IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC., PFIZER PHARMACEUTICALS, LLC, PFIZER LIMITED, C.P. PHARMACEUTICALS INTERNATIONAL C.V., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC and WARNER-LAMBERT EXPORT LTD.	)	
Plaintiffs,	)	
v.	)	Civil Action No. 07-___
RANBAXY LABORATORIES LIMITED, and RANBAXY INC.	)	
Defendants.	)	

COMPLAINT

Pfizer Inc., Pfizer Pharmaceuticals, LLC, Pfizer Limited, C.P. Pharmaceuticals International C.V., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company, LLC and Warner-Lambert Export Limited, (collectively referred to as "Pfizer"), by their attorneys, for their complaint against Ranbaxy Laboratories Limited ("Ranbaxy Laboratories") and Ranbaxy Inc. ("Ranbaxy Inc.")(collectively "Ranbaxy"), allege as follows:

1. This is an action by Pfizer against Ranbaxy for infringement of United States Letters Patent Nos. 4,681,893 ("the '893 patent") and 6,455,574 ("the '574 patent"). A copy of each patent is attached hereto as Exhibits A and B respectively.

2. On July 21, 1987, the United States Patent and Trademark Office ("PTO") issued the '893 patent, entitled "Trans-6-[2-(3- or 4-Carboxamido-Substituted Pyrrol-1-yl)Alkyl]-4-Hydroxypyran-2-One Inhibitors of Cholesterol Synthesis," on an application filed by Bruce D. Roth and assigned to Warner-Lambert Company.

3. On September 24, 2002, the PTO issued the '574 patent, entitled "Therapeutic Combination," on an application filed by Jan Buch and assigned to Pfizer Inc.

PARTIES, JURISDICTION AND VENUE

4. Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware and has a place of business at 235 East 42nd Street, New York, New York 10017. Pfizer Inc. has been the owner of record of the '574 patent since its issuance.

5. Pfizer Pharmaceuticals, LLC is a limited liability company organized and existing under the laws of the State of Delaware, United States of America, with offices at 235 East 42nd Street, New York, New York 10017.

6. Pfizer Limited is a company incorporated under the laws of England with offices at Ramsgate Road, Sandwich, Kent, England CT13 9NJ. Pfizer Limited is a wholly owned, indirect subsidiary of Pfizer Inc.

7. C.P. Pharmaceuticals International C.V. is a limited partnership (commanditaire vennootschap) organized under the laws of the Netherlands, having its registered seat in Rotterdam, and registered at the trade register held by the Chamber of Commerce in Rotterdam, the Netherlands, under number 24280998. C.P. Pharmaceuticals International C.V. is a wholly owned subsidiary of Pfizer Inc.

8. C.P. Pharmaceuticals International C.V. is the owner of NDA 21-540 for Caduet®.

9. Warner-Lambert Company is a corporation formerly organized under the laws of the State of Delaware with offices for service of process at 235 East 42nd Street, New York, New York 10017. Warner-Lambert Company has been the owner of record of the '893 patent since its issuance.

10. Warner-Lambert Company became a wholly owned subsidiary of Pfizer Inc. effective June 19, 2000.

11. Warner-Lambert Company was converted into Warner-Lambert Company, LLC, a Delaware limited liability company by certificate dated December 31, 2002. Warner-Lambert Company, LLC has offices located at 235 East 42nd Street, New York, New York 10017.

12. Pfizer Ireland Pharmaceuticals is a partnership, organized and existing under the laws of Ireland, with registered offices at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland. Pfizer Ireland Pharmaceuticals is a wholly owned, indirect subsidiary of Pfizer Inc.

13. Warner-Lambert Export, Ltd. is a corporation formerly organized under the laws of Ireland with a registered office located at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland.

14. The exclusive licensee of the '893 patent is Pfizer Ireland Pharmaceuticals, formerly Warner-Lambert Export, Ltd.

15. The exclusive licensee from Pfizer Limited of the '574 patent is Pfizer Pharmaceuticals, LLC by assignment from C.P. Pharmaceuticals International C.V.

16. Pfizer holds an approved New Drug Application for a formulation comprised of the active ingredients amlodipine besylate and atorvastatin calcium, which it sells in the United States under the registered name Caduet®.

17. The '893 patent is identified pursuant to 21 U.S.C. §355(b)(1) by the United States Food and Drug Administration ("FDA") as covering Pfizer's Caduet® product.

18. The '574 patent is identified pursuant to 21 U.S.C. §355(b)(1) by FDA as covering Pfizer's Caduet® product.

19. Ranbaxy Inc. is a corporation organized and existing under the laws of the State of Delaware, and has a place of business located at 600 College Road East, Princeton, New Jersey 08540.

20. Ranbaxy Inc. was formerly known as Ranbaxy Pharmaceuticals Inc.

21. Upon information and belief, Ranbaxy Laboratories is a corporation organized and existing under the laws of India, with corporate offices located at 19, Nehru Place New Delhi - 110019 India.

22. Upon information and belief, Ranbaxy Inc. is a wholly-owned subsidiary of Ranbaxy Laboratories.

23. This action arises under the Patent Laws of the United States, Title 35, United States Code. This Court has subject matter jurisdiction over this action pursuant to the provisions of Title 28, United States Code, Sections 1331 and 1338.

24. Ranbaxy Laboratories and Ranbaxy Inc. are subject to personal jurisdiction in this District.

25. Venue is proper in this District pursuant to the provisions of Title 28, United States Code, Sections 1391(c), (d) and 1400(b).

THE PRIOR INFRINGEMENT LITIGATION AGAINST RANBAXY

26. Pfizer, through Parke-Davis Pharmaceutical Research, a division of Warner-Lambert Company, holds an approved New Drug Application for a formulation containing atorvastatin calcium, which it sells under the registered name Lipitor®.

27. Pfizer received letters dated January 23, 2003 from Ranbaxy Pharmaceuticals, Inc. (the "January 23, 2003 letters") which notified Pfizer that Ranbaxy Laboratories had filed an Abbreviated New Drug Application (ANDA), ANDA No. 76-477, seeking approval from FDA

to engage in the commercial manufacture, use, and sale of a product containing atorvastatin calcium as its active ingredient ("Ranbaxy's Atorvastatin Product") prior to the expiration of the '893 patent.

28. Pursuant to 35 U.S.C. §271 (e)(2), Pfizer filed suits against Ranbaxy Laboratories and Ranbaxy Pharmaceuticals, Inc. in the United States District Court for the District of Delaware alleging that Ranbaxy's proposed ANDA product infringed the '893 patent.

29. Pfizer's Complaints were consolidated into Civil Action No. 03-209-JJF (collectively the "Lipitor® Litigation").

30. Ultimately, Pfizer alleged infringement of claims 1-4, 8 and 9 of the '893 patent in the Lipitor® Litigation.

31. In response to Pfizer's Complaints, Ranbaxy filed an Answer and several Counterclaims.

32. Ranbaxy's Answer and Counterclaims averred that it did not infringe the '893 patent.

33. Ranbaxy's Answer and Counterclaims also challenged the validity of the patent term extension granted by the PTO for the '893 patent.

34. At no time during the Lipitor® Litigation did Ranbaxy plead or assert that any claim in the '893 patent was invalid for obviousness under 35 U.S.C. §103.

35. EP 247 633 is the European counterpart to the '893 patent.

36. Prior to trial in the Lipitor® Litigation, Ranbaxy was aware of EP 247 633 and its prosecution before the European Patent Office.

37. Specifically, prior to trial in the Lipitor® Litigation, Ranbaxy was aware of the first examination report in the EP 247 633 prosecution, the citation of EP 179 559 in the first examination report and Warner-Lambert's response thereto.

38. EP 247 633 was marked as trial Exhibit PTX 244 in the Lipitor® Litigation.

39. A portion of the prosecution history of EP 247 633 was the subject of a stipulation in the Lipitor® Litigation, dated September 3, 2004 (D.I. 191).

40. EP 179 559 was produced in discovery as document number P0267818 in the Lipitor® Litigation.

41. Ranbaxy did not rely on EP 179 559 as prior art for any purpose in the Lipitor® Litigation or in any briefing filed by Ranbaxy after trial.

42. By its opinion dated December 16, 2005 in the Lipitor® Litigation, the District Court held that the '893 patent was not invalid or unenforceable.

43. The District Court also concluded that the '893 patent claims were not limited to racemic mixtures but also embraced individual trans-form isomers, corresponding to the R-trans and S-trans, as well as their trans-form mixtures, including racemates.

44. The District Court further held that Ranbaxy's Atorvastatin Product, the subject of ANDA No. 76-477, literally infringed claims 1-4 and 8-9 of the '893 patent.

45. The District Court additionally held that the patent term extension of the '893 patent was not invalid or unenforceable.

46. Ranbaxy appealed the District Court's decision in the Lipitor® Litigation to the United States Court of Appeals for the Federal Circuit ("Federal Circuit") in Appeal No. 06-1179 (the "Lipitor® Appeal").

47. In the Lipitor® Appeal, the Federal Circuit affirmed that the '893 patent was infringed, not invalid and not unenforceable.

48. The Federal Circuit further affirmed that the patent term extension of the '893 patent was not invalid and not unenforceable.

49. Ranbaxy filed a Petition for Rehearing and Rehearing En Banc in the Lipitor® Appeal and the Federal Circuit denied that petition.

50. An amended final judgment was entered by the District Court in the Lipitor Litigation, by Orders of the Court dated November 7, 2006 and November 30, 2006. A copy of the final judgment, as amended, is attached as Exhibit C.

51. Judgment has been entered in the Lipitor® Litigation "in favor of plaintiffs Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company LLC and Warner-Lambert Export, Ltd. (collectively "Pfizer") and against defendants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Incorporated (collectively "Ranbaxy") on Pfizer's claims that Ranbaxy has infringed claims 1-4, and 8-9 of the '893 patent…".

52. Judgment has been further entered in the Lipitor® Litigation, "that pursuant to 35 U.S.C. §271 (e) (4) (A), the effective date of any approval of Ranbaxy's Abbreviated New Drug Application No. 76-477 shall be a date which is not earlier than the date of expiration of the '893 Patent and its patent term extension (September 24, 2009, with attached six months of pediatric exclusivity ending on March 24, 2010, to which Pfizer is entitled)."

53. Judgment has also been entered in the Lipitor® Litigation, "that pursuant to 35 U.S.C. §271 (e) (4) (B), defendants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Incorporated, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them or either of them are permanently enjoined from

engaging in the manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any product comprising atorvastatin calcium covered by, or the use of which is covered by claims 1-4 and 8-9 of the '893 Patent."

54. The judgment entered in Civil Action No. CIV.A. 03-209-JJF is final for purposes of *res judicata.*

55. Ranbaxy is barred by res judicata and collateral estoppel from attacking the validity or enforceability of the patent term extension for the '893 patent and the infringement, validity and enforceability of the '893 patent.

FIRST CLAIM FOR RELIEF;
INFRINGEMENTOF THE '893 PATENT

56. Pfizer realleges paragraphs 1 through 55 above as if fully set forth herein.

57. Pfizer has received a letter dated January 24, 2007 from Ranbaxy Inc. (the "January 24, 2007 letter") which notified Pfizer that Ranbaxy Laboratories had filed an Abbreviated New Drug Application ("Ranbaxy's ANDA") seeking approval from FDA to engage in the commercial manufacture, use, and sale of a product containing amlodipine besylate and atorvastatin calcium as the active ingredients ("Ranbaxy's New ANDA Product") prior to the expiration of the '893 patent. A copy of the January 24, 2007 letter is attached hereto as Exhibit D.

58. The January 24, 2007 letter stated that "RLL's ANDA referred to in paragraph (1) has not been assigned a number to date, but this will be supplied to you as it is available."

