an acid, e.g. phosphoric acid or hydrochloric acid, to the solution of rosuvastatin sodium salt, thus obtaining rosuvastatin free acid.

The strong inorganic base used in the hydrolysis step may be sodium hydroxide or other alkali metal hydroxide, and the reaction is proceeded in the presence of water or in the presence of a mixture of aprotic solvents and water, such as a mixture of water and tetrahydrofuran, optionally under increased pressure. The obtained solution of rosuvastatin alkaline salt is optionally washed by water immiscible solvents selected from the group consisting of esters, ethers, chlorinated hydrocarbons or cyclic hydrocarbons, preferably from more user-friendly solvents such as acetate esters, cyclic hydrocarbons or alkanes, more preferably from ethyl acetate. The aqueous phase containing rosuvastatin alkaline salt is subsequently treated by a strong inorganic acid, preferably by phosphoric acid or hydrochloric acid.

Resulting rosuvastatinic acid (rosuvastatin free acid) is then extracted into water immiscible solvent and the obtained organic phase is converted to the ammonium salt of rosuvastatin by contacting with an appropriate amine. For the purpose of unification of water immiscible organic solvents, if said solvent is used to wash the reaction mixture, the same organic solvent may be used, for example an ester, preferably *iso*-propyl acetate, for the reaction with an amine.

In a further procedure the organic extract (above mentioned solution of rosuvastatinic acid in water immiscible solvent, e. g. isopropyl acetate) is treated with an appropriate amine to obtain the corresponding ammonium salt of rosuvastatin. Alternatively, if said salt remains dissolved it can be precipitated by an addition of an antisolvent selected from other unpolar solvents, such as esters, ethers or hydrocarbons, optionally after concentration of the solution. In another alternative, the extracting solvent can be completely removed to isolate the solid ammonium salt of rosuvastatin or if oily further treated with suitable solvent to induce solidification of the corresponding salt, which is finally collected, e.g. by filtration. The solvent for the isolation of solid ammonium salt of rosuvastatin in all these alternatives strictly

depends on solubility and physical properties of particular salt, but the preferred media are C<sub>2</sub>-C<sub>5</sub> acetate esters and ethers, most preferred *iso*-propyl acetate and *tert*-butyl methyl ether.

According to this described aspect of the invention the following solid ammonium salts of rosuvastatin in good quality may be isolated:

N-methylcyclohexylammonium salt (99.6% area by HPLC),  
cyclohexylammonium salt (99.71 % area);  
dicyclohexylammonium salt (99.82 % area);  
pyrrolidinium salt (99.71 % area);  
piperidinium salt (99.77% area);  
morpholinium salt (99.51 % area);  
1-adamantylammonium salt (99.75% area);  
*tert*-octylammonium salt (99.87 % area).

Some of the isolated solid ammonium salts of rosuvastatin are good crystalline products, and can be isolated substantially pure. A characteristic example is *tert*-octylammonium salt of rosuvastatin, which can be isolated in two different pseudopolymorphs and be because of its purity conveniently used as an analytical standard.

From acetonitrile, optionally after washing with hexane an anhydrous crystalline form is isolated having diffraction angles in X-ray powder analysis, shown in Table 3, that is the invention is embodied in crystalline *tert*-octylammonium salt of rosuvastatin having X-Ray powder diffraction pattern characteristic with peaks at 8.0, 15.0, 17.7, 18.4, 18.8, 20.3, and 23.4  $\pm 0.2^\circ 2\theta$  and/or m.p. around 121  $^\circ\text{C}$ .

From a mixture of acetonitrile and water a crystalline monohydrate is isolated having diffraction angles in X-ray powder analysis, shown in Table 4. The invention is embodied in crystalline monohydrate of *tert*-octylammonium salt of rosuvastatin having X-Ray powder diffraction pattern with characteristic peaks at 8.6, 16.5, 18.6, 19.1, and 19.7  $\pm 0.2^\circ 2\theta$ . Especially recrystallized anhydrous *tert*-octylammonium salt of rosuvastatin has stable defined structure, therefore is more suitable for use as an analytical standard than amorphous calcium salt with its hygroscopic properties and calcium assay variation. After determination of precise content of rosuvastatin, for example by NMR or titration, the substance can be used as weighing standard compound in HPLC analyses of rosuvastatin.

The formed ammonium salts of rosuvastatin can be converted into rosuvastatin calcium salt by adding a source of calcium ions to said ammonium salt of rosuvastatin, preferably calcium acetate or calcium hydroxide, using water as a solvent.

The following examples illustrate the invention, but do not limit it in any way:

Analytical data in examples were achieved by the following hardware:

Melting points were determined in Kofler hot stage microscope and differential dynamic calorimeter Mettler Toledo DSC822e

Powder X-ray diffraction spectra of the sample was recorded on Siemens D-5000 with reflexion technique: CuK $\alpha$  radiation, range from 2° to 37° 2Theta, step 0.04° 2Theta, integration time 1 sec. The accuracy in the diffractograms is believed to be  $\pm 0.2$ , preferably  $\pm 0.1$  2Theta.

#### Example 1

Hydrolysis of *tert*-butyl ester of rosuvastatin in aqueous solution of amines

7.5 g of *tert*-butyl ester of rosuvastatin

38 ml of demineralized water

2 to 5 equivalents of amine

The reactants and water as the solvent are stirred in the autoclave from 98° to 100°C for 1 to 4 hours. The reaction mixture is sampled and analyzed by HPLC ("High Pressure Liquid Chromatography") to find out the completion of reaction. Results are shown in Table 1.

