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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2012 (15.11.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/153181 A1

(51) International Patent Classification:
A61K 9/16 (2006.01) *A61K 33/08* (2006.01)
A61K 9/20 (2006.01) *A61K 33/10* (2006.01)
A61K 31/47 (2006.01)

(21) International Application Number:
PCT/IB2012/000911

(22) International Filing Date:
10 May 2012 (10.05.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
TR2011/04599 11 May 2011 (11.05.2011) TR

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2012/153181 A1

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING PITAVASTATIN OR ITS PHARMACEUTICALLY ACCEPTABLE SALTS

(57) Abstract: The present invention relates to a pharmaceutical composition comprising pitavastatin or its pharmaceutically acceptable salts, where such composition has high stability and a good dissolution profile.

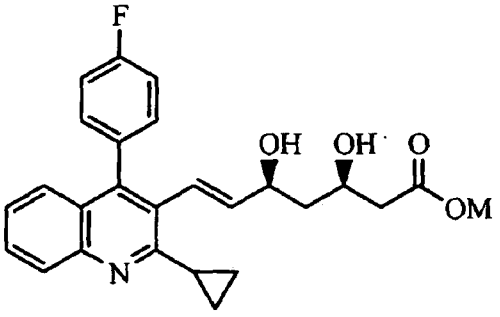
PHARMACEUTICAL COMPOSITION COMPRISING PITAVASTATIN OR ITS PHARMACEUTICALLY ACCEPTABLE SALTS

Field of the invention

The present invention relates to a pharmaceutical composition comprising pitavastatin or its pharmaceutically acceptable salts, where such composition has high stability and a good dissolution profile. The disclosed pharmaceutical composition is preferably in an oral dosage form such as a tablet, a capsule, a pellet, a minitablet, etc.

Introduction

The present invention relates to a pharmaceutical composition comprising pitavastatin calcium, which is chemically known as (+)monocalcium bis{(3R, 5S, 6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate} as presented below in structural formula "*Formula I*".



Formula I

Pitavastatin calcium is sold under the trade name LIVALO® in the US and is a synthetic lipid lowering agent. Pitavastatin is used in the treatment of hypercholesterolemia and mixed dyslipidemia.

European Patent No. 0814782 B1 discloses a pharmaceutical composition comprising pitavastatin or its salt or ester, to which a basic substance is added so that the aqueous solution or dispersion of the composition has a pH from 7 to 7.8 when it is dispersed in water.

U.S. Patent No. 6,465,477 discloses a pharmaceutical composition comprising pitavastatin or its salt or ester, to which a basic substance is added so that the aqueous

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solution or dispersion of the composition has a pH from 6 to 7.8 when it is dispersed in water. The same patent also discloses pitavastatin and its salts and esters which are unstable in a high pH range.

Potential impurities in formulations containing them include residual amounts of synthetic precursors to the active agent, by- products which arise during synthesis of the active agent, residual solvents, isomers of the active agent, excipients used in the preparation of the pharmaceutical formulation, and unidentified adventitious substances. Other impurities which may appear on storage include substances resulting from degradation of the active agent, for instance, by oxidation or hydrolysis.

It is well known in the art that, for human administration, safety considerations require the establishment, by national and international regulatory authorities, of very low limits for identified, but toxicologically uncharacterized impurities, before a product is commercialized. Typically, these limits are less than about 0.15 percent by weight of each impurity. Limits for unidentified and/or uncharacterized impurities are obviously lower, typically, less than 0.1 percent by weight.

Hence there is an established need for a simple, industrially feasible, inexpensive, scalable and safe-to-handle process for the synthesis. Also, as evidenced by the continuous disclosure of approaches disclosed in the art, there exists a need for a formulation of pitavastatin that provides comparable or higher bioavailability to marketed formulation of pitavastatin. In conclusion, there is a constant need for preparing a stable pharmaceutical composition comprising a greater pH range.

Summary of the invention

In one aspect, the present invention discloses a pharmaceutical composition comprising a therapeutically effective amount of pitavastatin and a base, wherein the pH of the composition is more than or equal to 9.0.