59. Ranbaxy Inc. is Ranbaxy Laboratories' agent for service of process under Ranbaxy's ANDA.

60. The original expiration date for the '893 patent was May 30, 2006.

61. On July 15, 1998, the PTO granted the '893 patent a 1,213 day patent term extension pursuant to 35 U.S.C. §156, extending the expiration date of the '893 patent to September 24, 2009.

62. Lipitor® was granted a further period of exclusivity under section 505 of the Food, Drug and Cosmetic Act to March 24, 2010.

63. Ranbaxy is barred from challenging the infringement, validity and enforceability of the '893 patent by the final judgment, as amended, entered in the Lipitor® Litigation.

64. Upon information and belief, Ranbaxy's New ANDA Product contains atorvastatin calcium, the same active ingredient contained in Ranbaxy's Atorvastatin Product found to infringe the '893 patent in the Lipitor® Litigation.

65. Ranbaxy Laboratories has infringed the '893 patent under 35 U.S.C. §271(e)(2) by filing Ranbaxy's ANDA seeking approval from the FDA to engage in the commercial manufacture, use, or sale of a product containing atorvastatin calcium as an active ingredient prior to the expiration of the '893 patent.

66. Alternatively, Ranbaxy Inc. has infringed the '893 patent under 35 U.S.C. §271(e)(2) by filing Ranbaxy's ANDA seeking approval from the FDA to engage in the commercial manufacture, use, or sale of a product containing atorvastatin calcium as an active ingredient prior to the expiration of the '893 patent.

67. Alternatively, Ranbaxy Inc. and Ranbaxy Laboratories have jointly infringed the '893 patent under 35 U.S.C. §271(e)(2) by filing Ranbaxy's ANDA seeking approval from the FDA to engage in the commercial manufacture, use, or sale of a product containing atorvastatin calcium as an active ingredient prior to the expiration of the '893 patent.

68. Pfizer will be irreparably harmed if Ranbaxy is not enjoined from infringing the '893 patent.

69. Because Ranbaxy is barred, *inter alia*, by the final judgment, as amended, in the Lipitor® Litigation from challenging the infringement, validity and enforceability of the '893 patent and the validity and enforceability of the '893 patent term extension and further barred from challenging infringement of the '893 patent by its Atorvastatin Product, the filing of the Ranbaxy ANDA containing a Paragraph IV certification to the '893 patent is a willful infringement of the '893 patent under 35 U.S.C. §271(e)(2), making this an exceptional case within the meaning of 35 U.S.C. §285 and thereby entitling Pfizer to its attorneys' fees.

SECOND CLAIM FOR RELIEF:
INFRINGEMENT OF THE '574 PATENT

70. Pfizer realleges paragraphs 1 through 69 above as if fully set forth herein.

71. Ranbaxy's January 24, 2007 Letter further notified Pfizer that Ranbaxy Laboratories had filed Ranbaxy's ANDA seeking approval from FDA to engage in the commercial manufacture, use, and sale of a product containing amlodipine besylate and atorvastatin calcium as the active ingredients prior to the expiration of the '574 patent.

72. The expiration date for the '574 patent is February 25, 2020.

73. Ranbaxy Laboratories has infringed the '574 patent under 35 U.S.C. §271(e)(2) by filing Ranbaxy's ANDA seeking approval from the FDA to engage in the commercial manufacture, use, or sale of a product containing amlodipine besylate and atorvastatin calcium as the active ingredients prior to the expiration of the '574 patent.

74. Alternatively, Ranbaxy Inc. has infringed the '574 patent under 35 U.S.C. §271(e)(2) by filing Ranbaxy's ANDA seeking approval from the FDA to engage in the

commercial manufacture, use, or sale of a product containing amlodipine besylate and atorvastatin calcium as the active ingredients prior to the expiration of the '574 patent.

75. Alternatively, Ranbaxy Inc. and Ranbaxy Laboratories have jointly infringed the '574 patent under 35 U.S.C. §271(e)(2) by filing Ranbaxy's ANDA seeking approval from the FDA to engage in the commercial manufacture, use, or sale of a product containing amlodipine besylate and atorvastatin calcium as the active ingredients prior to the expiration of the '574 patent.

76. Pfizer will be irreparably harmed if Ranbaxy is not enjoined from infringing the '574 patent.

WHEREFORE, Pfizer requests the following relief:

A. A judgment providing that pursuant to 35 U.S.C. §271 (e) (4) (A), the effective date of any FDA approval for Ranbaxy's ANDA be no earlier than March 24, 2010, the date of expiration of the '893 Patent and its patent term extension (September 24, 2009, with attached six months of pediatric exclusivity ending on March 24, 2010, to which Pfizer is entitled);

B. A judgment pursuant to 35 U.S.C. §271 (e) (4) (B) permanently enjoining Ranbaxy Inc. and Ranbaxy Laboratories, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them or either of them, from making, using, selling, offering to sell, or importing the atorvastatin product described in Ranbaxy's ANDA until March 24, 2010, the expiration date of the '893 patent;

C. A judgment providing that pursuant to 35 U.S.C. §271 (e) (4) (A), the effective date of any FDA approval for Ranbaxy's ANDA be no earlier than February 25, 2020, the date on which the '574 patent expires;

D. A judgment pursuant to 35 U.S.C. §271 (e) (4) (B) permanently enjoining Ranbaxy Inc. and Ranbaxy Laboratories, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them or either of them, from making, using, selling, offering to sell, or importing the atorvastatin product described in Ranbaxy's ANDA until February 25, 2020, the expiration date of the '574 patent;

E. Attorneys' fees in this action under 35 U.S.C. §285;

F. Costs and expenses in this action; and

G. Such further and other relief as this Court may deem just and proper.

RESPECTFULLY SUBMITTED,

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EXHIBIT A

United States Patent [19]

Roth

[11] **Patent Number: 4,681,893**

[45] **Date of Patent: Jul. 21, 1987**

[54] **TRANS-6-[2-(3- OR 4-CARBOXAMIDO-SUBSTITUTED PYRROL-1-YL)ALKYL]-4-HYDROXYPYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS**

[75] Inventor: **Bruce D. Roth**, Ann Arbor, Mich.

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[21] Appl. No.: **868,867**

[22] Filed: **May 30, 1986**

[51] **Int. Cl.**[4] **A61K 31/40**; A61K 31/35; C07D 207/327

[52] **U.S. Cl.** **514/422**; 514/423; 546/256; 546/275; 548/517; 548/537

[58] **Field of Search** 548/517, 537; 514/422, 514/423

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,983,140	9/1976	Endo et al.	549/292
4,049,495	9/1977	Endo et al.	435/125
4,137,322	1/1979	Endo et al.	548/344 X
4,198,425	4/1980	Mitsui et al.	514/460
4,255,444	3/1981	Oka et al.	549/292 X
4,262,013	4/1981	Mitsui et al.	549/292 X
4,375,475	3/1983	Willard et al.	514/460

OTHER PUBLICATIONS

Singer, et al.; Proc. Soc. Exper. Biol. Med.; vol. 102, pp. 370–373, (1959).

Hulcher; Arch. Biochem. Biophys., vol. 146, pp. 422–427, (1971).

Brown, et al.; New England Jour. of Med., vol. 305, No. 9, pp. 515–517, (1981).

Brown, et al.; J. Chem. Soc. Perkin I, (1976), pp. 1165–1170.

Journal of the Americas Medical Assoc.; (1984), vol. 251, pp. 351–364, 365–374.

Primary Examiner—Joseph Paul Brust

Attorney, Agent, or Firm—Jerry F. Janssen

[57] **ABSTRACT**

Certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase and are thus useful hypolipidemic or hypocholesterolemic agents. Pharmaceutical compositions containing such compounds, and a method of inhibiting the biosynthesis of cholesterol employing such pharmaceutical compositions are also disclosed.

9 Claims, No Drawings

TRANS-6-[2-(3- OR 4-CARBOXAMIDO-SUBSTITUTED PYRROL-1-YL)ALKYL]-4-HYDROXYPYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS

BACKGROUND OF THE INVENTION

The present invention is related to compounds and pharmaceutical compositions useful as hypocholesterolemic and hypolipidemic agents. More particularly, this invention concerns certain trans-6-[2-(3- or 4-carboxamidosubstitutedpyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase), pharmaceutical compositions containing such compounds, and a method of inhibiting the biosynthesis of cholesterol employing such pharmaceutical compositions.

High levels of blood cholesterol and blood lipids are conditions involved in the onset of arteriosclerosis. It is well known that inhibitors of HMG-CoA reductase are effective in lowering the level of blood plasma cholesterol, especially low density lipoprotein cholesterol (LDL-C), in man (cf. M. S. Brown and J. L. Goldstein, *New England Journal of Medicine,* 305, No. 9, 515–517 (1981). It has now been established that lowering LDL-C levels affords protection from coronary heart disease (cf. *Journal of the American Medical Association,* 251, No. 3, 351–374 (1984).

Moreover, it is known that certain derivatives of mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) and the corresponding ring-closed lactone form, mevalonolactone, inhibit the biosynthesis of cholesterol (cf. F. M. Singer et al., *Proc. Soc. Exper. Biol. Med.,* 102: 370 (1959) and F. H. Hulcher, *Arch. Biochem. Biophys.,* 146: 422 (1971)).

U.S. Pat. Nos. 3,983,140; 4,049,495 and 4,137,322 disclose the fermentative production of a natural product, now called compactin, having an inhibitory effect on cholesterol biosynthesis. Compactin has been shown to have a complex structure which includes a mevalonolactone moiety (Brown et al., *J. Chem. Soc. Perkin* I (1976) 1165.

U.S. Pat. No. 4,255,444 to Oka et al. discloses several synthetic derivatives of mevalonolactone having antilipidemic activity.

U.S. Pat. Nos. 4,198,425 and 4,262,013 to Mitsue et al. disclose aralkyl derivatives of mevalonolactone which are useful in the treatment of hyperlipidemia.

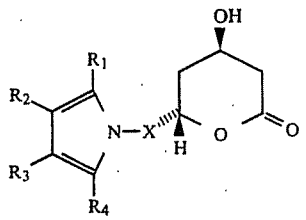
U.S. Pat. no. 4,375,475 to Willard et al. discloses certain substituted 4-hydroxytetrahydropyran-2-ones which, in the 4(R)-trans-stereoisomeric form, are inhibitors of cholesterol biosynthesis.

Published PCT application No. WO 84/01231 discloses certain indole analogs and derivatives of mevalonolactone having utility as hypolipoproteinemic and antiatherosclerotic agents.

SUMMARY OF THE INVENTION

In accordance with the present invention, there are provided certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened hydroxy-acids derived therefrom which are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase).

In particular, in its broadest aspect the present invention provides compounds of structural formula I



I

wherein X is —CH_2—, —CH_2CH_2—, —$CH_2CH_2CH_2$— or —$CH_2CH(CH_3)$—.

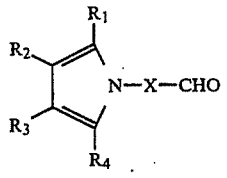
R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

Either R_2 or R_3 is —$CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

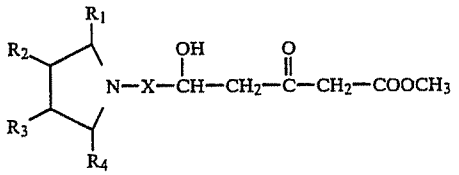
R_4 is alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl.

Also contemplated as falling within the scope of the present invention are the hydroxy acids, and pharmaceutically acceptable salts thereof, derived from the opening of the lactone ring of the compounds of structural formula I above.