Amine	Rosuvastatin salt with amine area%	Rosuvastatin <i>tert</i> - butyl ester, area%	Hydrolysis time from 95° to 100°C
N-methyl-N-( <i>iso</i> -propyl)- amine	98.9%	0 %	2 h
<i>iso</i> -propylamine	97.7%	0 %	3 h
diethylamine	98.4%	0 %	3.5 h
N,N-di( <i>iso</i> -propyl)amine	98.6%	0.05 %	3 h
<i>tert</i> -butylamine	98.4%	0 %	4 h
<i>sec</i> -butylamine	94.5%	1.0 %	4 h

Table 1

Example 2

Hydrolysis of rosuvastatin lactone in aqueous solution of N-methylcyclohexylamine

0.5 g of rosuvastatin lactone

0.5 ml of N-methylcyclohexylamine

3.0 ml of demineralized water

The reactants and the solvent are stirred 1 hour at 90°C forming clear solution and analysed as described in Example 1. HPLC analysis shows total consumption of the starting lactone.

Example 3

Hydrolysis of *tert*-butyl ester of rosuvastatin in a solution of strong organic nitrogen bases

The solution of *tert*-butyl ester of rosuvastatin in a mixture of a base, tetrahydrofuran and water in the ratio of 1:6:15 by volume is stirred at 50°C for few hours. The reaction mixture is sampled and analysed by HPLC to find out the completion of reaction. Results are shown in Table 2.

Amine	Rosuvastatin salt with amine area %	Rosuvastatin <i>tert</i> -butyl ester, area %	Hydrolysis time and temperature
N,N,N'-tetramethylguanidine	97.9 %	0 %	2 h (50 °C)
DBU	97.8 %	0 %	2 h (50 °C)
DBN	97.4 %	0 %	2 h (50 °C)
Tetramethylammonium hydroxide	99.5 %	0 %	1 h (40-45 °C)

Table 2

Example 4

Preparation of *iso*-propylammonium salt of rosuvastatin

7.2 g of *tert*-butyl ester of rosuvastatin

35 ml of demineralized water

4.5 ml of *iso*-propylamine

The reactants and water as the solvent are stirred in the autoclave from 98° to 100°C for 2 hours. The solution formed is then allowed to cool to room temperature and some very little amount of solid impurities is filtered off. Filtrate is washed twice with 20 ml of *iso*-propyl acetate and the aqueous phase is then evaporated under reduced pressure at 70°C and 15 mbar to remove solvents and *iso*-propylamine. 7.15 g of white solid residue of rosuvastatin *iso*-propylammonium salt is collected.

This amount is added to 70 ml acetonitrile and the suspension formed is heated under reflux (80°C) for 1h. Then, it is left for 2h at 0°C. Subsequently, the product is separated by filtration. Yield: 6.7 g of white crystals of the pure product (>99.9% area, HPLC)

<sup>1</sup>H-NMR: (CD<sub>3</sub>OD): 1.29 (12H,d, J=7Hz), 1.48 – 1.56 (1H,m), 1.62 – 1.72 (1H,m), 2.25 (1H,dd, J<sub>1</sub>=14Hz, J<sub>2</sub>=7,6Hz), 2.34 (1H,dd, J<sub>1</sub>=14Hz, J<sub>2</sub>=4.9Hz), 3.39 (1H,h, J=7Hz), 3.51 (1H,h, J=7Hz), 3.52 (3H,s), 3.53 (3H,s), 3.92 – 4.00 (1H,m), 4.33 – 4.40 (1H,m), 5.57 (1H,dd, J<sub>1</sub>=16Hz, J<sub>2</sub>=6Hz), 6.62 (1H,dd, J<sub>1</sub>=16Hz, J<sub>2</sub>=1.2Hz), 7.14 – 7.22 (1H,m), 7.69 – 7.75 (1H,m).

Analogously, *tert*-butylammonium salt of rosuvastatin is prepared with essentially the same yield:

<sup>1</sup>H-NMR: (CD<sub>3</sub>OD): 1.29.(6H,d, J=7Hz), 1.35.(9H,s), 1.48 – 1.56.(1H,m), 1.62 – 1.72.(1H,m), 2.25.(1H,dd, J<sub>1</sub>=15Hz, J<sub>2</sub>=7.6Hz), 2.34.(1H,dd, J<sub>1</sub>=15Hz, J<sub>2</sub>=4.9Hz), 3.51.(1H,h, J=7Hz), 3.52.(3H,s), 3.53.(3H,s), 3.92 – 4.00.(1H,m), 4.33 – 4.40.(1H,m), 5.57.(1H,dd, J<sub>1</sub>=16Hz, J<sub>2</sub>=6Hz), 6.62.(1H,dd, J<sub>1</sub>=16Hz, J<sub>2</sub>=1.2Hz), 7.14 – 7.22.(1H,m), 7.69 – 7.75.(1H,m).

#### Example 5

##### Preparation of N-methylcyclohexylammonium salt of rosuvastatin

50 g of *tert*-butyl ester of rosuvastatin

225 ml of demineralized water

25 ml of N-methylcyclohexylamine

The reactants and water as the solvent are stirred in the autoclave from 98° to 100°C for 3 hours. The solution formed is then allowed to cool to room temperature, 150 ml of additional demineralized water and 20 ml tetrahydrofuran are added and some very little amount of solid impurities is filtered off. The resulting solution is then washed with 2 x 200 ml methylcyclohexane and the aqueous phase is evaporated under reduced pressure at 70°C and 15 mbar to remove solvents and the N-methylcyclohexylamine. 50 ml toluene and 70 ml ethyl acetate are added and evaporated again to remove as much water as possible. To the oily residue 250 ml *tert*-butyl methyl ether is added and the mixture is digested forming white suspension. After cooling it at 0°C for 12 hours, the suspension is filtered and washed with 60 ml *tert*-butyl methyl ether and dried on the filter. Yield: 50.8 g of white solid of N-methylcyclohexylammonium salt of rosuvastatin.