In another aspect, the present invention discloses a process for preparing a pharmaceutical composition of pitavastatin involving direct compression comprising the steps of;

1) blending the pitavastatin calcium and one or more pharmaceutically acceptable excipients;

2) direct compression of the blend from Step (1) into a tablet,

3) optionally, the pitavastatin tablet obtained in Step (2) is coated.

In another aspect, the present invention discloses a process for the preparation of a pharmaceutical composition of pitavastatin calcium obtained by the above process, where the composition obtained is free of process related impurities.

In another aspect, the present invention discloses a process for the preparation of a pharmaceutical composition of pitavastatin calcium by direct compression which is free of impurities.

In another aspect, the present invention discloses a pharmaceutical composition of pitavastatin calcium prepared by the above process, where the composition obtained has a longer shelf life period without increase in any impurities.

Detailed description of the invention

In one aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of pitavastatin and a base, where in the pH of the composition is more than or equal to 9.0

The term "therapeutically effective amount" as used herein means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition is sufficient to effect such treatment. The therapeutically effective amount will vary depending on the compound, the disease and its severity as well as the age, weight, physical condition and responsiveness of the mammal to be treated.

In one aspect, the present invention discloses a pharmaceutical composition comprising a therapeutically effective amount of pitavastatin and a base, where the pH of the composition is equal to or more than 9.0.

Suitable base used to make the pH of the composition more than or equal to 9 includes (but is not limited to) organic bases, inorganic bases and their mixtures thereof. Suitable inorganic bases include (but are not limited to) alkali metal carbonates (such as sodium carbonate, potassium carbonate, calcium carbonate and the like), alkali earth metal

bicarbonates (such as sodium bicarbonate, potassium bicarbonate, magnesium bicarbonate and the like), earth alkali metal oxides (such as magnesium oxide or calcium oxide) as well as other similar materials known to those of ordinary skill in the art. Suitable organic bases include meglumine and the like, as well as other similar materials known to those of ordinary skill in the art. The examples set forth herein serve the purpose of aiding in the understanding of the application and are not intended to, and should not be construed to, limit its scope in any way. Such materials are well known to those of ordinary skill in the art and are described in numerous publications.

The base may be present in an amount less than 50%, more preferably less than 10%, and more preferably less than 5% by weight based on the total weight of the composition.

In another aspect, the present invention discloses a process for preparing a pharmaceutical composition involving direct compression comprising the steps of:

1) blending pitavastatin calcium and one or more pharmaceutically acceptable excipients,
2) direct compression of the blend from Step (1) into a tablet,
3) optionally, the pitavastatin tablet obtained in Step (2) is coated .

Step 1) involves, blending pitavastatin calcium and one or more pharmaceutically acceptable excipients:

Suitable pharmaceutically acceptable excipients include (but are not limited to) binders, diluents, disintegrants, surfactants and lubricants.

Suitable binders that can be used in Step (1) include (but are not limited to); polyvinylpyrolidone, copovidone, starches such as pregelatinized starch, cellulose derivatives such as hydroxyporpylmethyl cellulose, ethylcellulose, hydroxypropylcellulose and carboxymethylcellulose and their salts, gelatine, acacia, agar, alginic acid, carbomer, chitosan, dextrates, dextrin, glycerol dibehenate, guargum, hypromellose, maltodextrin, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethyacrylates, sodium alginate, sucrose, mixtures thereof and the like.

Suitable diluents that can be used in Step (1) include (but are not limited to); anhydrous lactose, lactose monohydrate, modified lactose, dibasic calcium phosphate, tribasic calcium phosphate, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, maize starch, pregelatinized starch, calcium carbonate, sucrose, glucose, dextrates, dextrins, dextrose, fructose, lactitol, mannitol, sorbitol starch, calcium lactate or mixtures of diluents.

Suitable disintegrants that can be used in Step (1) include (but are not limited to); starch, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, crospovidone, croscarmellose sodium, low-substituted hydroxypropyl cellulose, alginic acid, carboxy methyl cellulose sodium, sodium alginate, calcium alginate and chitosan.