In another aspect of the present invention, there is provided a method of preparing the compounds of structural formula I above which comprises the steps of (a) first reacting a substituted [(pyrrol-1-yl)alkyl]aldehyde compound of the formula

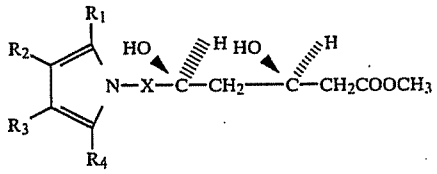


with the dilithio or sodio-lithio salt of methyl acetoacetate to form a compound of the structure



(b) reducing the product of step (a) with a trialkylborane compound such as tributylborane in the presence of sodium borohydride in an inert solvent;

(c) oxidizing the product of step (b) with alkaline aqueous hydrogen peroxide solution to produce a compound of the formula



and

(d) cyclizing the product step (c) to a lactone of formula I above by heating in an inert solvent such as toluene or, alternatively converting the product of step (c) to a pharmaceutically acceptable salt by conventional methods.

In yet another aspect, the present invention provides pharmaceutical compositions useful as hypolipidemic or hypocholesterolemic agents comprising a hypolipidemic or hypocholesterolemic effective amount of a compound in accordance with this invention as set forth above, in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering an effective amount of a pharmaceutical composition as defined above.

DETAILED DESCRIPTION

The compounds of the present invention comprise a class of trans-6-[2-(3- or 4-carboxamidosubstituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones in which the pyran-2-one moiety is attached, through an alkyl chain, to the substituted pyrrole nucleus at the nitrogen, or 1-position, of the pyrrole. The alkyl group may be methylene, ethylene, propylene, or methylethylene. The preferred alkyl chain linking the substituted pyrrole nucleus and the 4-hydroxypyran-2-one ring is ethylene.

The compounds of structural formula I above possess two asymmetric carbon centers, one at the 4-hydroxy position of the pyran-2-one ring, and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. This asymmetry gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans- and S-trans-isomers. This invention contemplates only the trans- form of the compounds of formula I above.

In the compounds of the present invention, position 2 of the substituted pyrrole nucleus is substituted with 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms. Preferred substituent groups at the 2-position of the pyrrole nucleus are phenyl and substituted phenyl.

In the compounds of this invention, position 5 of the pyrrole nucleus is substituted with alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl. Preferred substituents are alkyl or trifluoromethyl with isopropyl being particularly preferred.

The preferred reaction sequence which is used to prepare compounds of the present invention involves the cycloaddition of a disubstituted acetylene, in which one substituent is carboxamido or N-substituted carboxamido, to an appropriately substituted N-acylaminocarboxylic acid to form a substituted pyrrole. This addition may occur in either of two ways, leading to a substituted pyrrole addition product in which the carboxamido substituent resides on either carbon 3 or 4 of the pyrrole nucleus.

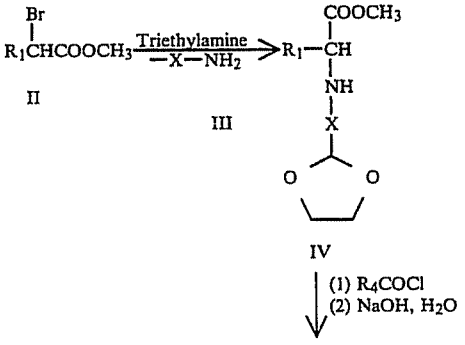
Thus, in compounds of the present invention, the substituent at either position 3 or 4 of the pyrrole nucleus is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms and the other of the two positions is unsubstituted or is substituted with alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

Preferred groups for R_5 and R_6 are hydrogen, phenyl, or substituted phenyl. In a particularly preferred group of compounds within the present invention, R_5 is hydrogen and R_6 is phenyl or substituted phenyl.

The compounds of this invention are prepared by the general reaction scheme outlined in Reaction Sequence 1 which takes advantage of the chemistry of mesionic compounds of the type described originally by R. Huisgen et al., *Ang. Chem. Int. Ed.*, 3: 136 (1964).

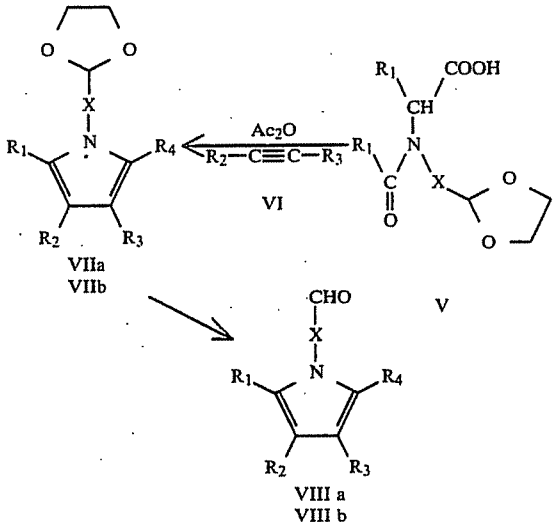
The known, or readily prepared, α-haloesters of structural formula II are reacted with the known 2-[1-(2-aminoalkyl)]-1,3-dioxalane, III, in the presence of an acid scavenger such as triethylamine to produce the N-alkyl-α-aminoesters, IV. The aminoesters, IV are

REACTION SEQUENCE I



-continued

REACTION SEQUENCE I



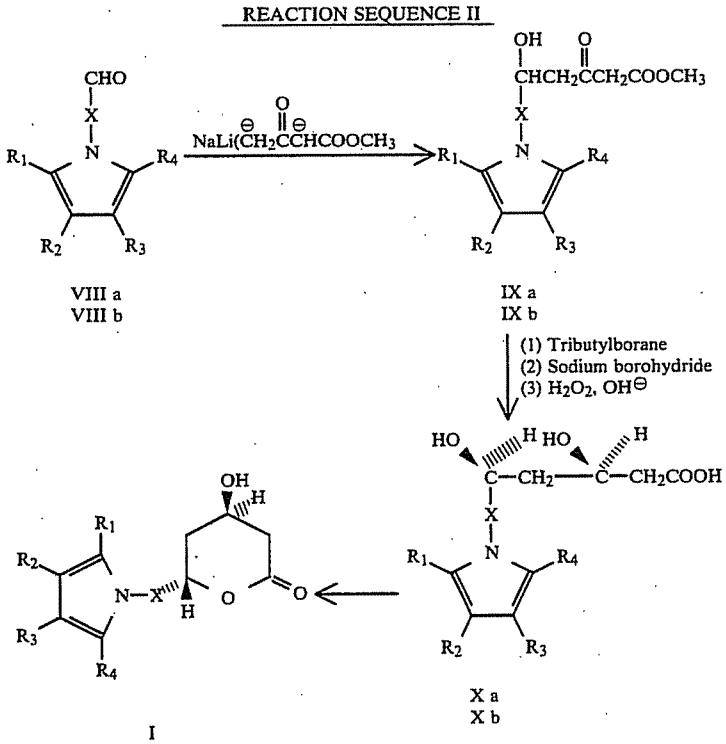
known in the art, and subsequently further purified, if desired, by recrystallization. On the other hand, in the case where R_4 is 1-methylethyl, the cyclo-addition reaction yields predominantly one product which can be purified by recrystallization alone.

Hydrolysis of the acetal function of compounds VIIa and VIIb in aqueous acid solution affords the aldehydes VIIIa and VIIIb. The aldehydes, VIII, are further converted to compounds of the present invention by the processes depicted in Reaction Sequence 2.

The aldehyde compounds, VIII, are reacted with the dilithium or lithio-sodio salt of methyl acetoacetate to produce the corresponding 7-(substituted-pyrrolyl)-5-hydroxy-3-oxoheptanoates, IX. The heptanoates, IX, are dissolved in a polar solvent such as tetrahydrofuran, through which a small amount of air has been bubbled. A slight excess of a trialkylborane, such as tributylborane, is added to the mixture which is then cooled to a temperature of preferably between about 0° C. and −78° C. after which sodium borohydride is added.

The mixture is stirred for about one to two hours and then oxidized by the addition of basic aqueous hydrogen peroxide solution. The reaction produces the 7-(substituted-pyrrolyl)-3,5-dihydroxyheptanoic acids,

REACTION SEQUENCE II



I

acylated with an acid halide and subsequently hydrolyzed in aqueous base solution to produce the N-acyl-N-alkyl aminoacids, V.

The N-acyl-N-alkyl aminoacids, V, are reacted with the appropriately substituted carboxamido acetylenic compounds, VI, in the presence of an acid anhydride to produce a mixture of the isomeric substituted pyrrole compounds VIIa and VIIb. Depending upon the substituents present, this cyclo-addition reaction affords differing ratios of the two products. For example, in the situation where R_4 is trifluoromethyl, the reaction yields roughly equimolar amounts of the two isomeric products. In such situations, the two isomeric products are separated by chromatographic techniques well

X, in which the product contains a predominance of the desired R*,R* configuration at carbon atoms three and five which bear the hydroxy groups.

The acids may be converted to a corresponding pharmaceutically acceptable salt by conventional means, if desired, or cyclized to the trans-6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones, I, by dehydration in an inert solvent such as refluxing toluene with azeotropic removal of water. This cyclization step has been found to produce material containing from 85–90% of the desired trans-configuration of the 4-hydroxy group relative to the 6-(substituted-pyrrol-1-yl)alkyl group on the pyran-2-one lactone ring.

The ring-opened hydroxy acids of structural formula II above are intermediates in the synthesis of the lactone compounds of formula I and may be used in their free acid form or in the form of a pharmaceutically acceptable metal or amine salt in the pharmaceutical method of the present invention. These acids react to form pharmaceutically acceptable metal and amine salts. The term "pharmaceutically acceptable metal salt" contemplates salts formed with the sodium, potassium, calcium, magnesium, aluminum, iron, and zinc ions. The term "pharmaceutically acceptable amine salt" contemplates salts with ammonia and organic nitrogenous bases strong enough to form salts with carboxylic acids. Bases useful for the formation of pharmaceutically acceptable nontoxic base addition salts of compounds of the present invention form a class whose limits are readily understood by those skilled in the art.

The free acid form of compounds of the present invention may be regenerated from the salt form, if desired, by contacting the salt with a dilute aqueous solution of an acid such as hydrochloric acid.

The base addition salts may differ from the free acid forms of the compounds of this invention in such physical characteristics as solubility and melting point, but are otherwise considered equivalent to the free acid form for the purposes of this invention.

The compounds of the present invention may exist in solvated or unsolvated form. In general, the solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for the purposes of this invention.

The compounds of this invention are useful as hypocholesterolemic or hypolipidemic agents by virtue of their ability to inhibit the biosynthesis of cholesterol through inhibition of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase).

The ability of compounds of the present invention to inhibit the biosynthesis of cholesterol was measured by two methods. A first method (designated CSI screen) utilized the procedure described by R. E. Dugan et al., *Archiv. Biochem. Biophys.*, (1972), 152, 21–27. In this method, the level of HMG-CoA enzyme activity in standard laboratory rats is increased by feeding the rats a chow diet containing 5% cholestyramine for four days, after which the rats are sacrificed.

The rat livers are homogenized, and the incorporation of cholesterol-^{14}C-acetate into nonsaponifiable lipid by the rat liver homogenate is measured. The micromolar concentration of compound required for 50% inhibition of sterol synthesis over a one-hour period is measured, and expressed as an IC_{50} value.

A second method (designated COR screen) employed the procedure detailed by T. Kita, et al., *J. Clin. Invest.*, (1980), 66: 1094–1100. In this method, the amount of ^{14}C-HMG-CoA converted to ^{14}C-mevalonate in the presence of a purified enzyme preparation of HMG-CoA reductase was measured. The micromolar concentration of compound required for 50% inhibition of cholesterol synthesis was measured and recorded as an IC_{50} value.