#### Example 6

##### Preparation of N-methylcyclohexylammonium salt of rosuvastatin from N,N,N',N'-tetramethylguanidine salt of rosuvastatin

5.0 g of *tert*-butyl ester of rosuvastatin

1.4 ml of N,N,N',N'-tetramethylguanidine

25 ml of demineralized water  
10 ml of tetrahydrofuran

The reactants and solvents are stirred at 50°C for 2h. The solution formed is then allowed to cool to room temperature and washed twice with 40 ml of methylcyclohexane. The aqueous phase is partially evaporated to 25 g of total weight of the residue. 0.1 g of charcoal is added to aqueous phase and resulting suspension is stirred for 30 minutes. Charcoal and some solid impurities are filtered off and filtrate is diluted to 30 ml of total volume.

To 30 ml of the obtained solution 40 ml *tert*-butyl methyl ether is added 1.3 ml of 85% phosphoric acid in 5 ml of water and the resulting mixture is stirred for 15 minutes. A two-phase system is formed. Organic layer is separated and washed with 5 ml of water and dried with 5 g of anhydrous magnesium sulphate for 2 h. Magnesium sulphate is then separated by filtration.

To filtrate is then added 1.5 ml N-methylcyclohexylamine and the reaction mixture is stirred for 2 hours at room temperature and then it is left resting at 0°C for 12 hours. White precipitate of N-methylcyclohexylammonium salt of rosuvastatin is filtered off and washed with 5 ml of *tert*-butyl methyl ether and dried on the filter for 2 hours. Yield: 4.04 g of the title product (99.6% area, HPLC)

<sup>1</sup>H-NMR: (CD<sub>3</sub>OD): 1.10 – 1.45 (12H,m), 1.31 (d, J=7Hz), 1.48 – 1.56 (1H,m), 1.62 – 1.72 (1H,m), 1.82 – 1.90 (2H,m), 2.03 – 2.10 (2H,m), 2.25 (1H,dd, J<sub>1</sub>=14Hz, J<sub>2</sub>=7.6Hz), 2.34 (1H,dd, J<sub>1</sub>=14Hz, J<sub>2</sub>=4.9Hz), 2.62 (3H,s), 2.85 – 2.97 (1H,m), 3.51 (1H,h, J=7Hz), 3.52 (3H,s), 3.54 (3H,s), 3.92 – 3.97 (1H,m), 4.33 – 4.40 (1H,m), 5.56 (1H,dd, J<sub>1</sub>=16Hz, J<sub>2</sub>=6Hz), 6.62 (1H,dd, J<sub>1</sub>=16Hz, J<sub>2</sub>=1.2Hz), 7.14 – 7.22 (1H,m), 7.69 – 7.75 (1H,m).

#### Example 7

General procedure for preparing isolated ammonium salts of rosuvastatin

5 g of *tert*-butyl ester of rosuvastatin  
1.75 ml of 8 M NaOH  
25 ml of demineralized water  
10 ml of tetrahydrofuran

The reactants and the solvents are stirred from 50° to 55°C for 1 hour. The solution formed is then allowed to cool to room temperature and washed with 50 ml methylcyclohexane yielding 33 ml of aqueous solution of sodium salt of rosuvastatin.

To 33 ml of sodium rosuvastatin solution prepared in the above described experiment is added 1.3 ml 85% phosphoric acid, previously dissolved in 5 ml of water. Reaction mixture is extracted with 40 ml of *iso*-butyl acetate. Organic layer is separated off and dried with 5 g of anhydrous magnesium sulphate. Drying agent is filtered off and washed with 10 ml *iso*-butyl acetate obtaining 52 ml of filtrate containing rosuvastatinic acid, which is divided into smaller portions for preparing various ammonium salts.

To 5 ml of the obtained solution 1.5 equivalents of appropriate amine and 5 ml *tert*-butyl methyl ether are added. Rosuvastatin substituted ammonium salt is filtered off and dried on filter. The following solid salts are prepared:

- cyclohexylammonium salt of rosuvastatin: 0.45 g, 99.71% area by HPLC;

<sup>1</sup>H-NMR: (CD<sub>3</sub>OD): 1.10 – 1.45 (12H,m), 1.31 (6H,d, J=7Hz), 1.48 – 1.56 (1H,m), 1.62 – 1.72 (1H,m), 1.80 – 1.87 (2H,m), 1.97 – 2.03 (2H,m), 2.25 (1H,dd, J<sub>1</sub>=14Hz, J<sub>2</sub>=7.6Hz), 2.34 (1H,dd, J<sub>1</sub>=14Hz, J<sub>2</sub>=4.9Hz), 2.98 – 3.09 (1H,m), 3.51 (1H,h, J=7Hz), 3.52 (3H,s), 3.54 (3H,s), 3.92 – 3.97 (1H,m), 4.33 – 4.40 (1H,m), 5.56 (1H,dd, J<sub>1</sub>=16Hz, J<sub>2</sub>=6Hz), 6.62 (1H,dd, J<sub>1</sub>=16Hz, J<sub>2</sub>=1.2Hz), 7.14 – 7.22 (2H,m), 7.69 – 7.75 (1H,m);

- dicyclohexylammonium salt of rosuvastatin: 0.35 g, 99.82% area;

