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(54) Title: STABLE ORAL PHARMACEUTICAL COMPOSITION CONTAINING A PHARMACEUTICALLY ACCEPTABLE SALT OF [(E)-7-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2- [METHYL(METHYLSULFONYL)AMINO]PYRIMIDINE-5-YL] (3R, 5S) - 3,5 DIHYDROXYHEPT-6- ENOIC ACID

(57) Abstract: The stable oral pharmaceutical composition containing as the active ingredient [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) - 3,5 dihydroxyhept-6-enoic acid or its pharmaceutically acceptable salt, one or more fillers, one or more disintegrants, one or more lubricants, coating agents, and one or more stabilizers.

Stable oral pharmaceutical composition containing a pharmaceutically acceptable salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5 dihydroxyhept-6-enoic acid.

The present invention relates to a stable oral pharmaceutical composition containing the pharmaceutically acceptable calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5 dihydroxyhept-6-enoic acid.

The calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5 dihydroxyhept-6-enoic acid known under the International Nonpropiertary Name (INN) rosuvastatin calcium as a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is used in the treatment of primary hypercholesterolemia and combined dyslipidemia as a supplementary treatment when a diet and other non-pharmacological methods of therapy are insufficient.

The calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5 dihydroxyhept-6-enoic acid was for the first time disclosed in the EP 521471B patent, while a pharmaceutical composition containing the calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5 dihydroxyhept-6-enoic acid is known under the trade name CRESTOR® and was disclosed for the first time in the international publication of the patent application No. WO 01/54669 [PL 196808 B, PL 341855 A].

[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid and its calcium salt belong to the group of 3,5-dihydroxy-6-heptenoic acids substituted at the 7-position. Some of the substances in this group of chemicals act as inhibitors of HMG-CoA reductase and this is the reason why they are used in preparing drugs. However, when 3,5-dihydroxy-6-heptenoic acids substituted at the 7-position are active components of pharmaceutical compositions, there arises the problem of maintaining stability of the pharmaceutical

composition. Therefore various methods are applied to preserve stability of the pharmaceutical composition.

In the Polish PatentPL 186907 B [WO 97/23200] it is disclosed that 3,5-dihydroxy-6-heptenoic acids substituted at the 7-position are unstable at low pH and require special procedures while they are used to prepare pharmaceutical compositions. These procedures comprise i.a. the use of an alkaline agent like calcium carbonate or sodium carbonate to obtain the product of pH 8 or higher and an alkaline agent like magnesium oxide or sodium hydroxide to obtain the product of pH 9 or higher.

Likewise, in the United Kingdom patent specification GB 2262229 A it was disclosed that salts of 3,5-dihydroxy-6-heptenoic acid substituted at the 7-position are susceptible to degradation under influence of pH below about 8, light or heat. Pharmaceutical compositions containing these salts require the presence of an alkaline agent that is capable of maintain a pH of at least 8. On the other hand, in the international publication of the patent application WO 01/54669 it was disclosed that under specified conditions salts of 3,5-dihydroxy-6-heptenoic acid are sensitive to degradation to a respective (3R, 5S) lactone and oxidation product where the hydroxyl group neighbouring to carbon-carbon double bond (C=C) is oxidized to a ketone group. Stabilization of the pharmaceutical composition was achieved by the use of an inorganic salt with a multivalent cation.

From the international publication of the patent application WO 01/54668 [PL 196808 B] it is known that tribasic phosphate salts with multivalent cations can be applied to stabilize pharmaceutical compositions containing salts of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid, especially its calcium salt.

Moreover, in the international publication of the patent application No. WO 2007/071357 it was disclosed that stabilization of the composition containing the calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid is possible with the use of silicified microcrystalline cellulose and corn starch, which, used in adequate proportions (10-70%) to the tablet mass, prevent degradation process of the calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid.

The problem of pharmaceutical composition stability applies also to the composition in which the active ingredient is an amorphous form of the calcium salt of [(E)7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid.

In the international publication of the patent application No. WO 2008/035128 it is disclosed that substances like magnesium hydroxide, aluminum acetate, calcium gluconate, calcium glycerophosphate and aluminum hydroxide may stabilize the pharmaceutical composition containing the amorphous calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid.

The above-mentioned stabilization methods of pharmaceutical compositions containing [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid and its calcium salt consist in addition of stabilizing substances that constitute composition elements. However, there are known stable pharmaceutical composition production methods involving making a high pharmaceutical purity calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid and subsequently using it for the preparation of a stable pharmaceutical composition.