The activity of several representative examples of compounds in accordance with the present invention appears in Table 1, and is compared with that of the prior art compound, compactin.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersable granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

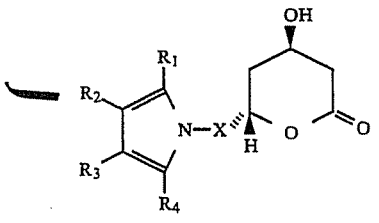
In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

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

Powders and tablets preferably contain between about 5 to about 70% by weight of the active ingredient. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is

TABLE 1



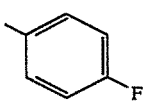
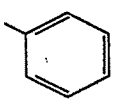
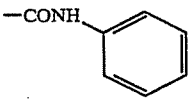
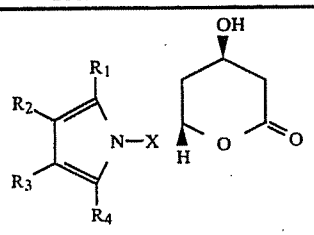
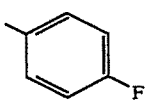
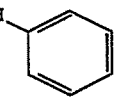
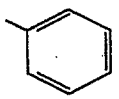
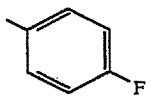
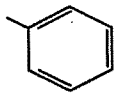
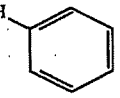
Compound	X	R_1	R_2	R_3	R_4	IC_{50} (Micromoles/liter) CSI	COR
1	$-CH_2CH_2-$			—CONH— 	$-CH(CH_3)_2$	0.035	0.050

TABLE 1-continued



Compound	X	R_1	R_2	R_3	R_4	IC_{50} (Micromoles/liter) CSI	COR
2	$-CH_2CH_2-$		—CONH 		$-CF_3$	0.40	0.40
3	$-CH_2CH_2-$			—CONH 	$-CF_3$	0.018	0.020
Compactin (Prior art)						0.026	0.028

surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions suitable for oral or parenteral administration, or suspensions and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol may be mentioned as examples of liquid preparations suitable for parenteral administration.

Sterile solutions may be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

In therapeutic use as hypolipidemic or hypocholesterolemic agents, the compounds utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from 40 mg to 600 mg per day. For a normal human adult of approximately 70 kg or body weight, this translates to a dosage of from about 0.5 mg/kg to about 8.0 mg/kg of body weight per day.

The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of optimum dosages for a particular situation is within the skill of the art.

The following examples illustrate particular methods for preparing compounds in accordance with this invention. These examples are illustrative and are not to be read as limiting the scope of the invention as it is defined by the appended claims.

EXAMPLE 1

Preparation of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo2H-pyran-2-yl)ethyl]-pyrrole-3-carboxamide

Step A: Preparation of α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester

A solution of 26 g (220 mmol) of 2-[1-(2-aminoethyl)]-1,3-dioxalane in 50 ml of acetonitrile was added at room temperature with stirring to a solution of 200 mmol of α-bromo-4-fluorobenzeneacetic acid, ethyl ester (J. W. Epstein et al., *J. Med. Chem.*, 24: 481–490 (1981)) and 42 ml (300 mmol) of triethylamine in 350 ml of acetonitrile. The resulting mixture was stirred at room temperature overnight and then poured into 500 ml of diethyl ether. The resulting suspension was extracted with 300 ml of water and then twice with 300-ml portions of 2M hydrochloric acid. The combined extracts were made basic with 25% aqueous sodium hydroxide solution and extracted twice with 500-ml portions of ethyl acetate. The ethyl acetate extracts were combined, washed successively with water and brine, and then dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the residue concentrated to yield 49.5 g of α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester.

The 90 MHz proton magnetic resonance spectrum of the product in deuterochloroform exhibited signals at 1.18 (triplet, 3H, J=7 Hz); 1.85 (multiplet, 2H); 2.20

(broad singlet, 1H); 2.6 (multiplet, 2H); 3.85 (multiplet, 4H); 4.1 (quartet, 2H, J=7 Hz); 4.22 (singlet, 1H); 4.83 (triplet, 1H, J=4.5 Hz); and 6.8–7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step B. Preparation of α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid, ethyl ester.

Thirty grams (100 mmol) of α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester from Step A were dissolved in 200 ml of dichloromethane together with 28.6 ml (205 mmol) of triethylamine and the resulting mixture was cooled to 0° C. under dry nitrogen. A solution of 11 ml (105 mmol) of isobutyryl chloride in 50 ml of dichloromethane was slowly added with stirring. After addition was complete, the mixture was stirred for an additional 60 minutes and then poured into 100 ml of diethyl ether. The ether solution was washed successively with portions of water, 2M hydrochloric acid, sodium bicarbonate solution, and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvents yielded 35 g of α-[[2-(1,3-dioxolan-2-yl)-ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzene-acetic acid, ethyl ester.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the product exhibited signals at 1.2 (multiplet, 9H); 1.7 (multiplet, 2H); 2.85 (multiplet, 1H); 3.35 (multiplet, 2H); 3.80 (multiplet, 4H); 4.20 (quartet, 2H, J=7 Hz); 4.60 (triplet, 1H, J=4.5 Hz); 5.81 (singlet, 1H); and 6.8–7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step C. Preparation of α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid

A solution of 35 g (95.3 mmol) of the ester from Step B and 12 g (300 mmol) of sodium hydroxide in 480 ml of 5:1 methanol water was heated under reflux and stirred for two hours. The solution was cooled to room temperature, concentrated, and diluted by the addition of 500 ml of water. The resulting solution was extracted with ether and the aqueous layer was acidified with ice-cold 6M hydrochloric acid and then extracted twice with 300-ml portions of ethyl acetate.

The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, and evaporated to yield 30 g of crude α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid which was used without further purification.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the product exhibited signals at 1.11 (doublet, 6H, J=7 Hz); 1.4–1.9 (multiplet, 2H); 2.85 (multiplet, 1H); 3.32 (multiplet, 2H); 3.75 (multiplet, 4H); 4.52 (triplet, 1H, J=4.5 Hz); 5.73 (singlet, 1H); and 6.8–7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step D. Preparation of N,3-diphenylpropynamide

A solution of 171 mmol of dicyclohexylcarbodiimide in 250 ml of dichloromethane was added dropwise over a two hour period at 0° C. to a suspension of 171 mmol of propiolic acid, 179.6 mmol of aniline, and 5 mmol of 4-dimethylaminopyridine in 400 ml of dichloromethane. After addition was complete, the mixture was stirred for an additional 30 minutes and then diluted with diethyl ether. The resulting mixture was filtered through silica gel, concentrated, and the residue recrystallized to provide 30.5 g of N,3-diphenyl-2-propynamide, mp 122°–123° C.

Analyzed for $C_{15}H_{13}NO$: Calc.: C, 80.69%; H, 5.87%; N, 6.27%; Found: C, 80.54%; H, 5.58%; N, 6.52%.

The infrared spectrum of a KBr pellet of the compound showed principal peaks at 2215, 1630, 1595,1549, 1490, 1445, 1330, 756, and 691 reciprocal centimeters.

Step E. Preparation of 1-[2-(1,3-dioxalan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide

A solution of 95 g (280 mmol) of α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid, prepared as described in Step C above, and 98 g (439 mmol) of N,2-diphenylpropenoic carboxamide, prepared as described in Step D above, was heated at 90° C. with stirring for four hours, (Vigorous gas evolution occurred for two hours.) After this time, the mixture was cooled to room temperature and chromatographed twice on silica gel, eluting with 4:1 hexane:ethyl acetate to separate the product (R_f=0.35) from the starting material (R_f=0.5).

Recrystallization of the product from isopropyl ether provided 59.5 g (119.3 mmol) of 1-[2-(1,3-dioxalan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, mp 159°–162° C.

Analyzed for $C_{31}H_{31}FN_2O_3$: Calc.: C, 74.68%; H, 6.27%; N, 5.62%; Found: C, 75.04%; H, 6.12%; N, 5.89%.

Step F. Preparation of 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide

A solution of 59 g (118.3 mmol) of 1-[2-(1,3-dioxalan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, from Step E above, and 0.4 ml of concentrated hydrochloric acid in 1200 ml of anhydrous ethanol was heated under reflux with stirring for 24 hours. After this time the mixture was cooled to room temperature, concentrated, and the residue taken up in 1200 ml of 3:1 acetone:water and 5 g of p-toluenesulfonic acid was added. This mixture was heated under reflux with stirring for two days after which time the solution was cooled to room temperature and partitioned between 1 liter of diethyl ether and 200 ml of brine solution.

The organic phase was separated, washed successively with sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate and concentrated. The oil which resulted was dissolved in the minimum amount required of hot isopropyl ether. The crystals which formed upon cooling were collected by filtration to yiled 36.8 g of 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide. A further crop of 9.8 g of crystals were obtained from the mother liquor.

Analyzed for $C_{29}H_{27}FN_2O_3$: Calc.: C, 76.63%; H, 5.99%; N, 6.16%; Found: C, 76.48%; H, 6.20%; N, 6.14%.

Step G. Preparation of 2-(4-fluorophenyl)-δ-hydroxy-5-(1-methylethyl)-β-oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester

A solution of methyl acetoacetate (26.4 ml, 243 mmol) in 250 ml of anhydrous tetrahydrofuran was added dropwise to a stirred suspension of hexane-washed sodium hydride (6.4 g, 267 mmol) in 200 ml of tetrahydrofuran at 0° C. When gas evolution was complete, 97.2 ml of 2.5M n-butyl lithium was added dropwise over a period of 60 minutes.

The resulting solution was stirred for 30 minutes at 0° C. and then cooled to −78° C. after which a solution of

36.8 g (80.9 mmol) of 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, from Step F above, in 100 ml of tetrahydrofuran was added over a period of thirty minutes. The resulting solution was stirred for 30 minutes at −78° C. and then warmed to 0° C. where it was held for an additional 60 minutes.

The mixture was then acidified by the dropwise addition of 300 ml of ice-cold 3M hydrochloric acid, diluted with ether, washed successively with water and brine, dried over anhydrous magnesium sulfate, and concentrated. Flash chromatography of the residue yielded 37.9 g of 2-(4-fluorophenyl)-δ-hydroxy-5-(1-methylethyl)-β-oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester.

The 90 MHz proton magnetic resonance spectrum of the product exhibited signals at 1.50 (doublet, 6H, J=7 Hz); 1.8 (multiplet, 2H); 2.45 (doublet, 2H, J=7 Hz); 2.8 (broad, 1H); 3.33 (singlet, 2H); 3.5 (multiplet, 1H); 3.67 (singlet, 3H); 3.8–4.0 (multiplet, 2H); and 6.8–7.3 (multiplet, 14H) parts per million downfield from tetramethylsilane.

Step H. Preparation of R*,R*-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid and trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide

Air (60 ml) was bubbled via a syringe through a solution of 2-(4-fluorophenyl)-δ-hydroxy-5-(1-methylethyl)-β-oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester (48 g, 84.1 mmol) and 92.5 ml of 1M tributylborane in 100 ml of anhydrous tetrahydrofuran. The mixture was stirred overnight at room temperature and then cooled to −78° C. Sodium borohydride (3.85 g, 101.8 mmol) was added to the cooled mixture in one portion. The mixture was allowed to warm slowly to 0° C. over a period of three hours, during which there was vigorous gas evolution.

The dry ice-acetone bath applied to the reaction vessel was replaced by an ice bath and 18.3 ml of glacial acetic acid were added dropwise, followed by 204 ml of 3M aqueous sodium hydroxide solution and 30.5 ml of 30% aqueous hydrogen peroxide solution.

The mixture was vigorously stirred while being allowed to warm to room temperature overnight. The mixture was then partitioned between diethyl ether and water and the aqueous layer was separated, acidified, and extracted with ethyl acetate.

The ethyl acetate extract was washed with brine, dried, and evaporated to yield crude R*,R*-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid which was used without further purification.

The crude acid was taken up in toluene and lactonized by heating under reflux for six hours. This mixture was chromatographed to provide 30 g of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide as a foamy solid, mp 90°–97° C.