Suitable lubricants that can be used in Step (1) include (but are not limited to) magnesium stearate, stearic acid, palmitic acid, talc, and aerosil.

Suitable surfactants that can be used in Step (1) include (but are not limited to) polysorbate 80, polyoxyethylene sorbitan, polyoxyethylene-polyoxy-propylene copolymer and sodium lauryl sulphate.

Step 2) involves, direct compression of the blend from Step (1) into a tablet:

The obtained pitavastatin blend with the pharmaceutically acceptable excipients, after lubricating the blend, will be directly compressed into suitably sized tablets by direct compression already known in the art.

Step 3) involves, optionally, coating on the blend of one or more pharmaceutically acceptable excipients.

The tablets may be film coated in a conventional manner, e.g. for appearance, for palatability or for production purposes. Suitable coating compositions include (but are not limited to) binders selected from hydroxypropylcellulose, hydroxyethylmethyl cellulose, povidone, hydroxypropyl cellulose, hydroxyethyl cellulose, low-substituted hydroxypropyl cellulose, hydroxypropylmethyl cellulose acrylate and/or methacrylate co-polymers, resins etc. Alternatively, the coating may be an enteric coating, e.g. which is insoluble in acidic gastric juice but soluble in alkaline digestive juice. Such a coating enables the tablet to pass through the stomach into the duodenum, where it dissolves. For example, a suitable enteric

coating might be cellulose acetate phthalate. The coating composition may further include colorants, plasticizers, surfactants and anti-adherents, all of which are widely known in the art.

Pitavastatin calcium obtained by the process described above has good stability under 40°C and 75% RH storage conditions.

In yet another aspect, the present disclosure provides pharmaceutical compositions containing dosage forms about 1 mg, 2 mg and 4 mg strength. Such preferred pharmaceutical compositions are administered as an adjunctive therapy to reduce total cholesterol (TC), low density lipoprotein (LDL-C) apolipoprotein B (Apo B), triglycerides ((TG) and to increase HDL-C in adult patients with primary hyperlipidemia and mixed dyslipidemia.

In another aspect, the present invention discloses a process for the preparation of a pharmaceutical composition of pitavastatin calcium obtained by the above process which is free of process related impurities.

Pitavastatin calcium obtained according to the process of the present invention is substantially pure. "Substantially pure" means, pitavastatin calcium prepared in accordance with the process of the present invention has a purity of more than 99.5% by weight and contains impurities less than 0.5% by weight, where all process related impurities are taken into account.

In another aspect, the present invention discloses a process for the preparation of a pharmaceutical composition of pitavastatin calcium by direct compression which is free of impurities during long term stability.

In another aspect, the present invention discloses pitavastatin calcium prepared by the process described above having a longer shelf life period without substantial increase in any impurities.

The condition that was used to study the stability of pitavastatin calcium by direct compression was 40°C and 75% RH.

Certain specific aspects and embodiments of this invention are described in further detail by the examples below, where such examples are provided only for the purpose of illustration and are not intended to limit the scope of the appended claims in any manner.

Having thus described the application with reference to particular embodiments and illustrative examples, those in the art may appreciate modifications to the application as described and illustrated that do not depart from the spirit and scope of the application as disclosed in the specification. The examples are set forth to aid in understanding the application but are not intended to, and should not be construed to, limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications.

Example 1: Preparation of pitavastatin calcium tablet (using magnesium aluminum metasilicate)

Ingredient	**Qty (in mg)**
Pitavastatin calcium	2.09
Lactose monohydrate granules (spray dried)	100.31
Low substituted hydroxy propyl cellulose LH 21	6.0
Hydroxy propyl methyl cellulose	2.0
Magnesium aluminium metasilicate	2.4
Magnesium stearate	1.2
Tablet core weight	120
Opadry white	q.s.

1. Divide lactose monohydrate into 3 portions.
2. Sift part quantity of lactose granules through ASTM 30 sieve followed by pitavastatin calcium, magnesium aluminium metasilicate and remaining quantity of lactose anhydrous (portion II) and load into granulator.
3. Sift low substituted hydroxyl propyl cellulose LH 21 and remaining quantity of lactose monohydrate (portion II) through ASTM 30 sieve and load into granulator.