<sup>1</sup>H-NMR: (CD<sub>3</sub>OD): 1.12 – 1.76 (20H,m), 1.29 (d, J=7Hz), 1.48 – 1.56 (1H,m), 1.62 – 1.72 (1H,m), 1.83 – 1.92 (4H,m), 2.01 – 2.09 (4H,m), 2.25 (1H,dd, J<sub>1</sub>=14Hz, J<sub>2</sub>=7.6Hz), 2.34 (1H,dd, J<sub>1</sub>=14Hz, J<sub>2</sub>=4.9Hz), 3.07 – 3.17 (2H,m), 3.51 (1H,h, J=7Hz), 3.52 (3H,s), 3.54 (3H,s), 3.92 – 3.97 (1H,m), 4.33 – 4.40 (1H,m), 5.56 (1H,dd, J<sub>1</sub>=16Hz, J<sub>2</sub>=6Hz), 6.62 (1H,dd, J<sub>1</sub>=16Hz, J<sub>2</sub>=1.2Hz), 7.14 – 7.22 (2H,m), 7.69 – 7.75 (2H,m);

- pyrrolidinium salt of rosuvastatin: 0.28 g, 99.71% area,

<sup>1</sup>H-NMR: (CD<sub>3</sub>OD): 1.29 (6H,d, J=7Hz), 1.48 – 1.56 (1H,m), 1.62 – 1.72 (1H,m), 1.96 – 2.01 (4H,m), 2.25 (1H,dd, J<sub>1</sub>=14Hz, J<sub>2</sub>=7.6Hz), 2.34 (1H,dd, J<sub>1</sub>=14Hz, J<sub>2</sub>=4.9Hz), 3.20 – 3.25 (4H,m), 3.51 (1H,h, J=7Hz), 3.52 (3H,s), 3.54 (3H,s), 3.92 – 3.97 (1H,m), 4.33 – 4.40



(1H,m), 5.56 (1H,dd,  $J_1=16\text{Hz}$ ,  $J_2=6\text{Hz}$ ), 6.62 (1H,dd,  $J_1=16\text{Hz}$ ,  $J_2=1.2\text{Hz}$ ), 7.14 – 7.22 (2H,m), 7.69 – 7.75 (2H,m);

- piperidinium salt of rosuvastatin: 0.28 g, 99.77% area;

$^1\text{H-NMR}$ : ( $\text{CD}_3\text{OD}$ ): 1.29 (6H,d,  $J=7\text{Hz}$ ), 1.48 – 1.56 (1H,m), 1.62 – 1.81 (7H,m), 2.25 (1H,dd,  $J_1=14\text{Hz}$ ,  $J_2=7.6\text{Hz}$ ), 2.34 (1H,dd,  $J_1=14\text{Hz}$ ,  $J_2=4.9\text{Hz}$ ), 3.09 – 3.13 (4H,m), 3.51 (1H,h,  $J=7\text{Hz}$ ), 3.52 (3H,s), 3.54 (3H,s), 3.92 – 3.97 (1H,m), 4.33 – 4.40 (1H,m), 5.56 (1H,dd,  $J_1=16\text{Hz}$ ,  $J_2=6\text{Hz}$ ), 6.62 (1H,dd,  $J_1=16\text{Hz}$ ,  $J_2=1.2\text{Hz}$ ), 7.14 – 7.22 (1H,m), 7.69 – 7.75 (2H,m);

- morpholinium salt of rosuvastatin: 0.30 g, 99.51% area;

$^1\text{H-NMR}$ : ( $\text{CD}_3\text{OD}$ ): 1.29 (6H,d,  $J=7\text{Hz}$ ), 1.49 – 1.57 (1H,m), 1.62 – 1.72 (1H,m), 2.25 (1H,dd,  $J_1=14\text{Hz}$ ,  $J_2=7.6\text{Hz}$ ), 2.34 (1H,dd,  $J_1=14\text{Hz}$ ,  $J_2=4.9\text{Hz}$ ), 3.12 – 3.16 (4H,m), 3.51 (1H,h,  $J=7\text{Hz}$ ), 3.52 (3H,s), 3.53 (3H,s), 3.81 – 3.85 (4H,m), 3.92 – 4.00 (1H,m), 4.33 – 4.40 (1H,m), 5.57 (1H,dd,  $J_1=16\text{Hz}$ ,  $J_2=6\text{Hz}$ ), 6.62 (1H,dd,  $J_1=16\text{Hz}$ ,  $J_2=1.2\text{Hz}$ ), 7.14 – 7.22 (2H,m), 7.69 – 7.75 (1H,m);

- 1-adamantylammonium salt of rosuvastatin: 0.66 g, 99.75% area;

$^1\text{H-NMR}$ : ( $\text{CD}_3\text{OD}$ ): 1.29 (6H,d,  $J=7\text{Hz}$ ), 1.48 – 1.56 (1H,m), 1.62 – 1.85 (16H,m), 2.15 (3H,s (broad)), 2.25 (1H,dd,  $J_1=14\text{Hz}$ ,  $J_2=7.6\text{Hz}$ ), 2.34 (1H,dd,  $J_1=14\text{Hz}$ ,  $J_2=4.9\text{Hz}$ ), 3.51 (1H,h,  $J=7\text{Hz}$ ), 3.52 (3H,s), 3.54 (3H,s), 3.92 – 3.97 (1H,m), 4.33 – 4.40 (1H,m), 5.56 (1H,dd,  $J_1=16\text{Hz}$ ,  $J_2=6\text{Hz}$ ), 6.62 (1H,dd,  $J_1=16\text{Hz}$ ,  $J_2=1.2\text{Hz}$ ), 7.14 – 7.22 (2H,m), 7.69 – 7.75 (1H,m).

#### Example 8

##### Preparation of N-cyclohexylammonium salt of rosuvastatin

10 g *tert*-butyl ester of rosuvastatin

3.5 ml 8 M NaOH

50 ml demineralized water

20 ml tetrahydrofuran

The reactants and the solvents are stirred from 50° to 55°C for 1 hour. The solution formed is then allowed to cool to room temperature and washed with 100 ml methylcyclohexane yielding 66 ml of aqueous solution of sodium rosuvastatin.