Analyzed for $C_{33}H_{33}FN_2O_4$: Calc.: C, 73.31%; H, 6.15%; N, 5.18%; Found: C, 73.46%; H, 6.31%; N, 5.28%.

This material was found by HPLC analysis to comprise a 9:1 molar ratio of the cis- and trans-isomeric forms of the product. Recrystallization from toluene-ethyl acetate yield the essentially pure trans-form, mp 148°–149° C.

EXAMPLE 2

Preparation of R*,R*-2-(4-fluoro-phenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, sodium salt

A mixture of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (10 g, 18.5 mmol) and 0.74 g (18.5 mmol) of sodium hydroxide in 90 ml of a 1:2 mixture of tetrahydrofuran-water was cooled to 0° C. This mixture was allowed to warm slowly to 25° C., after which time it was concentrated and the residual solid dried under vacuum.

The infrared spectrum of the product exhibited principal absorption peaks at 3400, 1651, 1598, 1565, 1511, 1438, 1412, 1316, 1224, 1159, 844, 754, and 702 reciprocal centimeters.

The 90 MHz proton magnetic resonance spectrum of a hexadeutero dimethylsulfoxide solution of the product exhibited signals at 1.34 (doublet, J=7 Hz, 6H); 1.5 (multiplet, 4H); 1.80 (doublet of doublets, J=15, 8 Hz, 1H); 1.99 (doublet of doublets, J=15, 4 Hz, 1H); 3–4 (multiplet, 8H); 6.9–7.3 (multiplet, 12H); 7.50 (doublet, J=8 Hz, 2H); and 9.85 (singlet, 1H) parts per million downfield from tetramethylsilane.

EXAMPLES 3 AND 4

Preparation of trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide and trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)pyrrole-3-carboxamide

Step A. Preparation of α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid.

α-[[2-(1,3-Dioxolan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester (36.5 g, 122.8 mmol, prepared as described above in Example 1, Step A) was dissolved in 1500 ml of a 5:1 mixture of methanol-water together with 7.6 g of sodium hydroxide. This mixture was heated under reflux for a period of two and one-half hours after which time the solvents were removed under vacuum.

The solid residue was taken up in 325 ml of water and a mixture of 14 ml of glacial acetic in 28 ml of water was added with stirring. After stirring for a time, an additional 3 ml of glacial acetic acid were added and the mixture was chilled for 75 minutes. The solids were collected by filtration, washed with water and then ethyl acetate and dried to yield α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, mp 218°–220° C.

Step B. Preparation of a mixture of 5-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide and 2-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-5-(trifluoromethyl)-1H-pyrrole-3-carboxamide

α-[[2-(1,3-Dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid (6.06 g, 22.5 mmol) was dissolved in 45 ml of trifluoroacetic anhydride and 7.47 g (33.8 mmol) of N,3-diphenyl-2-propynamide (prepared as described above in Example 1, Step D) was added. The resulting mixture was heated under reflux for a period of five and one-half hours. The mixture was then cooled, and 1.74

ml of trifluoroacetic acid were added and the mixture was stirred overnight.

The excess trifluoroacetic anhydride was removed under vacuum, and water was added, followed by sufficient acetone to give a homogenous solution. This solution was stirred at room temperature for three hours. The mixture was seeded with N,3-diphenyl-2-propynamide, and a precipitate formed. After three hours, this precipitate was removed by filtration.

The acetone was removed from the filtrate under vacuum and the solid residue was taken up in ether, washed successively with two portions of water, two portions of sodium bicarbonate solution, and two portions of brine and dried over anhydrous magnesium sulfate. The ether was removed under vacuum to yield a crude mixture of the two title compounds.

This mixture was separated by column chromatography on 600 g of silica gel, eluting with a 4:1 mixture of hexane-ethyl acetate.

The first fraction eluted was 5-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of this material exhibited signals at 2.73 (triplet, J=7 Hz, 2H); 4.21 (triplet, J=7 Hz, 2H); 6.7–7.3 (multiplet, 5H); 7.40 (singlet, 5H), and 9.43 (singlet, 1H) parts per million downfield from tetramethylsilane.

The second compound eluted from the column was 2-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-5-(trifluoromethyl)-1H-pyrrole-3-carboxamide.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of this material exhibited signals at 2.67 (triplet, J=7 Hz, 2H); 4.25 (triplet, J=7 Hz, 2H); 7.0–7.3 (multiplet, 14H); and 9.43 (singlet, 1H) parts per million downfield from tetramethylsilane.

Step C. Preparation of trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide and trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide

Employing the general methods detailed in Example 1, Steps G and H, the title compounds were prepared from the aldehyde compounds of this example, Step B.

The elemental analyses of the two title compounds were:

For trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide:

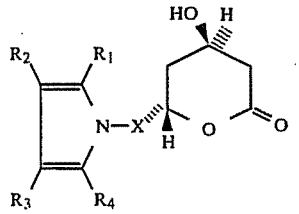
Analyzed for $C_{31}H_{26}N_2O_4$: Calc.: C, 65.72%; H, 4.63%; N, 4.94%; Found: C, 65.82%; H, 4.91%; N, 4.69%.

The trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide was found, upon recrystallization from toluene to contain 0.25 mols of toluene as solvent of crystallization, mp 106°–111° C.

Analyzed for $C_{31}H_{26}N_2O_4.0.25C_7H_8$: Calc.: C, 66.72%; H, 4.79%; N, 4.72%; Found: C, 66.81%; H, 4.86%; N, 4.60%.

I claim:

1. A compound of structural formula I



I

wherein

X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH(CH_3)-$;

R_1 is

1-naphthyl;
2-naphthyl;
cyclohexyl;
norbornenyl;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxyl,
trifluoromethyl,
alkyl of from one to four carbon atoms,
alkoxy of from one to four carbon atoms, or
alkanoyloxy of from two to eight carbon atoms;

either of R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are

independently
hydrogen;
alkyl of from one to six carbon atoms;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
cyano,
trifluoromethyl, or
carboalkoxy of from three to eight carbon atoms;

and the other of R_2 or R_3 is

hydrogen;
alkyl of from one to six carbon atoms;
cyclopropyl;
cyclobutyl;
cyclopentyl;
cyclohexyl;
phenyl; or
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxyl,
trifluoromethyl,
alkyl of from one to four carbon atoms,
alkoxy of from one to four carbon atoms, or
alkanoyloxy of from two to eight carbon atoms;

R_4 is

alkyl of from one to six carbon atoms;
cyclopropyl;
cyclobutyl;
cyclopentyl;
cyclohexyl; or
trifluoromethyl;

or a hydroxy acid or pharmaceutically acceptable salts thereof, corresponding to the opened lactone

ring of the compounds of structural formula I above.

2. A compound as defined by claim 1 wherein X is $—CH_2CH_2—$.

3. A compound as defined by claim 2 wherein R_1 is phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

4. A compound as defined by claim 2 wherein R_4 is alkyl of from one to six carbon atoms.

5. A compound as defined by claim 1 having the name trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

6. A compound as defined by claim 1 having the name trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-trifluoromethyl-1H-pyrrole-3-carboxamide.

7. A compound as defined by claim 1 having the name trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-trifluoromethyl-1H-pyrrole-3-carboxamide.

8. A pharmaceutical composition, useful as a hypocholesterolemic agent, comprising a hypocholesterolemic effective amount of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

9. A method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering a pharmaceutical composition as defined by claim 8.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.	:	4,681,893
ISSUED	:	July 21, 1987
INVENTOR(S)	:	Bruce D. Roth
PATENT OWNER	:	Warner-Lambert Company

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

1,213 days

from May 30, 2006, the original expiration date of the patent, subject to the provisions of 35 U.S.C. § 41(b), with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).



I have caused the seal of the Patent and Trademark Office to be affixed this 15th day of July 1998.

Bruce A. Lehman

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

EXHIBIT B

US006455574B1

(12) **United States Patent**
Buch

(10) **Patent No.: US 6,455,574 B1**
(45) **Date of Patent: Sep. 24, 2002**

(54) **THERAPEUTIC COMBINATION**

(75) Inventor: **Jan Buch**, Greenwich, CT (US)

(73) Assignee: **Pfizer Inc.**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/512,914**

(22) Filed: **Feb. 25, 2000**

Related U.S. Application Data

(63) Continuation of application No. PCT/IB98/01225, filed on Aug. 11, 1998.
(60) Provisional application No. 60/057,275, filed on Aug. 29, 1997.

(51) **Int. Cl.**[7] **A61K 31/40**; A61K 31/435; A61K 31/44

(52) **U.S. Cl.** **514/427**; 514/277; 514/408; 514/422; 514/423; 514/356

(58) **Field of Search** 514/422, 423, 514/356, 427, 408, 277

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Primary Examiner—Minna Moezie
Assistant Examiner—S. Jiang
(74) *Attorney, Agent, or Firm*—Peter C. Richardson; Gregg C. Benson; Robert T. Ronau

(57) **ABSTRACT**

This invention relates to pharmaceutical combinations of amlodipine or a pharmaceutically acceptable acid addition salt thereof and atorvastatin or a pharmaceutically acceptable salt thereof, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of amlodipine and atorvastatin whereby those synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms of cardiac risk, including humans.

12 Claims, No Drawings

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THERAPEUTIC COMBINATION

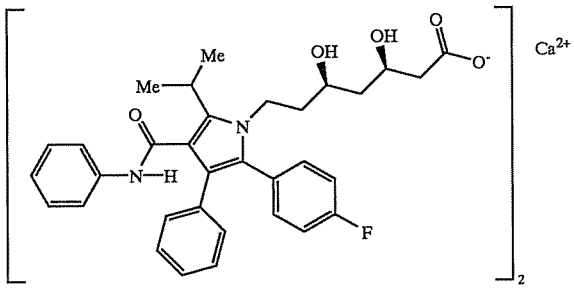
This application claims priority from copending International Patent Application Number PCT/IB98/01225 filed Aug. 11, 1998, which claims priority from U.S. Provisional Application No. 60/057,275, filed Aug. 29, 1997.

This invention relates to pharmaceutical combinations of amlodipine and pharmaceutically acceptable acid addition salts thereof and atorvastatin and pharmaceutically acceptable salts thereof, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of amlodipine and atorvastatin whereby those additive and synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms or signs of cardiac risk, including humans.

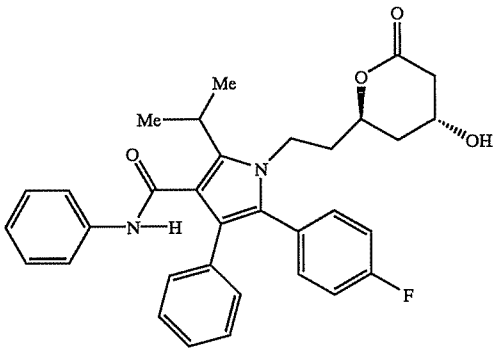
BACKGROUND OF THE INVENTION

The conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate is an early and rate-limiting step in the cholesterol biosynthetic pathway. This step is catalyzed by the enzyme HMG-CoA reductase. Statins inhibit HMG-CoA reductase from catalyzing this conversion. As such, statins are collectively potent lipid lowering agents.

Atorvastatin calcium, disclosed in U.S. Pat. No. 5,273,995, which is incorporated herein by reference, is currently sold as Lipitor® and has the formula

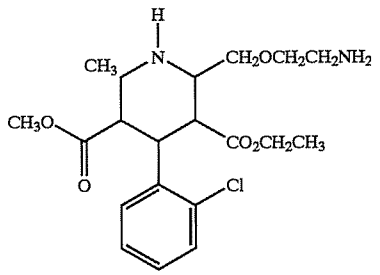


Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA. As such, atorvastatin calcium is apotent lipid lowering compound. The free carboxylic acid form of atorvastatin exists predominantly as the lactone of the formula



and is disclosed in U.S. Pat. No. 4,681,893, which is incorporated herein by reference.