The international publication of the patent application No. WO 2005/051921 discloses the production method of the calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid and the pharmaceutical composition containing this salt. The high purity calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid is obtained through conversion of crystalline ammonium salt of this acid. Subsequently, the calcium salt obtained by this method is used to produce the pharmaceutical composition. In the patent description of this invention, the many excipients that might be used in the production of a pharmaceutical composition include calcium carbonate, magnesium carbonate or magnesium oxide, used as fillers, magnesium aluminosilicate as an example of a binder or magnesium trisilicate being an lubricant.

The above-mentioned excipients and their identical function in the pharmaceutical composition were described in the international publication of the patent application No. WO 2007/022366, concerning a method of obtaining the calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid with low level of contamination with other salts of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid, especially its chloride and acetate salts, as well as the use of thus produced calcium salt in a pharmaceutical composition.

Functions of excipients used in pharmaceutical compositions described in both international patent applications No. WO 2005/051921 and WO 2007/022366 are known in professional literature.

The publication by A. H. Kibbe, *Handbook of Pharmaceutical Excipients*, 3rd edition, published by the American Pharmaceutical Association in 2000, describes properties and applications of particular excipients used in pharmaceutical industry. In solid drug forms, calcium carbonate and magnesium carbonate play a role of fillers, while magnesium oxide is used as an alkaline diluent; magnesium trisilicate is used as a lubricant while magnesium aluminosilicate is used as a binder and disintegrant or stabilizer – wherein is in the concentration range of 0.5-2.5%.

The aim of the present invention is development of a new stable oral pharmaceutical composition containing a pharmaceutically acceptable salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid, especially a calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid.

Surprisingly, it turned out that pharmaceutical compositions containing the calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino] pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid can be stabilized by substances like magnesium carbonate, magnesium oxide, magnesium trisilicate, magnesium aluminosilicate and calcium lactate.

According to the present invention, particularly preferable agents that stabilize pharmaceutical compositions containing calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid are magnesium carbonate and magnesium oxide.

Additionally, it surprisingly turned out that in case of magnesium carbonate, used as a stabiliser, an increase the amount of the magnesium carbonate in a pharmaceutical composition results in significant increase the stability of the pharmaceutical composition, with a maintain the disintegration time set for this type of pharmaceutical composition.

The proportion of the amount of magnesium carbonate to that of the calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid is within the range 0.75:1 up to 3:1. The most preferable proportion of magnesium carbonate to the calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid is 2:1.

In the pharmaceutical composition according to the present invention intended for an oral use it is preferable to use a single stabilizer or a mixture of stabilizers chosen from the group comprising magnesium carbonate, magnesium oxide, magnesium trisilicate, magnesium aluminosilicate and calcium lactate, with the whole content of stabilizing agents preferably within the range of 5-20% by weight of the tablet core.

The pharmaceutical composition according to the present invention, containing the calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid in the oral form, apart from a single stabilizer or a mixture thereof, also preferably includes fillers, disintegrants, lubricants and coating agents as pharmaceutically acceptable excipients.

In the pharmaceutical composition according to the present invention in the oral form pharmaceutically acceptable fillers were chosen from the group comprising lactose, microcrystalline cellulose, and calcium hydrogen phosphate. Lactose monohydrate or microcrystalline cellulose are preferably used as fillers in the pharmaceutical composition of the invention.

In the pharmaceutical composition according to the present invention, preferably, the content of a filler or a mixture of two or more fillers ranges from 70 to 90% by weight of the tablet core.

In the pharmaceutical composition according to the present invention pharmaceutically acceptable disintegrants were chosen from the group comprising crospovidone, sodium croscarmellose and sodium carboxymethyl starch. The preferable disintegrant in the pharmaceutical composition of the invention is crospovidone.

In the composition of the invention the content of a disintegrant or a mixture of two or more disintegrants is preferably 5% by weight of the tablet core.

In the pharmaceutical composition of the invention pharmaceutically acceptable lubricants were chosen from the group comprising magnesium stearate, calcium stearate, stearic acid and stearyl fumarate. The preferable lubricant in the pharmaceutical composition of the invention is magnesium stearate.

In the composition of the invention the content of a lubricant or a mixture of two or more lubricants is preferably 1.5% by weight of the tablet core.