To 33 ml of the obtained solution is added 1.3 ml 85% phosphoric acid in 5 ml demineralized water. Rosuvastatinic acid is extracted with 40 ml *iso*-propyl acetate. 4.7 g of anhydrous magnesium sulphate and 0.5 g charcoal is added to organic phase and suspension is stirred for 45 min. Magnesium sulphate and charcoal are filtered off yielding 41 ml of filtrate.

16 ml of the filtrate is separated and treated by addition of 0.5 ml of cyclohexylamine in 8 ml of *iso*-propyl acetate during stirring and rosuvastatin cyclohexylammonium salt precipitate instantaneously as white solid. It is separated by filtration, precipitate is washed on the filter with 10 ml of *iso*-propyl acetate and dried on the filter yielding 1.34 g of the desired product (99.52% area, HPLC).

#### Example 9

##### Preparation of crystalline rosuvastatin *tert*-octylammonium salt

Rosuvastatin *tert*-butyl ester (27.0 g, 50.2 mmol) is dissolved in 225 ml of a mixture of tetrahydrofuran and water in the ratio of 4:1 by volume. The clear solution is warmed to 30 °C and 8.0 M NaOH (6.75 ml, 54.0 mmol) is added portionwise. The reaction mixture is stirred at 30 °C for 2 hours giving a clear yellow solution. Then tetrahydrofuran is removed completely under the reduced pressure (20 mbar) at 40 °C. The remaining aqueous solution is diluted with water to 225 ml and washed with ethyl acetate (3×90 ml). To a vigorously stirring solution of sodium rosuvastatin is added dropwise HCl 37 % (4.2 ml, 50.2 mmol) at ambient temperature.

The obtained white emulsion of rosuvastatin free acid is extracted with ethyl acetate (150 ml). After separation from the organic layer aqueous phase is additionally extracted with ethyl acetate (2×50 ml). Organic layers are combined and washed with water (3×30 ml). Then ethyl acetate is removed under reduced pressure (20 mbar) at 40 °C. The residue is dissolved in a minimal amount of acetonitrile and the solvent is rapidly evaporated under reduced pressure (20 mbar) at 40 °C to give 25.48 g of the solid residue. This solid is then dissolved in acetonitrile (100 ml) to give a clear solution. To a vigorously stirring solution of rosuvastatin free acid is added dropwise *tert*-octylamine (6.83 g, 50.2 mmol) over 1 minute at

ambient temperature. In less than 10 minutes white solid precipitates abundantly from the solution, which cause solidification of the mixture. This solid is then treated with 75 ml of a mixture of hexane and acetonitrile in the ratio of 1:2 mixture by volume to give a dense suspension. The white precipitate is filtered and dried in vacuum at 40 °C to give 27.6 g of a white powder. This powder is suspended in hexane (100 ml) and vigorously stirred for 1 hour at ambient temperature. The undissolved precipitate is collected by filtration, washed with hexane (50 ml) and dried in vacuum at 40 °C to give 27.4 g (89.4 %) of rosuvastatin *tert*-octylammonium salt as white crystalline powder.

Melting point: 121 °C (DSC, onset)

X-Ray powder analysis – diffraction angles (2 theta) – Figure 1:

Angle (° 2θ)	Relative intensity ( %)
7.13	14.45
8.00	39.04
9.18	19.37
10.40	19.55
12.47	39.04
14.42	33.65
14.97	42.00
15.48	28.38
15.78	34.00
15.95	33.65
17.68	100.00
18.44	83.35
18.77	39.87
19.68	33.53
20.27	44.55
23.35	45.85
24.24	30.27
29.31	28.79

Table 3

#### Example 10

Preparation of crystalline rosuvastatin *tert*-octylammonium monohydrate salt

Rosuvastatin *tert*-octylammonium salt (19.5 g) from Example 9 is dissolved in 429 ml of a mixture of acetonitrile and water in the ratio of 10 :1 by volume at ambient temperature. The solution is left to stand at 6 °C for a few days. The white needles that crystallizes from the

mixture are collected by filtration and dried in vacuum at 50 °C to give 10.48 g (53.7 %) of crystalline rosuvastatin *tert*-octylammonium monohydrate salt as white needles.

Melting point: 129 °C (DSC, onset), dehydration 85° to 105°C

X-Ray powder analysis – diffraction angles (2 theta) – Figure 2:

Angle (° 2θ)	Relative intensity ( %)
4.68	19.36
8.63	51.97
9.36	21.74
10.15	21.58
10.42	10.28
14.10	34.45
14.37	29.04
16.54	41.32
16.98	34.51
18.59	100.00
19.14	65.60
19.72	81.83
27.31	20.01

Table 4

#### Example 11

Preparation of rosuvastatin calcium from *tert*-butyl ester of rosuvastatin via DBU salt

1.0 g of *tert*-butyl ester of rosuvastatin  
0.32 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)  
5 ml of demineralized water  
2 ml of tetrahydrofuran

The reactants and the solvents are stirred at 50°C for 2 h. The solution formed is then allowed to cool to room temperature and 2 ml demineralized water is added. Reaction mixture is washed twice with 10 ml methylcyclohexane. Combined organic phases are washed with 2 ml demineralized water. Combined aqueous phases are partially evaporated reducing original weight for 3.7 g. To remaining solution 0.25 ml of 4M calcium chloride is added during stirring and cooling on ice-bath for 15 minutes. White precipitate of rosuvastatin calcium is filtered off and washed with 1 ml demineralized water. 0.64 g of the desired

amorphous product is collected after drying for 12 hours at room temperature in vacuum desiccator.

#### Example 12

Preparation of rosuvastatin calcium from rosuvastatin lactone via DBU salt

0.5 g rosuvastatin lactone  
0.20 ml DBU  
3.0 ml water

The reactants and the solvent are stirred 1 hour at 90°C forming clear solution. HPLC shows total consumption of the starting lactone.