4. Carry out the dry mixing of materials from Step (2) and Step (3) in granulator for 10 minutes.
5. Dissolve hydroxy propylmethyl cellulose in purified water under stirring to get a clear solution.
6. Granulate the material of Step (4), using the binder solution of Step (5).
7. Unload the wet granules from the granulator and dry at 60 °C for 45 minutes till the LOD reaches not more than 2.5% w/w.
8. Pass the dried granules of Step (7) through ASTM 30 (600 microns) sieve.
9. Sift low substituted hydroxypropyl cellulose LH 11 through ASTM 30 sieve and mix with the milled granules of Step (8).
10. Sift magnesium stearate through ASTM 40 sieve and mix the material of Step (9) to obtain final blend.
11. Compress the final blend of Step (10) using the suitable tooling for pitavastatin calcium tablets 2 mg.
12. Prepare the respective coating using purified water and coat the core tablets till a weight build up of 4.17 % is achieved.

Example 2: Preparation of pitavastatin calcium tablet (using calcium carbonate)

Ingredient	**Qty (in mg)**
Pitavastatin calcium	2.09
Lactose monohydrate fine powder	97.71
Low substituted hydroxy propyl cellulose LH 21	6.0
Hydroxy propyl methyl cellulose	2.0
Calcium carbonate	5.0
Purified water	q.s
Low substituted hydroxy propyl cellulose LH 11	6.0
Magnesium stearate	1.2

1. Divide lactose monohydrate into 3 portions.
2. Sift part quantity of lactose granules (portion I) through ASTM 30 sieve followed by pitavastatin calcium, calcium carbonate and remaining quantity of lactose anhydrous (portion II) and load into granulator.
3. Sift low substituted hydroxyl propyl cellulose LH 21 and remaining quantity of lactose monohydrate (portion II) through ASTM 30 sieve and load into granulator.
4. Carry out the dry mixing of materials from Step (2) and Step (3) in granulator for 10 minutes.
5. Dissolve hydroxy propylmethyl cellulose in purified water under stirring to get a clear solution.
6. Granulate the material from step (4), using the binder solution from Step (5).
7. Unload the wet granules from the granulator and dry at 60° C for 45 minutes till the LOD reaches not more than 2.5% w/w.
8. Pass the dried granules of Step (7) through ASTM 30 (600 microns) sieve.
9. Sift low substituted hydroxypropyl cellulose LH 11 through ASTM 30 sieve and mix with the milled granules from Step (8).
10. Sift magnesium stearate through ASTM 40 sieve and mix the material from Step (9) to obtain a final blend.
11. Compress the final blend from Step (10) using the suitable tooling for pitavastatin calcium tablets 2 mg.
12. Prepare the respective coating using purified water and coat the core tablets till a weight build up of 4.17 % is achieved.

Example 3: Preparation of pitavastatin calcium tablet (using calcium carbonate)

Ingredient	Qty (in mg)
Pitavastatin calcium	2.09
Lactose monohydrate granules (spray dried)	97.71
Low substituted hydroxy propyl cellulose LH 11	12.0
Hydroxy propyl methyl cellulose	2.0
Calcium carbonate	5.0
Purified water	q.s
Magnesium stearate	1.2

1. Divide Lactose monohydrate into three portions.
2. Sift part quantity of Lactose granules [Portion I] through ASTM # 30 sieve, followed by Pitavastatin Calcium, Calcium carbonate and remaining quantity of Lactose anhydrous [Portion II] and mix.
3. Sift part quantity of Lactose granules [Portion II] through ASTM # 30 sieve, followed by the material from Step (2), low substituted Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose and remaining quantity of Lactose granules [Portion II] and mix.
4. Sift part quantity of Lactose granules [Portion III] through ASTM # 30 sieve, followed by the material from Step (3), and remaining quantity of Lactose anhydrous [Portion III] and mix.
5. Sift Magnesium stearate through ASTM # 40 sieve and mix with the material from Step (4).
6. Compress the final blend from Step (5), using the suitable tooling for Pitavastatin Calcium Tablets 2 mg.
7. Prepare the respective coating solutions using purified water and coat the core tablets, till a weight build up of 4.17 % is achieved.