Amlodipine and related dihydropyridine compounds are disclosed in U.S. Pat. No. 4,572,909, which is incorporated herein by reference, as potent ant-ischemic and antihypertensive agents. U.S. Pat. No. 4,879,303, which is incorporated herein by reference, discloses amlodipine benzenesulfonate salt (also termed amlodipine besylate). Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers. As such, amlodipine, amlodipine besylate and other pharmaceutically acceptable acid addition salts of amlodipine have utility as antihypertensive agents and as antiischemic agents. Amlodipine and its pharmaceutically acceptable acid addition salts are also disclosed in U.S. Pat. No. 5,155,120 as having utility in the treatment of congestive heart failure. Amlodipine besylate is currently sold as Norvasce®. Amlodipine has the formula



Atherosclerosis is a condition characterized by irregularly distributed lipid deposits in the intima of arteries, including coronary, carotid and peripheral arteries. Atherosclerotic coronary heart disease (hereinafter termed "CHD") accounts for 53% of all deaths attributable to a cardiovascular event. CHD accounts for nearly one-half (about $50–60 billion) of the total U.S. cardiovascular healthcare expenditures and about 6% of the overall national medical bill each year. Despite attempts to modify secondary risk factors such as, inter alia, smoking, obesity and lack of exercise, and treatment of dyslipidemia with dietary modification and drug therapy, CHD remains the most common cause of death in the United States.

High levels of blood cholesterol and blood lipids are conditions involved in the onset of atherosclerosis. It is well known that inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) are effective in lowering the level of blood plasma cholesterol, especially

low density lipoprotein cholesterol (LDL-C), in man (Brown and Goldstein, New England Journal of Medicine, 1981, 305, No. 9, 515–517). It has now been established that lowering LDL-C levels affords protection from coronary heart disease (see, e.g., The Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S), Lancet, 1994, 344, 1383–89; and Shepherd, J. et al., Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia, New England Journal of Medicine, 1995, 333,1301–07).

Angina pectoris is a severe constricting pain in the chest, often radiating from the precordium to the left shoulder and down the left arm. Often angina pectoris is due to ischemia of the heart and is usually caused by coronary disease.

Currently the treatment of symptomatic angina pectoris varies significantly from country to country. In the U.S., patients who present with symptomatic, stable angina pectoris are frequently treated with surgical procedures or PTCA. Patients who undergo PTCA or other surgical procedures designed to treat angina pectoris frequently experience complications such as restenosis. This restenosis may be manifested either as a short term proliferative response to angioplasty-induced trauma or as long term progression of the atherosclerotic process in both graft vessels and angioplastied segments.

The symptomatic management of angina pectoris involves the use of a number of drugs, frequently as a combination of two or more of the following classes: beta blockers, nitrates and calcium channel blockers. Most, if not all, of these patients require therapy with a lipid lowering agent as well. The National Cholesterol Education

Program (NCEP) recognizes patients with existing coronary artery disease as a special class requiring aggressive management of raised LDL-C.

Amlodipine helps to prevent myocardial ischemia in patients with exertional angina pectoris by reducing Total Peripheral Resistance, or afterload, which reduces the rate pressure product and thus myocardial oxygen demand at any particular level of exercise. In patients with vasospastic angina pectoris, amlodipine has been demonstrated to block constriction and thus restore myocardial oxygen supply. Further, amlodipine has been shown to increase myocardial oxygen supply by dilating the coronary arteries.

Hypertension frequently coexists with hyperlipidemia and both are considered to be major risk factors for developing cardiac disease ultimately resulting in adverse cardiac events. This clustering of risk factors is potentially due to a common mechanism. Further, patient compliance with the management of hypertension is generally better than patient compliance with hyperlipidemia. It would therefore be advantageous for patients to have a single therapy which treats both of these conditions.

Coronary heart disease is a multifactorial disease in which the incidence and severity are affected by the lipid profile, the presence of diabetes and the sex of the subject. Incidence is also affected by smoking and left ventricular hypertrophy which is secondary to hypertension. To meaningfully reduce the risk of coronary heart disease, it is important to manage the entire risk spectrum. For example, hypertension intervention trials have failed to demonstrate full normalization in cardiovascular mortality due to coronary heart disease. Treatment with cholesterol synthesis inhibitors in patients with and without coronary artery disease reduces the risk of cardiovascular morbidity and mortality.

The Framingham Heart Study, an ongoing prospective study of adult men and women, has shown that certain risk

factors can be used to predict the development of coronary heart disease. (see Wilson et al., Am. J. Cardiol. 1987, 59(14):91G–94G). These factors include age, gender, total cholesterol level, high density lipoprotein (HDL) level, systolic blood pressure, cigarette smoking, glucose intolerance and cardiac enlargement (left ventricular hypertrophy on electrocardiogram, echocardiogram or enlarged heart on chest X-ray). Calculators and computers can easily be programmed using a multivariate logistic function that allows calculation of the conditional probability of cardiovascular events. These determinations, based on experience with 5,209 men and women participating in the Framingham study, estimate coronary artery disease risk over variable periods of follow-up. Modeled incidence rates range from less than 1% to greater than 80% over an arbitrarily selected six year interval. However, these rates are typically less than 10% and rarely exceed 45% in men and 25% in women.

Kramsch et al., Journal of Human Hypertension (1995) (Suppl. 1), 53–59 disclose the use of calcium channel blockers, including amlodipine, to treat atherosclerosis. That reference further suggests that atherosclerosis can be treated with a combination of amlodipine and a lipid lowering agent. Human trials have shown that calcium channel blockers have beneficial effects in the treatment of early atherosclerotic lesions. (see, e.g., Lichtlen, P. R. et al., Retardation of angiographic progression o coronary artery disease by nifedipine, Lancet, 1990, 335, 1109–13; and Waters, D. et al., A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis, Circulation, 1990, 82, 1940–53.) U.S. Pat. No. 4,681,893 discloses that certain statins, including atorvastatin, are hypolipidemic agents and as such are useful in treating atherosclerosis. Jukema et al., Circulation, 1995 (Suppl. 1), 1–197, disclose that there is evidence that calcium channel blockers act synergistically in combination with lipid lowering agents (e.g., HMG-CoA reductase inhibitors), specifically pravastatin. Orekhov et al., Cardiovascular Drugs and Therapy, 1997, 11, 350 disclose the use of amlodipine in combination with lovastatin for the treatment of atherosclerosis.

SUMMARY OF THE INVENTION

This invention is directed to a pharmaceutical composition, hereinafter termed "Composition A", comprising:

a. an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof;

b. an amount of atorvastatin or a pharmaceutically acceptable salt thereof; and

c. a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition AA", of Composition A comprising amlodipine besylate.

This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition AB", of Composition A comprising the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition B", for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater than the sum of the antihypertensive and hypolipidemic effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition com-

prises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition BA", of Composition B wherein said second pharmaceutical composition comprises amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition BB", of Composition BA comprising the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition C", for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater than the sum of the antihypertensive and hypolipidemic effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition CA", of Composition C comprising amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition CB", of Composition CA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition D", for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater than the antihypertensive and hypolipidemic effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition DA", of Composition D comprising amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition DB", of Composition DA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition E", for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from hypertension and hyperlipidemia, which effects are greater than the antihypertensive and hypolipidemic effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition EA", of Composition E wherein said second pharmaceutical composition comprises amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition EB" of Composition EA comprising the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition F", for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering from angina pectoris, which effect is greater than the sum of the antiangina effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition FA", of Composition F comprising amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition FB", of Composition FA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition G", for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering from angina pectoris, which effect is greater than the sum of the antiangina effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition G", of Composition G wherein said second pharmaceutical composition comprises amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition GB", of Composition G comprising the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition H", for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering from angina pectoris, which effect is greater than the antianginal effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical

composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent. acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition HA", of Composition H comprising amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition HB", of Composition HA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition J", for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering from angina pectoris, which effect is greater than the antianginal effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition JA", of Composition J wherein said second pharmaceutical composition comprises amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition JB", of Composition JA comprising the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition K", for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the sum of the antiatherosclerotc effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition KA", of Composition K wherein said second pharmaceutical composition comprises amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition KB", of Composition KA comprising the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a composition, hereinafter termed "Composition KC", of Composition KB wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition KC wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

This invention is also particularly directed to a composition of Composition KB wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

This invention is also particularly directed to a composition of Composition KB wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

This invention is more particularly directed to a composition, hereinafter termed "Composition KD", of Composition KB wherein said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition KD wherein said regression of atherosclerotic plaques occurs in coronary arteries.

This invention is also particularly directed to a composition of Composition KD wherein said regression of atherosclerotic plaques occurs in carotid arteries.

This invention is also particularly directed to a composition of Composition KD wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition L", for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the sum of the antiatherosclerotic effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition LA", of Composition L comprising amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition LB", of Composition LA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a composition, hereinafter termed "LC", of Composition LB wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition LC wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

This invention is also particularly directed to a composition of Composition LC wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

This invention is also particularly directed to a composition of Composition LC wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

This invention is more particularly directed to a composition, hereinafter termed "Composition LD", of Composition LB wherein said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition LD wherein said regression of atherosclerotic plaques occurs in coronary arteries.

This invention is also particularly directed to a composition of Composition LD wherein said regression of atherosclerotic plaques occurs in carotid arteries.

This invention is also particularly directed to a composition of Composition LD wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition M", for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the antiatherosclerotic effects achieved by administering said first or second pharmaceutical composi-

tions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition MA", of Composition M comprising amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition MB", of Composition MA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a composition, hereinafter termed "Composition MC", of Composition MB wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition MC wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

This invention is also particularly directed to a composition of Composition MC wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

This invention is also particularly directed to a composition of Composition MC wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

This invention is more particularly directed to a composition, hereinafter termed "Composition MD", of Composition MB wherein said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition MD wherein said regression of atherosclerotic plaques occurs in coronary arteries.

This invention is also particularly directed to a composition of Composition MD wherein said regression of atherosclerotic plaques occurs in carotid arteries.

This invention is also particularly directed to a composition of Composition MD wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition N", for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is greater than the antiatherosclerotic effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition NA", of Composition N wherein said second pharmaceutical composition comprises amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition, hereinafter termed "Composition NB", of Composition NA comprising the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a composition, hereinafter termed "Composition NC", of Composition NB wherein said antiatherosclerotic effect is manifested by a slowing of the progression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition NC wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

This invention is also particularly directed to a composition of Composition NC wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

This invention is also particularly directed to a composition of Composition NC wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

This invention is more particularly directed to a composition, hereinafter termed "Composition ND", of Composition NB wherein said antiatherosclerotic effect is manifested by a regression of atherosclerotic plaques.

This invention is still more particularly directed to a composition of Composition ND wherein said regression of atherosclerotic plaques occurs in coronary arteries.

This invention is also particularly directed to a composition of Composition ND wherein said regression of atherosclerotic plaques occurs in carotid arteries.

This invention is also particularly directed to a composition of Composition ND wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition P", for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the sum of the cardiac risk management effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable add addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition PA", of Composition P comprising amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition of Composition PA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition Q", for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the sum of the cardiac risk management effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition QA", of Composition Q wherein said second pharmaceutical composition comprises amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition of Composition QA comprising the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition R", for use

with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the cardiac risk management effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition RAD", of Composition R comprising amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition of Composition RA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition S", for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the cardiac risk management effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a first pharmaceutical composition, hereinafter termed "Composition SA", of Composition S wherein said second pharmaceutical composition comprises amlodipine besylate.