In the pharmaceutical composition of the invention the pharmaceutically acceptable coating agent used is known under the trade name of Opadry®. Preferably, the coating contains hypromelose, lactose monohydrate, titanium dioxide, iron oxide, polyethylene glycol, and triacetin and is known under the trade name of Opadry® II.

The composition of the invention has a solid form and is intended for oral administration as a tablet or capsule, preferably a tablet.

The invention ensures the stable oral pharmaceutical composition containing the pharmaceutically acceptable calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid, which is characterized by advantageous composition stability properties and a simple way of preparation.

The invention is illustrated with the following examples that do not limit the invention in any way.

These examples are provided to illustrate the preparation of the composition where the active ingredient is calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid. Specific doses (5 mg, 10 mg, 10 mg, 40 mg) of the composition are proportional to each other, i.e. they are prepared from the same tablet mass.

Preparation of tablet cores

Preparation procedure of the tablet core for examples 1-6 is as follows:

a) the active ingredient, fillers, disintegrants and stabilizers are sieved;
b) the sieved ingredients are mixed in the stirrer;
c) lubricants are added to the mixture obtained in point b) and the mixture is stirred until a uniform tablet mass is obtained;
d) the tablet mass obtained in point c) is subjected to tabletting in a rotary tablet press.

All percentages are expressed by weight of the tablet core.

Preparation of coated tablets

Tablet cores obtained in examples 1-6 are covered with a layer of coating. The coating is performed in a coating machine loaded with uncoated tablet cores prepared according to the procedure described above, which are subsequently coated with aqueous solution of a mixture of hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol, triacetin, lactose monohydrate, and iron oxide - commercially available under the trade name of Opadry ® II. The coating accounts for about 3% of the tablet core weight.

Preparation of samples and investigation methods for examples 1-5.

Coated tablets in aluminum blister packs (Al//OPA/Al/PVC foil) were subjected to accelerated stability tests. They were seasoned for one month at 50°C and relative humidity 75%. A comparative pharmaceutical composition was prepared, where the stabilizer was tribasic calcium phosphate disclosed in the patent application No. WO 01/54669 (composition of the original preparation CRESTOR®). The amount

of tribasic calcium phosphate in the composition was the same as the amount of the stabilizer used in respective examples.

The stability test of the pharmaceutical composition comprised the determination of impurities level (main decomposition products of salts of [(E)-7- [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5-dihydroxyhept-6-enoic acid are diastereoisomer and lactone) .

EXAMPLE 1

Ingredients of the core	**(% by weight of the tablet core)**
Active ingredient	6.67
Lactose monohydrate	62.11
Microcrystalline cellulose	17.44
Crospovidone	5.00
Magnesium carbonate	7.56
Magnesium stearate	1.22

Results of the test are presented in the table:

Stabilizer	Amount of the stabilizer (% by weight of the tablet core)	Impurity 1 diastereoisomer	Impurity 2 lactone	Other impurities	Total impurities
Tribasic calcium phosphate Vide patent application No. WO01/54668	7.56	0.07	0.13	0.12	0.32
Magnesium carbonate	7.56	0.07	0.08	0.10	0.25

A substantial decrease in the amount of impurity 2 and total impurities was observed, which indicates that magnesium carbonate positively affects stability of the pharmaceutical composition.

EXAMPLE 2

Ingredients of the core	**(% by weight of the tablet core)**
Active ingredient	6.67
Lactose monohydrate	62.11
Microcrystalline cellulose	17.44
Crospovidone	5.00
Magnesium oxide	7.56
Magnesium stearate	1.22

Results of the test are presented in the table:

Stabilizer	Amount of the stabilizer (% by weight of the tablet core)	Impurity 1 diastereoisomer	Impurity 2 lactone	Other impurities	Total impurities
Tribasic calcium phosphate Vide patent application No. WO01/54668	7.56	0.07	0.13	0.12	0.32
Magnesium oxide	7.56	0.06	Not detected	0.12	0.18

When using magnesium oxide as a stabilizer, impurity 2 was not detected and total impurities decreased by half, which indicates that magnesium oxide particularly positively affects stability of the pharmaceutical composition.