Example 4: Preparation of pitavastatin calcium tablet (using meglumine)

Ingredient	**Qty (in mg)**
Pitavastatin calcium	2.09
Lactose monohydrate granules (spray dried)	101.71
Low substituted hydroxy propyl cellulose LH 11	12.0
Hydroxy propyl methyl cellulose	2.0
Meglumine	1.0
Purified water	q.s
Magnesium stearate	1.2

1. Divide Lactose monohydrate into three portions.
2. Sift part quantity of Lactose granules [Portion I] through ASTM # 30 sieve, followed by Pitavastatin Calcium, Meglumine and remaining quantity of Lactose anhydrous [Portion II] and mix.
3. Sift part quantity of Lactose granules [Portion II] through ASTM # 30 sieve, followed by the material from Step (2), low substituted Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose and remaining quantity of Lactose granules [Portion II] and mix.
4. Sift part quantity of Lactose granules [Portion III] through ASTM # 30 sieve, followed by the material from Step (3), and remaining quantity of Lactose anhydrous [Portion III] and mix.
5. Sift Magnesium stearate through ASTM # 40 sieve and mix with the material from Step (4).
6. Compress the final blend from Step (5), using suitable tooling for Pitavastatin Calcium Tablets 2 mg.
7. Prepare the respective coating solutions using purified water and coat the core tablets, till a weight build up of 4.17 % is achieved.

Example 5: Preparation of pitavastatin calcium tablet (using magnesium carbonate)

Ingredient	Qty (in mg)
Pitavastatin calcium	2.09
Lactose monohydrate (spray dried)	92.71
Low substituted hydroxy propyl cellulose LH 11	12.0
Hydroxy propyl methyl cellulose	2.0
Magnesium carbonate	10.0
Purified water	q.s
Magnesium stearate	1.20

1. Divide Lactose monohydrate into three portions.
2. Sift part quantity of Lactose granules [Portion I] through ASTM # 30 sieve, followed by Pitavastatin Calcium, Magnesium carbonate and remaining quantity of Lactose anhydrous [Portion II] and mix.
3. Sift part quantity of Lactose granules [Portion II] through ASTM # 30 sieve, followed by the material from Step (2), low substituted Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose and remaining quantity of Lactose granules [Portion II] and mix.
4. Sift part quantity of Lactose granules [Portion III] through ASTM # 30 sieve, followed by the material from Step (3), and remaining quantity of Lactose anhydrous [Portion III] and mix.
5. Sift Magnesium stearate through ASTM # 40 sieve and mix with the material from Step (4).
6. Compress the final blend from Step (5), using suitable tooling for Pitavastatin Calcium Tablets 2 mg.
7. Prepare the respective coating solutions using purified water and coat the core tablets, till a weight build up of 4.17 % is achieved.

Example 6: Preparation of pitavastatin calcium tablet (using magnesium oxide)

Ingredient	Qty (in mg)
Pitavastatin calcium	2.09
Lactose monohydrate (spray dried)	92.71
Low substituted hydroxy propyl cellulose LH 11	12.0
Hydroxy propyl methyl cellulose	2.0
Magnesium oxide	10.0
Purified water	q.s
Magnesium stearate	1.20

1. Divide Lactose monohydrate into three portions.
2. Sift part quantity of Lactose granules [Portion I] through ASTM # 30 sieve, followed by Pitavastatin Calcium, Magnesium oxide and remaining quantity of Lactose anhydrous [Portion II] and mix.
3. Sift part quantity of Lactose granules [Portion II] through ASTM # 30 sieve, followed by the material from Step (2), low substituted Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose and remaining quantity of Lactose granules [Portion II] and mix.
4. Sift part quantity of Lactose granules [Portion III] through ASTM # 30 sieve, followed by the material from Step (3), and remaining quantity of Lactose anhydrous [Portion III] and mix.
5. Sift Magnesium stearate through ASTM # 40 sieve and mix with the material from Step (4).
6. Compress the final blend from Step (5), using the suitable tooling for Pitavastatin Calcium Tablets 2 mg.
7. Prepare the respective coating solutions using purified water and coat the core tablets, till a weight build up of 4.17 % is achieved.