Then, 0.16 g of calcium acetate monohydrate in 2 ml of water is added and the suspension formed is treated with ultraturrax at 15000 rpm for 5 minutes. The white precipitate of rosuvastatin calcium is separated by filtration. Yield: 0.42 g of the amorphous product.

#### Example 13

Preparation of rosuvastatin calcium from *iso*-propylammonium salt of rosuvastatin

7.5 g of *tert*-butyl ester of rosuvastatin  
37 ml of water  
3.5 ml of *iso*-propylamine  
calcium hydroxide

The reactants and the solvent are stirred in the autoclave from 95° to 100°C for 2 hours. Reaction mixture is allowed to cool to room temperature and subsequently 20 ml of demi-water is added. Reaction mixture is washed twice with 37 ml methylcyclohexane. To aqueous phase 0.08 g charcoal is added and the resulting suspension is stirred for 45 minutes. Charcoal and some little amounts of solid impurities are filtered off. Resulting clear solution (containing rosuvastatin *iso*-propylammonium salt) is evaporated at reduced pressure to oily residue, which is diluted with water to 70 ml of total volume. To the obtained solution of rosuvastatin *iso*-propylammonium salt is added 2.0 g of moist calcium hydroxide paste (cca 50% content) and resulting suspension is stirred for 1 h at room temperature

under nitrogen and for additional 15 min on ice-bath. White precipitate is then filtered off and washed with 8 ml of ice-cold demineralized water. The product is dried under vacuum at 60°C for 3 hours. Yield: 6.15 g of amorphous rosuvastatin calcium.

#### Example 14

Preparation of rosuvastatin calcium from *iso*-propylammonium salt of rosuvastatin

2.0 g of rosuvastatin *iso*-propylammonium salt

13 ml of demineralized water

2.0 ml of 1M calcium acetate

The reactants and the solvent are digested with ultraturrax for 2 minutes at 10000 rpm under nitrogen and then stirred 10 minutes with magnetic bar at 10°C. White precipitate is filtered off and washed with 2 ml demineralized water. It is dried 1 hour on the filter and 2 hours from 50° to 60°C at 10 mbars. Yield: 1.67 g of amorphous rosuvastatin calcium (>99.8% area, HPLC, <0.1% sodium calculated on the content of calcium)

#### Example 15

Preparation of rosuvastatin calcium from N-methylcyclohexylammonium salt of rosuvastatin

1.0 g rosuvastatin N-methylcyclohexylammonium salt

0.48 g of calcium palmitate

5.0 ml *iso*-butyl acetate

The reactants and the solvent are stirred 5 minutes at 80°C. Gradually, 6 ml of methylcyclohexane is added within 5 minutes at 80°C. The reaction mixture is then stirred for 20 minutes at room temperature. Resulting precipitate is separated by filtration and washed on filter with 5 ml methylcyclohexane. 0.40 g of amorphous rosuvastatin calcium is collected (99.26% area, HPLC)

#### Example 16

Preparation of rosuvastatin lactone

20.0 g rosuvastatin *tert*-butyl ester  
6.5 ml 8M KOH  
40 ml tetrahydrofuran  
100 ml demineralized water

The reactants and the solvents are stirred 1.5 hours from 40° to 45°C hydrolysing starting rosuvastatin ester into its potassium salt. The clear solution formed is washed twice with 50 ml methylcyclohexane followed by filtration to remove some little amount of solid impurities. Then, the filtrate is treated with 100 ml ethyl acetate and 4.3 ml of 85% phosphoric acid forming two layers. The upper layer is separated and washed with 20 ml of water. To the organic phase is then added 1.0 ml of 85% phosphoric acid and the reaction mixture is heated 5 minutes on the water-bath of the rotavapor at 50°C at atmospheric pressure. Then, the solvent is evaporated at reduced pressure. To the syrupy residue another 100 ml of ethyl acetate is added and the process of heating, evaporation and adding ethyl acetate is repeated three times. At last, the ethyl acetate solution of rosuvastatin lacton is washed with 20 ml of 5% solution of sodium bicarbonate and twice with 30 ml water. The solvent is evaporated at reduced pressure giving 17.0 g of syrupy residue, which crystallized on standing (91% area by HPLC).

By consecutive treatment with ultraturrax at 15000 rpm in 80 ml of *tert*-butyl methyl ether, filtration and recrystallization from *iso*-propyl acetate / diisopropyl ether the purity is enhanced to 95% area.

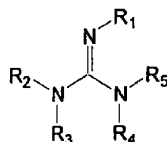
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

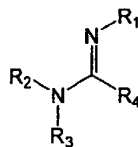
1. A process for producing pure amorphous rosuvastatin calcium which comprises:
  - a) hydrolysis of C<sub>1</sub>-C<sub>5</sub> alkyl esters of rosuvastatin with an organic nitrogen base in the presence of water, optionally containing an aprotic solvent,
  - b) converting thus obtained rosuvastatin salt of organic nitrogen base with a source of calcium to obtain rosuvastatin calcium,
  - c) isolating pure amorphous rosuvastatin calcium.
2. A process according to claim 1, wherein C<sub>1</sub>-C<sub>5</sub> alkyl ester of rosuvastatin is *tert*-butyl rosuvastatin.
3. A process according to claim 1, wherein the organic nitrogen base is selected from the group consisting of:

a) guanidines of the formula:



wherein each of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> independently denotes a hydrogen atom or a chained, branched or cyclic C<sub>1</sub>-C<sub>6</sub> alkyl group or each pair of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> independently denotes a C<sub>1</sub>-C<sub>6</sub> alkylene group connection which forms a ring,