EXAMPLE 3

Ingredients of the core	**(% by weight of the tablet core)**
Active ingredient	6.67
Lactose monohydrate	62.11
Microcrystalline cellulose	17.44
Crospovidone	5.00
Magnesium trisilicate	7.56
Magnesium stearate	1.22

Results of the test are presented in the table:

Stabilizer	Amount of the stabilizer (% by weight of the tablet core)	Impurity 1 diastereoisomer	Impurity 2 lactone	Other impurities	Total impurities
Tribasic calcium phosphate Vide patent application No. WO01/54668	7.56	0.07	0.13	0.12	0.32
Magnesium trisilicate	7.56	0.06	0.12	0.11	0.29

When using magnesium trisilicate as a stabilizer, a similar level of impurities was observed as with the use of tribasic calcium phosphate as a stabilizer, which indicates that magnesium trisilicate has similar stabilizing properties to tribasic calcium phosphate.

EXAMPLE 4

Ingredients of the core	**(% by weight of the tablet core)**
Active ingredient	6.67
Lactose monohydrate	62.11
Microcrystalline cellulose	17.44
Crospovidone	5.00
Magnesium aluminosilicate	7.56
Magnesium stearate	1.22

Results of the test are presented in the table:

Stabilizer	Amount of the stabilizer (% by weight of the tablet core)	Impurity 1 diastereoisomer	Impurity 2 lactone	Other impurities	Total impurities
Tribasic calcium phosphate Vide patent application	7.56	0.07	0.13	0.12	0.32

No. WO01/54668					
Magnesium aluminosilicate	7.56	0.06	0.09	0.13	0.28

When using magnesium aluminosilicate as a stabilizer, the test revealed a similar amount of impurity 1 and a lower amount of impurity 2 than with the use of tribasic calcium phosphate as a stabilizer, which indicates that magnesium aluminosilicate has better stabilizing properties then tribasic calcium phosphate.

EXAMPLE 5

Ingredients of the core	**(% by weight of the tablet core)**
Active ingredient	6.67
Lactose monohydrate	62.11
Microcrystalline cellulose	17.44
Crospovidone	5.00
Calcium lactate	7.56
Magnesium stearate	1.22

Results of the test are presented in the table:

Stabilizer	Amount of the stabilizer (% by weight of the tablet core)	Impurity 1 diastereoisomer	Impurity 2 lactone	Other impurities	Total impurities
Tribasic calcium phosphate Vide patent application No. WO01/54668	7.56	0.07	0.13	0.12	0.32
Calcium lactate	7.56	0.06	0.16	0.12	0.34

When using calcium lactate as a stabilizer, the test revealed a similar level of total impurities as with the use of tribasic calcium phosphate as a stabilizer, which indicates that calcium lactate has stabilizing properties very similar to that of tribasic calcium phosphate.

EXAMPLE 6

Additional experiments were performed in order to evaluate the influence of the amount of the stabilizer on the stability of the pharmaceutical composition.

To this end, pharmaceutical compositions containing the same stabilizing agents as those in examples 1-5 were prepared; their content in the tablet core was:

- variant a) 5%
- variant b) 20%.

For comparison, a pharmaceutical composition was also prepared in which the stabilizing agent was tribasic calcium phosphate disclosed in patent application No. WO 01/54669 (composition of the original preparation CRESTOR®).

Coated tablets in aluminum blister packs (Al/PVC foil) were subjected to accelerated stability tests. They were seasoned for 9 days at 50°C and relative humidity 75%.

Ingredients of the core	**variant a)** (% by weight of the tablet core)	**variant b)** (% by weight of the tablet core)
Active ingredient	6.67	6.67
Lactose monohydrate	64.68	49.68
Microcrystalline cellulose	17.43	17.43
Crospovidone	5.00	5.00
Stabilizer	**5.00**	**20.00**
Magnesium stearate	1.22	1.22

Results of the test are presented in the table:

Composition	Stabilizer	Amount of the stabilizer (% by weight of the tablet core)	Impurity 1 diastereoisomer	Impurity 2 lactone	Other impurities	Total impurities
a	Tribasic calcium phosphate Vide patent application No. WO01/54668	5%	0.18	0.69	1.34	2.21
b	Tribasic calcium phosphate Vide patent application	20%	0.17	0.70	1.31	2.18

	No. WO01/54668					
a	**Magnesium carbonate**	**5%**	**0.20**	**0.19**	**0.90**	**1.29**
b	**Magnesium carbonate**	**20%**	**0.10**	**-**	**0.47**	**0.57**
a	Magnesium oxide	5%	0.16	-	1.22	1.38
b	Magnesium oxide	20%	0.17	-	1.29	1.46
a	Magnesium trisilicate	5%	0.16	-	1.24	1.4
b	Magnesium trisilicate	20%	0.18	-	1.30	1.48
a	Magnesium aluminosilicate	5%	0.10	0.61	1.00	1.71
b	Magnesium aluminosilicate	20%	0.18	0.73	1.34	2.25
a	Calcium lactate	5%	0.16	0.77	1.26	2.19
b	Calcium lactate	20%	0.19	0.75	1.39	2.33