Example 7: Preparation of pitavastatin calcium tablet (using magnesium hydroxide)

Ingredient	Qty (in mg)
Pitavastatin calcium	2.09
Lactose monohydrate (spray dried)	92.71
Low substituted hydroxy propyl cellulose LH 11	12.0
Hydroxy propyl methyl cellulose	2.0
Magnesium hydroxide	10.0
Purified water	q.s
Magnesium stearate	1.20

1. Divide Lactose monohydrate into three portions.
2. Sift part quantity of Lactose granules [Portion I] through ASTM # 30 sieve, followed by Pitavastatin Calcium, Magnesium hydroxide and remaining quantity of Lactose anhydrous [Portion II] and mix.
3. Sift part quantity of Lactose granules [Portion II] through ASTM # 30 sieve, followed by the material from Step (2), low substituted Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose and remaining quantity of Lactose granules [Portion II] and mix.
4. Sift part quantity of Lactose granules [Portion III] through ASTM # 30 sieve, followed by the material of step 3, and remaining quantity of Lactose anhydrous [Portion III] and mix.
5. Sift Magnesium stearate through ASTM # 40 sieve and mix with the material from Step (4).
6. Compress the final blend from Step (5), using suitable tooling for Pitavastatin Calcium Tablets 2 mg.
7. Prepare the respective coating solutions using purified water and coat the core tablets, till a weight build up of 4.17 % is achieved.

Example 8: Preparation of pitavastatin calcium tablet (using sodium carbonate)

Ingredient	**Qty (in mg)**
Pitavastatin calcium	2.09
Lactose monohydrate (spray dried)	92.71
Low substituted hydroxy propyl cellulose LH 11	12.0
Hydroxy propyl methyl cellulose	2.0
sodium carbonate	10.0
Purified water	q.s
Magnesium stearate	1.20

1. Divide Lactose monohydrate into three portions.
2. Sift part quantity of Lactose granules [Portion I] through ASTM # 30 sieve, followed by Pitavastatin Calcium, sodium carbonate and remaining quantity of Lactose anhydrous [Portion II] and mix.
3. Sift part quantity of Lactose granules [Portion II] through ASTM # 30 sieve, followed by the material from Step (2), low substituted Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose and remaining quantity of Lactose granules [Portion II] and mix.
4. Sift part quantity of Lactose granules [Portion III] through ASTM # 30 sieve, followed by the material from Step (3), and remaining quantity of Lactose anhydrous [Portion III] and mix.
5. Sift Magnesium stearate through ASTM # 40 sieve and mix with the material from Step (4).
6. Compress the final blend from Step (5), using the suitable tooling for Pitavastatin Calcium Tablets 2 mg.
7. Prepare the respective coating solutions using purified water and coat the core tablets, till a weight build up of 4.17 % is achieved.

Comparative stability data is presented below in Table 1 and Table 2:

5 **Table 1 (at 40° C& 75% RH)**

S.No	Product	Livalo tablets	Example 1		Example 2		Example 3	
	Strength	2 mg	2 mg		2 mg		2 mg	
	Batch detail		Magnesium aluminum meta silicate		Calcium carbonate		Calcium carbonate	
	Manufacturing process		Wet granulation		Wet granulation		Direct compression	
	Impurity profile	1 month	3 months	6 months	3 months	6 months	1 month	2 months
	Known impurities	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
1.	**Desfluro**	ND	0.079	0.088	0.081	0.087	0.017	0.017
2.	**Anti isomer**	0.044	ND	0.007	ND	0.008	0.015	0.011
3.	**Z-isomer**	ND	ND	0.000	ND	0.000	ND	0.000
4.	**Methyl ester**	0.013	0.017	0.017	0.017	0.017	0.019	0.016
5.	**Lactone**	0.279	0.261	0.432	0.081	0.196	0.025	0.035
6.	**Tertiary butyl ester**	0.009	0.011	0.025	0.012	0.026	ND	0.018
	Unknown impurities							
7.	**Highest individual unknown**	0.249	0.128	0.189	0.111	0.152	0.016	0.019
8.	**Total unknown**	0.340	0.184	0.289	0.158	0.253	0.062	0.069
9.	**Total impurities**	0.679	0.550	0.856	0.348	0.586	0.138	0.165