This invention is more particularly directed to a first pharmaceutical composition of Composition S comprising the hemicalcium salt of atorvastatin.

This invention is also directed to a kit, hereinafter termed "Kit A", for achieving a therapeutic effect in a mammal comprising:

a. an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;

b. an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and

c. container means for containing said first and second dosage forms.

This invention is particularly directed to a kit, hereinafter termed "Kit M", of Kit A comprising amlodipine besylate.

This invention is more particularly directed to a kit, hereinafter termed "Kit AB", of Kit AA comprising the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a kit, hereinafter termed "Kit AC", of Kit AB wherein said therapeutic effect is treatment of hypertension and hyperlipidemia.

This invention is still more particularly directed to a kit, hereinafter termed "Kit AD", of Kit AB wherein said therapeutic effect is treatment of angina pectoris.

This invention is also particularly directed to a kit, hereinafter termed "Kit AE"of Kit AB wherein said therapeutic effect is management of cardiac risk.

This invention is also particularly directed to a kit, hereinafter termed "Kit AF", of Kit AB wherein said therapeutic effect is treatment of atherosclerosis.

This invention is still more particularly directed to a kit, hereinafter termed "Kit AG", of Kit AF wherein said treatment of atherosclerosis slows the progression of atherosclerotic plaques.

This invention is further directed to a kit, hereinafter termed "Kit AH", of Kit AG wherein said progression of atherosclerotic plaques is slowed in coronary arteries.

This invention is still further directed to a kit, hereinafter termed "Kit AJ", of Kit AG wherein said progression of atherosclerotic plaques is slowed in carotid arteries.

This invention is still further directed to a kit, hereinafter termed "Kit AK", of Kit AG wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

This invention is still further directed to a kit, hereinafter termed "Kit AL", of Kit AF wherein said treatment of atherosclerosis causes the regression of atherosclerotic plaques.

This invention is still further directed to a kit of Kit AL wherein said regression of atherosclerotic plaques occurs in coronary arteries.

This invention is still further directed to a kit of Kit AL wherein said regression of atherosclerotic plaques occurs in carotid arteries.

This invention is still further directed to a kit of Kit AL wherein said regression of atherosclerotic plaques occurs in the peripheral arterial system.

This invention is also directed to a method, hereinafter termed "Method A", for treating a mammal in need of therapeutic treatment comprising administering to said mammal

(a) an amount of a first compound, said first compound being amlodipine or a pharmaceutically acceptable acid addition salt thereof; and

(b) an amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof;

wherein said first compound and said second compound are each optionally and independently administered together with a pharmaceutically acceptable carrier or diluent.

This invention is particularly directed to a method, hereinafter Method B, of Method A comprising amlodipine besylate.

This invention is more particularly directed to a method, hereinafter termed "Method C", of Method B comprising the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a method, hereinafter termed "Method D", of Method A wherein said first compound and said second compound are administered simultaneously.

This invention is still more particularly directed to a method, hereinafter termed "Method E", of Method A wherein said first compound and said second compound are administered sequentially in either order.

This invention is also particularly directed to a method, hereinafter termed "Method F", of Method C wherein said first compound and said second compound are administered simultaneously.

This invention is further directed to a method, hereinafter termed "Method G", of Method C wherein said first compound and said second compound are administered sequentially in either order.

This invention is still further directed to a method of Method A wherein said therapeutic treatment comprises antihypertensive treatment and antihyperlipidemic treatment.

This invention is still further directed to a method of Method F wherein said therapeutic treatment comprises antihypertensive treatment and antihyperlipidemic treatment.

This invention is still further directed to a method of Method G wherein said therapeutic treatment comprises antihypertensive treatment and antihyperlipidemic treatment.

This invention is further directed to a method of Method A wherein said therapeutic treatment comprises antianginal treatment.

This invention is further directed to a method of Method F wherein said therapeutic treatment comprises antianginal treatment.

This invention is further directed to a method of Method G wherein said therapeutic treatment comprises antianginal treatment.

This invention is further directed to a method of Method A wherein said therapeutic treatment comprises cardiac risk management.

This invention is further directed to a method of Method F wherein said therapeutic treatment comprises cardiac risk management.

This invention is further directed to a method of Method G wherein said therapeutic treatment comprises cardiac risk management.

This invention is further directed to a method of Method A wherein said therapeutic treatment comprises antiatherosclerotic treatment.

This invention is further directed to a method of Method F wherein said therapeutic treatment comprises antiatherosclerotic treatment.

This invention is further directed to a method of Method G wherein said therapeutic treatment comprises antiatherosclerotic treatment.

Amlodipine is a racemic compound due to the symmetry at position 4 of the dihydropyridine ring. The R and S enantiomers may be prepared as described by Arrowsmith et al., J. Med. Chem., 1986, 29, 1696. The calcium channel blocking activity of amlodipine is substantially confined to the S(−) isomer and to the racemic mixture containing the R(+) and S(−) forms. (see International Patent Application Number PCT/EP94/02697). The R(+) isomer has little or no calcium channel blocking activity. However, the R(+) isomer is a potent inhibitor of smooth muscle cell migration. Thus, the R(+) isomer is useful in the treatment or prevention of atherosclerosis. (see International Patent Application Number PCT/EP95/00847). Based on the above, a skilled person could choose the R(+) isomer, the S(−) isomer or the racemic mixture of the R(+) isomer and the S(−) isomer for use in the combination of this invention.

Where used herein, the term "cardiac risk", means the likelihood that a subject will suffer a future adverse cardiac event such as, e.g., myocardial infarction, cardiac arrest, cardiac failure, cardiac ischaemia. Cardiac risk is calculated using the Framingham Risk Equation as set forth above. The term "cardiac risk management" means that the risk of future adverse cardiac events is substantially reduced.

DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutical compositions of this invention comprise amlodipine or a pharmaceutically acceptable acid addition salt thereof and/or atorvastatin or a pharmaceutically acceptable salt thereof.

Amlodipine may readily be prepared as described in U.S. Pat. No. 4,572,909 which is incorporated herein by reference. Amlodipine besylate, which is currently sold as Norvasc®, may be prepared as described in U.S. Pat. No. 4,879,303, which is incorporated herein by reference. Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers.

The expression "pharmaceutically-acceptable acid addition salts" is intended to define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, besylate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

Other acid addition salts of amlodipine may be prepared by reacting the free base form of amlodipine with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base of amlodipine and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

Atorvastatin may readily be prepared as described in U.S. Pat. No. 4,681,892, which is incorporated herein by reference. The hemicalcium salt of atorvastatin, which is currently sold as Lipitor®, may readily be prepared as described in U.S. Pat. No. 5,273,995, which is incorporated herein by reference.

The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. The expression "pharmaceutically-acceptable cationic salts" is intended to define but is not limited to such salts as the alkali metal salts, (e.g. sodium and potassium), alkaline earth metal salts (e.g. calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically-acceptable acid addition salts" is intended to define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

Other pharmaceutically-acceptable cationic salts of atorvastatin may be readily prepared by reacting the free add form of atorvastatin with an appropriate base, usually one equivalent in a co-solvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, piperazine and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent In many cases, salts are preferably prepared by mixing a solution of the acid with a solution of a different salt of the cation (e.g., sodium or potassium ethylhexanoate, magnesium oleate) and employing a solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates. The salts may also be isolated by concentrating the reaction solution and/or by adding a non-solvent.

The acid addition salts of atorvastatin may be readily prepared by reacting the free base form of atorvastatin with

the appropriate add. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent

In addition, amlodipine, pharmaceutically acceptable acid addition salts thereof, atorvastatin and pharmaceutically acceptable salts thereof may occur as hydrates or solvates. Said hydrates and solvates are also within the scope of the invention.

The pharmaceutical combinations and methods of this invention are all adapted to therapeutic use as agents in the treatment of atherosclerosis, angina pectoris, and a condition characterized by the presence of both hypertension and hyperlipidemia in mammals, particularly humans. Further, since these diseases and conditions are closely related to the development of cardiac disease and adverse cardiac conditions, these combinations and methods, by virtue of their action as antiatherosclerotic, antianginals, antihypertensives and antihyperlipidemics, are useful in the management of cardiac risk.

The utility of the compounds of the present invention as medical agents in the treatment of atherosclerosis in mammals (e.g. humans) is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

Effect of Amlodipine and Atorvastatin, Alone and in Combination, on the Treatment of Atherosclerosis

This study is a prospective randomized evaluation of the effect of a combination of amlodipine and atorvastatin on the progression/regression of coronary and carotid artery disease. The study is used to show that a combination of amlodipine and atorvastatin is effective in sowing or arresting the progression or causing regression of existing coronary artery disease (CAD) as evidenced by changes in coronary angiography or carotid ultrasound, in subjects with established disease.

This study is an angiographic documentation of coronary artery disease carried out as a double-blind, placebo-controlled trial of a minimum of about 500 subjects and preferably of about 780 to about 1200 subjects. It is especially preferred to study about 1200 subjects in this study. Subjects are admitted into the study after satisfying certain entry criteria set forth below.

Entry criteria: Subjects accepted for entry into this trial must satisfy certain criteria. Thus the subject must be an adult, either male or female, aged 18–80 years of age in whom coronary angiography is clinically indicated. Subjects will have angiographic presence of a significant focal lesion such as 30% to 50% on subsequent evaluation by quantitative coronary angiography (QCA) in a minimum of one segment (non-PTCA, non-bypassed or non-MI vessel that is judged not likely to require intervention over the next 3 years. It is required that thee segments undergoing analysis have not been interfered with. Since percutaneous transluminal cardiac angioplasty (PTCA) interferes with segments by the insertion of a balloon catheter, non-PTCA segments are required for analysis. It is also required that the segments to be analyzed have not suffered a thrombotic event, such as a myocardial infarct (MI). Thus the requirement for non-MI vessels. Segments that will be analyzed include: left main, proximal, mid and distal left anterior descending, first and second diagonal branch, proximal and distal left circumflex, first or largest space obtuse marginal, proximal, mid and distal right coronary artery. Subjects will have an ejection fraction of greater than 30% determined by catheterization or radionuclide ventriculography or ECHO cardiogram at the time of the qualifying angiogram or within the previous three months of the acceptance of the qualifying angiogram provided no intervening event such as a thrombotic event or procedure such as PTCA has occurred.

Generally, due to the number of patients and the physical limitations of any one facility, the study is carried out at multiple sites. At entry into the study, subjects undergo quantitative coronary angiography as well as B-mode carotid artery ultrasonography and assessment of carotid arterial compliance at designated testing centers. This establishes baselines for each subject. Once admitted into the test, subjects are randomized to receive amlodipine besylate (10 mgs) and placebo or atorvastatin calcium (80 mgs) and placebo or amlodipine besylate (10 mgs) and atorvastatin calcium (80 mgs). All doses set forth in this protocol are per day doses. The amount of amlodipine besylate may be varied as required. Generally, a subject will start out taking 10 mg and the amount will be titrated down to as little as 5 mg as determined by the clinical physician. The amount of atorvastatin calcium will similarly be titrated down from 80 mg if it is determined by the physician to be in the best interests of the subject. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of atorvastatin calcium may be used in this invention. Calculation of the dosage amount for these other forms of atorvastatin calcium and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

The subjects are monitored for a one to three year period, generally three years being preferred. B-mode carotid ultrasound assessment of carotid artery atherosclerosis and compliance are performed at regular intervals throughout the study.

Generally, six month intervals are suitable. Typically this assessment is performed using B-mode ultrasound equipment. However, a person skilled in the art may use other methods of performing this assessment. Coronary angiography is performed at the conclusion of the one to three year treatment period. The baseline and post-treatment angiograms and the intervening carotid artery B-mode ultrasonograms are evaluated for new lesions or progression of existing atherosclerotic lesions. Arterial compliance measurements are assessed for changes from baseline and over the 6 month evaluation periods.