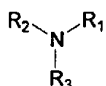
b) amidines of the formula:





wherein each of  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and  $R_5$  independently denotes a hydrogen atom or a chained, branched or cyclic  $C_1$ - $C_6$  alkyl group or each pair of  $R_1$ ,  $R_2$ ,  $R_3$ , and  $R_4$  independently denotes a  $C_1$ - $C_6$  alkylene group connection which forms a ring;

c) amines of the formula



wherein each of  $R_1$ ,  $R_2$  and  $R_3$  independently denotes a hydrogen atom or a chained, branched or cyclic  $C_1$ - $C_{12}$  alkyl group, unsubstituted or substituted on one or more C-members of the alkyl chain with a radical selected from the group consisting of hydroxy,  $C_1$ - $C_6$  alkoxy, amino,  $C_1$ - $C_6$  alkylamino, di- $C_1$ - $C_6$  alkylamino, phenyl, pyridinyl,  $C_1$ - $C_6$  alkylamino or each pair of  $R_1$ ,  $R_2$  and  $R_3$  independently denotes  $C_1$ - $C_6$  alkylene connection which forms a ring;

d) quaternary ammonium hydroxides of formula:



wherein each of  $R_1$ ,  $R_2$  and  $R_3$  independently denotes a hydrogen atom or a chained, branched or cyclic  $C_1$ - $C_6$  alkyl group or each pair of  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  independently denotes  $C_1$ - $C_6$  alkylene connection which forms a ring.

4. A process according to claims 1 and 3 a), wherein the organic nitrogen base is N,N,N',N'-tetramethylguanidine .
5. A process according to claims 1 and 3 b), wherein the organic nitrogen base is selected from the group consisting of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

6. A process according to claims 1 and 3 c), wherein the organic nitrogen base is selected from the group consisting of *iso*-propylamine, *sec*-butylamine, *tert*-butylamine, diethylamine, N,N-diisopropylamine, N-methyl-isopropylamine, N-methylcyclohexylamine.
7. A process according to claim 1, wherein the source of calcium is selected from the group consisting of calcium chloride, calcium nitrate, calcium hydroxide and calcium salt of C<sub>1</sub>-C<sub>20</sub> alkanolic acid.
8. A process according to claims 1 and 7, wherein the calcium salt of C<sub>1</sub>-C<sub>20</sub> alkanolic acid is selected from the group consisting of calcium palmitate, calcium pivalate and calcium acetate or its monohydrate.
9. A process according to claim 1, wherein the aprotic solvent is tetrahydrofuran.
10. A process for preparing pure amorphous rosuvastatin calcium, which comprises:
  - a) hydrolysis of C<sub>1</sub>-C<sub>5</sub> alkyl ester of rosuvastatin with an alkali metal hydroxide in a mixture of an aprotic solvent and water,
  - b) washing the reaction mixture with water immiscible organic solvent,
  - c) acidifying the aqueous solution of rosuvastatin alkali salt with an acid,
  - d) extraction of the resulted aqueous solution of rosuvastatinic acid into a water immiscible organic solvent,
  - e) adding an amine selected from the group consisting of pyrrolidine, piperidine, morpholine, 1-adamantane, cyclohexylamine, N,N-dicyclohexylamine, *iso*-propylamine and *tert*-octylamine to the obtained extract containing rosuvastatinic acid to convert said rosuvastatinic acid into ammonium salt of rosuvastatin,
  - f) converting ammonium salt of rosuvastatin with a source of calcium to obtain rosuvastatin calcium,
  - g) isolation of amorphous rosuvastatin calcium.
11. A process according to claim 10, wherein C<sub>1</sub>-C<sub>5</sub> alkyl ester of rosuvastatin is *tert*-butyl rosuvastatin.

2006261087 01 Feb 2010

- 29 -

12. A process according to claim 10, wherein an alkali metal hydroxide is sodium hydroxide.
13. A process according to claim 10, wherein the aprotic solvent is tetrahydrofuran.
14. A process according to claim 10, wherein water immiscible organic solvent is selected from the group consisting of C<sub>2</sub>-C<sub>5</sub> alkyl acetate, ethers, chlorinated hydrocarbons and cyclic hydrocarbons.
15. A process according to claims 10 and 14, wherein C<sub>2</sub>-C<sub>5</sub> alkyl acetate is selected from the group consisting of ethyl acetate, *iso*-propyl acetate and *iso*-butyl acetate.
16. A process according to claim 10, wherein the water immiscible organic solvent is methylcyclohexane.
17. A process according to claim 10, wherein the acid is selected from the group consisting of phosphoric acid and hydrochloric acid.
18. A process according to claim 10, wherein the source of calcium is selected from the group consisting of calcium chloride, calcium nitrate, calcium hydroxide and calcium salt of C<sub>1</sub>-C<sub>20</sub> alkanolic acid.
19. A process according to claims 10 and 18, wherein the calcium salt of C<sub>1</sub>-C<sub>20</sub> alkanolic acid is selected from the group consisting of calcium palmitate, calcium pivalate and calcium acetate, or its monohydrate.
20. A process according to claim 10, wherein the ammonium salt of rosuvastatin is optionally isolated and purified by recrystallization before conversion to pure amorphous rosuvastatin calcium.
21. Solid pyrrolidinium salt of rosuvastatin.
22. Solid piperidinium salt of rosuvastatin.
23. Solid morpholinium salt of rosuvastatin.