Table 2 (at 40° C& 75% RH)

S.No	Product	Livalo tablets	Example 6		Example 7	Example 8
	Strength	2 mg	2 mg		2 mg	2 mg
	Batch detail		Magnesium oxide		Magnesium hydroxide	Sodium carbonate
	Manufacturing process		Direct compression		Direct compression	Direct compression
	Impurity profile	1 month	1 month	2 months	1 month	1 month
	Known impurities	% w/w	% w/w	% w/w	% w/w	% w/w
1.	**Desfluro**	ND	0.084	0.078	0.082	0.081
2.	**Anti isomer**	0.044	0.015	0.007	0.014	0.013
3.	**Z-isomer**	ND	ND	0.000	ND	ND
4.	**Methyl ester**	0.013	0.020	0.016	0.019	0.019
5.	**Lactone**	0.279	ND	0.013	0.073	ND
6.	**Tertiary butyl ester**	0.009	0.010	0.018	ND	ND
	Unknown impurities					
7.	**Highest individual unknown**	0.249	0.027	0.033	0.034	0.044
8.	**Total unknown**	0.340	0.108	0.110	0.094	0.131
9.	**Total impurities**	0.679	0.236	0.241	0.280	0.244

CLAIMS

1) A pharmaceutical composition comprising a therapeutically effective amount of pitavastatin and a base, wherein the pH of the composition is more than or equal to 9.0.

2) A pharmaceutical composition according to Claim (1), wherein the base used is selected from the group comprising alkali metal carbonates, earth alkali metal carbonates, alkali metal bicarbonates, earth alkali metal bicarbonates, earth alkali metal oxides, meglumine and magnesium aluminium metasilicate, or any mixture thereof.

3) A pharmaceutical composition according to Claim (2), wherein the alkali metal carbonate is sodium carbonate, potassium carbonate, magnesium carbonate, calcium carbonate, or any mixture thereof.

4) A pharmaceutical composition according to Claim (2), wherein the alkali metal bicarbonate is sodium bicarbonate, potassium bicarbonate, magnesium bicarbonate, or any mixture thereof.

5) A pharmaceutical composition according to Claim (2), wherein the earth alkali metal oxide is magnesium oxide.

6) A process for the preparation of a pharmaceutical composition of pitavastatin calcium involving direct compression comprising the steps of:

a) blending pitavastatin calcium and one or more pharmaceutically acceptable excipients,

b) direct compression of such blend into a tablet.

7) A pharmaceutical composition according to Claim (6); wherein the tablet is coated with suitable coating agents.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/000911

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K31/47 A61K33/08 A61K33/10
ADD.

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)
A61K

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 practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/051346 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; DESSET-BRETHES SABINE [CH) 9 June 2005 (2005-06-09) page 8, line 4 - page 10, line 18; examples -----	1,2
X	WO 2004/010980 A1 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; MEYER ANDREAS [DE]; OGORK) 5 February 2004 (2004-02-05) page 9, line 9 - page 11, line 18; examples -----	1,2,4
X	EP 0 336 298 A1 (SQUIBB & SONS INC [US]) 11 October 1989 (1989-10-11) claims; examples -----	1-7
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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"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
24 July 2012	31/07/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/000911

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 00/35425 A1 (LEK TOVARNA FARMACEVTSKIH [SI]; KERC JANEZ [SI]) 22 June 2000 (2000-06-22) claims; examples	1-7
A	US 6 465 477 B1 (MURAMATSU TOYOJIRO [JP] ET AL) 15 October 2002 (2002-10-15) table 7	1-7

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