The obtained results indicate that among all the stabilizing agents the largest influence on the stability of the pharmaceutical composition depending on the amount of the stabilizer is exerted by magnesium carbonate. When using 20% of magnesium carbonate (by weight of the tablet core), total impurities were almost 2.5 times lower than in the case of using 5% of magnesium carbonate (by weight of the tablet core). When magnesium carbonate is compared with tribasic calcium phosphate (both substances used in the amount of 20% by weight of the tablet core), total impurities were almost 4 times lower. This indicates that magnesium carbonate particularly positively influences the stability of the pharmaceutical composition.

EXAMPLE 7

Packaging

Coated tablets obtained in examples 1-6 are packed into aluminum blister packs (Al//OPA/Al/PVC foil) or into packaging of similar barrier properties (PVC/PCTFE foil).

What is claimed is:

1. The stable oral pharmaceutical composition containing as an active ingredient [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidine-5-yl] (3R, 5S) – 3,5 dihydroxyhept-6-enoic acid or its pharmaceutically acceptable salt, one or more fillers, one or more disintegrants, one or more lubricants and coating, **wherein** said composition contains one or more stabilizers.
2. The stable oral pharmaceutical composition according to claim 1, **wherein** an active ingredient is calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5 dihydroxyhept-6-enoic acid.
3. The stable oral pharmaceutical composition according to claim 1, **wherein** the stabilizers are chosen from the group comprising magnesium carbonate, magnesium oxide, magnesium trisilicate, magnesium aluminosilicate, calcium lactate, preferably magnesium carbonate or magnesium oxide.
4. The stable oral pharmaceutical composition according to claim 1, **wherein** the proportion of magnesium carbonate to calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5 dihydroxyhept-6-enoic acid is within the range of 0.75:1 up to 3:1, preferably 2:1.
5. The stable oral pharmaceutical composition containing the calcium salt of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-yl] (3R, 5S) – 3,5 dihydroxyhept-6-enoic acid, **wherein** one stabilizer or a mixture thereof is contained, as well as a filler or a mixture thereof, a disintegrant or a mixture thereof, a lubricant or a mixture thereof and the coating.
6. The stable oral pharmaceutical composition according to claim 3 or 5, **wherein** the total content of the stabilizer or a mixture thereof is within the range of 5-20% by weight of the tablet core.
7. The stable oral pharmaceutical composition according to claim 5, **wherein** stabilizers are chosen from the group comprising magnesium carbonate,

magnesium oxide, magnesium trisilicate, magnesium aluminosilicate, calcium lactate, preferably magnesium carbonate or magnesium oxide.

8. The stable oral pharmaceutical composition according to claim 1 or 5, **wherein** the filler is chosen from the group comprising lactose, microcrystalline cellulose, calcium hydrogen phosphate, preferably monohydrate lactose or microcrystalline cellulose.
9. The stable oral pharmaceutical composition according to claim 8, **wherein** the total content of the filler is within the range from 70 to 90% by weight of the tablet core.
10. The stable oral pharmaceutical composition according to claim 1 or 5, **wherein** the disintegrant is chosen from the group comprising crospovidone, sodium croscarmellose, sodium carboxymethyl starch, preferably crospovidone.
11. The stable oral pharmaceutical composition according to claim 10, **wherein** the total content of a single filler or a mixture thereof is 5% by weight of the tablet core.
12. The stable oral pharmaceutical composition according to claim 1 or 5, **wherein** the lubricant is chosen from the group comprising magnesium stearate, calcium stearate, stearic acid, stearic fumarate, preferably magnesium stearate.
13. The stable oral pharmaceutical composition according to claim 12, **wherein** the total content of the lubricant is 1.5% by weight of the tablet core.
14. The stable oral pharmaceutical composition according to claim 1 or 5, **wherein** the coating contains hypromelose, lactose monohydrate, titanium dioxide, iron oxide, polyethylene glycol, triacetin.
15. The stable pharmaceutical composition according to claims 1-14, **wherein** the oral composition is in solid form.
16. The stable pharmaceutical composition according to claims 1-15, **wherein** the oral composition is a tablet or a capsule, preferably a tablet.