23 Aug 2010

2006261087

- 30 -

24. Solid 1-adamantylammonium salt of rosuvastatin.

25. Solid N-methylcyclohexylammonium salt of rosuvastatin.

5 26. Solid *tert*-octylammonium salt of rosuvastatin.27. Crystalline *tert*-octylammonium salt of rosuvastatin having X-Ray powder diffraction pattern with peaks:

	Angle (°2θ)	Relative intensity ( %)
10	7.13	14.45
	8.00	39.04
	9.18	19.37
	10.40	19.55
15	12.47	39.04
	14.42	33.65
	14.97	42.00
	15.48	28.38
	15.78	34.00
20	15.95	33.65
	17.68	100.00
	18.44	83.35
	18.77	39.87
	19.68	33.53
25	20.27	44.55
	23.35	45.85
	24.24	30.27
	29.31	28.79

30

28. Crystalline *tert*-octylammonium salt of rosuvastatin as monohydrate having X-Ray powder diffraction pattern with peaks:

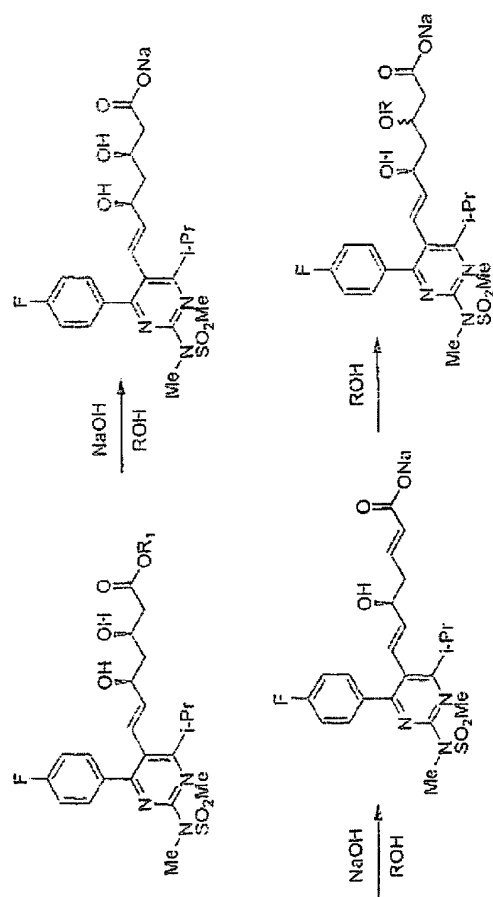
	Angle (°2θ)	Relative intensity ( %)
35	4.68	19.36
	8.63	51.97
	9.36	21.74
	10.15	21.58
	10.42	10.28
40	14.10	34.45
	14.37	29.04
	16.54	41.32
	16.98	34.51
	18.59	100.00
45	19.14	65.60
	19.72	81.83
	27.31	20.01

2006261087 23 Aug 2010

- 31 -

29. Use of crystalline *tert*-octylammonium salt of rosuvastatin monohydrate as analytical standard.
- 5 30. Pure amorphous rosuvastatin calcium when produced by the process according to any one of claims 1 to 20.
- 10 31. A process according to claim 1 or 10, a salt of rosuvastatin according to any one of claims 21 to 28, a use according to claim 29, or pure amorphous rosuvastatin calcium according to claim 30, substantially as hereinbefore described and/or exemplified.

1 / 3



Scheme 1

2 / 3

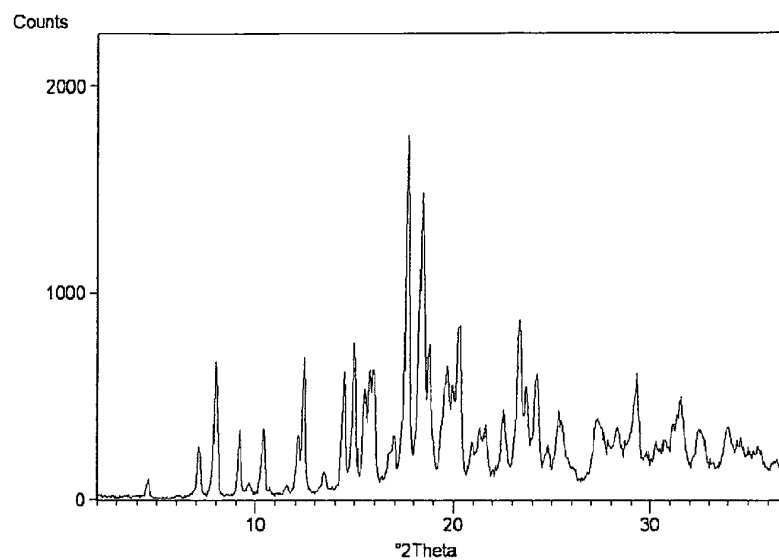


Figure 1

3 / 3

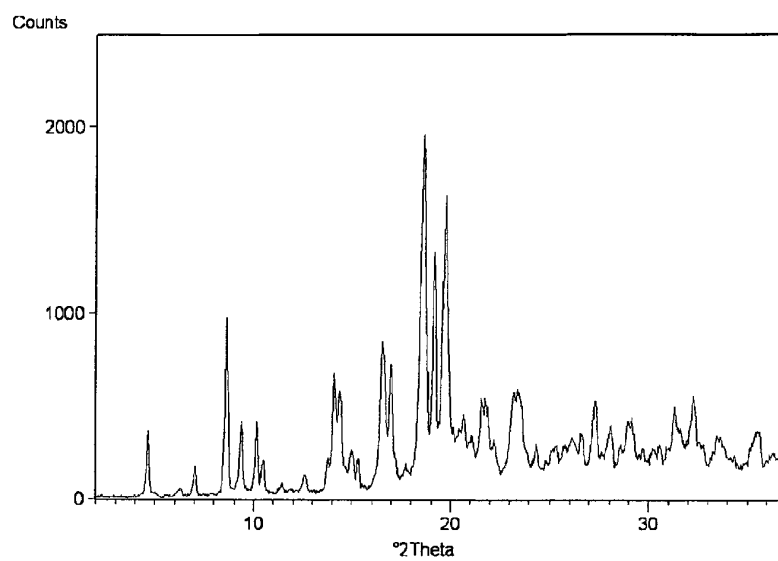


Figure 2