The primary objective of this study is to show that the combination of amlodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof reduces the progression of atherosclerotic lesions as measured by quantitative coronary angiography (QCA) in subjects with clinical coronary artery disease. QCA measures the opening in the lumen of the arteries measured.

The primary endpoint of the study is the change in the average mean segment diameter of the coronary artery tree.

Thus, the diameter of an arterial segment is measured at various portions along the length of that segment. The average diameter of that segment is then determined. After the average segment diameter of many segments has been determined, the average of all segment averages is determined to arrive at the average mean segment diameter. The mean segment diameter of subjects taking atorvastatin or pharmaceutically acceptable salts thereof and amlodipine or pharmaceutically acceptable acid addition salts thereof will decline more slowly, will be halted completely, or there will be an increase in the mean segment diameter. These results represent slowed progression of atherosclerosis, halted progression of atherosclerosis and regression of atherosclerosis, respectively.

The secondary objective of this study is to show that the combination of amlodipine or a pharmaceutically acceptable acid addition salt thereof and atorvastatin or a pharmaceutically salt thereof reduces the rate of progression of atherosclerosis in the carotid arteries as measured by the slope of the maximum intimal-medial thickness measurements averaged over 12 separate wall segments (Mean Max) as a function of time, more than does amlodipine or a pharmaceutically acceptable acid addition salt thereof or atorvastatin or a pharmaceutically acceptable salt thereof alone. The intimal-medial thickness of subjects taking atorvastatin or a pharmaceutically acceptable salt thereof and amlodipine or a pharmaceutically acceptable acid addition salt thereof will increase more slowly, will cease to increase or will decrease. These results represent slowed progression of atherosclerosis, halted progression of atherosclerosis and regression of atherosclerosis, respectively.

The utility of the compounds of the present invention as medical agents in the treatment of angina pectoris in mammals (e.g., humans) is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

Effect of Amlodipine and Atorvastatin, Alone and in Combination, on the Treatment of Angina

This study is a double blind, parallel arm, randomized study to show the effectiveness of amlodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof given in combination in the treatment of symptomatic angina.

Entry criteria: Subjects are males or females between 18 and 80 years of age with a history of typical chest pain associated with one of the following objective evidences of cardiac ischemia: (1) stress test segment elevation of about one millimeter or more from the ECG; (2) positive treadmill stress test; (3) new wall motion abnormality on ultrasound; or (4) coronary angiogram with a significant qualifying stenosis. Generally a stenosis of about 30–50% is considered to be significant.

Each subject is evaluated for about ten to thirty-two weeks. At least ten weeks are generally required to complete the study. Sufficient subjects are used in this screen to ensure that about 200 to 800 subjects and preferably about 400 subject are evaluated to complete the study. Subjects are screened for compliance with the entry criteria, set forth below, during a four week run in phase. After the screening criteria are met, subjects are washed out from their current anti-anginal medication and stabilized on a long acting nitrate such as, for example, nitroglycerin, isosorbide-5-mononitrate or isosorbide dinitrate. The term "washed out", when used in connection with this screen, means the withdrawal of current anti-anginal medication so that substantially all of said medication is eliminated from the body of the subject. A period of eight weeks is preferably allowed for both the wash out period and for the establishment of the subject on stable doses of said nitrate. Subjects having one or two attacks of angina per week while on stable doses of long acting nitrate are generally permitted to skip the wash out phase. After subjects are stabilized on nitrates, the subjects enter the randomization phase provided the subjects continue to have either one or two angina attacks per week. In the randomization phase, the subjects are randomly placed into one of the four arms of the study set forth below. After completing the wash out phase, subjects in compliance with the entry criteria undergo twenty four hour ambulatory electrocardiogram (ECG) such as Holter monitoring, exercise stress testing such as a treadmill and evaluation of myocardial perfusion using PET (photon emission tomography) scanning to establish a baseline for each subject. When conducting a stress test, the speed of the treadmill and the gradient of the treadmill can be controlled by a technician. The speed of the treadmill and the angle of the gradient are generally increased during the test. The time intervals between each speed and gradient increase is generally determined using a modified Bruce Protocol.

After the baseline investigations have been completed, subjects are initiated on one of the following four arms of the study: (1) placebo; (2) atorvastatin calcium (about 2.5 mg to about 160 mg); (3) amlodipine besylate(about 2.5 mg to about 20 mg); or (4) a combination of the above doses of amlodipine besylate and atorvastatin calcium together. The subjects are then monitored for two to twenty four weeks. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of atorvastatin calcium may be used in this invention. Calculation of the dosage amount for these other forms of atorvastatin calcium and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

After the monitoring period has ended, subjects will undergo the following investigations: (1) twenty four hour ambulatory ECG, such as Holter monitoring; (2) exercise stress testing (e.g. treadmill using said modified Bruce Protocol); and (3) evaluation of myocardial perfusion using PET scanning. Patients keep a diary of painful ischemic events and nitroglycerine consumption. It is generally desirable to have an accurate record of the number of anginal attacks suffered by the patient during the duration of the test. Since a patient generally takes nitroglycerin to ease the pain of an anginal attack, the number of times that the patient administers nitroglycerine provides a reasonably accurate record of the number of anginal attacks.

To demonstrate the effectiveness of the drug combination of this invention, and to determine the dosage amounts of the drug combination of this invention, the person conducting the test will evaluate the subject using the tests described. Successful treatment will yield fewer instances of ischemic events as detected by ECG, will allow the subject to exercise longer or at a higher intensity level on the treadmill, or to exercise without pain on the treadmill, or will yield better perfusion or fewer perfusion defects on photoemission tomography (PET).

The utility of the compounds of the present invention as medical agents in the treatment of hypertension and hyperlipidemia in mammals (e.g., humans) suffering from a combination of hypertension and hyperlipidemia is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

Effect of Amlodipine and Atorvastatin, Alone and in Combination, on the Treatment of Subjects Having Both Hypertension and Hyperlipidemia

This study is a double blind, parallel arm, randomized study to show the effectiveness of amlodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof given in combination in controlling both hypertension and hyperlipidemia in subjects who have mild, moderate, or severe hypertension and hyperlipidemia.

Each subject is evaluated for 10 to 20 weeks and preferably for 14 weeks. Sufficient subjects are used in this screen to ensure that about 400 to 800 subjects are evaluated to complete the study.

Entry criteria: Subjects are male or female adults between 18 and 80 years of age having both hyperlipidemia and hypertension. The presence of hyperlipidemia is evidenced by evaluation of the low density lipoprotein (LDL) level of the subject relative to certain positive risk factors. If the subject has no coronary heart disease (CHD) and has less than two positive risk factors, then the subject is considered to have hyperlipidemia if the LDL of the subject is greater than or equal to 190. If the subject has no CHD and has two or more positive risk factors, then the subject is considered to have hyperlipidemia if the LDL of the subject is greater than or equal to 160. If the subject has CHD, then the subject is considered to have hyperlipidemia if the LDL of the subject is greater than or equal to 130.

Positive risk factors include (1) male over 45, (2) female over 55 wherein said female is not undergoing hormone replacement therapy (HRT), (3) family history of premature cardiovascular disease, (4) the subject is a current smoker, (5) the subject has diabetes, (6) an HDL of less than 45, and (7) the subject has hypertension. An HDL of greater than 60 is considered a negative risk factor and will offset one of the above mentioned positive risk factors.

The presence of hypertension is evidenced by a sitting diastolic blood pressure (BP) of greater than 90 or sitting systolic BP of greater than 140. All blood pressures are generally determined as the average of three measurements taken five minutes apart.

Subjects are screened for compliance with the entry criteria set forth above. After all screening criteria are met, subjects are washed out from their current antihypertensive and lipid lowering medication and are placed on the NCEP ATP II Step 1 diet. The NCEP ATP II (adult treatment panel, 2nd revision) Step 1 diet sets forth the amount of saturated and unsaturated fat which can be consumed as a proportion of the total caloric intake. The term "washed out" where used in connection with this screen, means the withdrawal of current antihypertensive and lipid lowering medication so that substantially all of said medication is eliminated from the body of the subject. Newly diagnosed subjects generally remain untreated until the test begins. These subjects are also placed on the NCEP Step 1 diet. After the four week wash out and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure and (2) fasting lipid screen. The fasting lipid screen determines baseline lipid levels in the fasting state of a subject. Generally, the subject abstains from food for twelve hours, at which time lipid levels are measured.

After the baseline investigations are performed subjects are started on one of the following: (1) a fixed dose of amlodipine besylate, generally about 2.5 to 10 mg; (2) a fixed dose of atorvastatin calcium, generally about 10 to 80 mg; or (3) a combination of the above doses of amlodipine besylate and atorvastatin calcium together. Subjects remain on these doses for a minimum of six weeks, and generally for no more than eight weeks. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of atorvastatin calcium may be used in this invention. Calculation of the dosage amount for these other forms of atorvastatin calcium and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. The subjects return to the testing center at the conclusion of the six to eight weeks so that the baseline evaluations can be repeated. The blood pressure of the subject at the conclusion of the study is compared with the blood pressure of the subject upon entry. The lipid screen measures the total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apoB, VLDL (very low density lipoprotein) and other components of the lipid profile of the subject. Improvements in the values obtained after treatment relative to pretreatment values indicate the utility of the drug combination.

The utility of the compounds of the present invention as medical agents in the management of cardiac risk in mammals (e.g., humans) at risk for an adverse cardiac event is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

Effects of Amlodipine and Atorvastatin, Alone and in Combination on Subjects at Risk of Future Cardiovascular Events

This study is a double blind, parallel arm, randomized study to show the effectiveness of amlodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof given in combination are effective in reducing the overall calculated risk of future events in subjects who are at risk for having future cardiovascular events. This risk is calculated by using the Framingham Risk Equation. A subject is considered to be at risk of having a future cardiovascular event if that subject is more than one standard deviation above the mean as calculated by the Framingham Risk Equation. The study is used to evaluate the efficacy of a fixed combination of amlodipine and atorvastatin in controlling cardiovascular risk by controlling both hypertension and hyperlipidemia in patients who have both mild to moderate hypertension and hyperlipidemia.

Each subject is evaluated for 10 to 20 weeks and preferably for 14 weeks. Sufficient subjects are recruited to ensure that about 400 to 800 subjects are evaluated to complete the study.

Entry criteria: Subjects included in the study are male or female adult subjects between 18 and 80 years of age with a baseline five year risk which risk is above the median for said subject's age and sex, as defined by the Framingham Heart Study, which is an ongoing prospective study of adult men and women showing that certain risk factors can be used to predict the development of coronary heart disease. The age, sex, systolic and diastolic blood pressure, smoking habit, presence or absence of carbohydrate intolerance, presence or absence of left ventricular hypertrophy, serum cholesterol and high density lipoprotein (HDL) of more than one standard deviation above the norm for the Framingham Population are all evaluated in determining whether a patient is at risk for adverse cardiac event. The values for the risk factors are inserted into the Framingham Risk equation and calculated to determine whether a subject is at risk for a future cardiovascular event.

Subjects are screened for compliance with the entry criteria set forth above. After all screening criteria are met, patients are washed out from their current antihypertensive and lipid lowering medication and any other medication which will impact the results of the screen. The patients are then placed on the NCEP ATP II Step 1 diet, as described above. Newly diagnosed subjects generally remain untreated until the test begins. These subjects are also placed on the NCEP ATP II Step 1 diet. After the four week wash out and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure; (2) fasting; (3) lipid screen; (4) glucose tolerance test; (5) ECG; and (6) cardiac ultrasound. These tests are carried out using standard procedures well known to persons skilled in the art. The ECG and the cardiac ultrasound are generally used to measure the presence or absence of left ventricular hypertrophy.

After the baseline investigations are performed patients will be started on one of the following: (1) a fixed dose of amlodipine (about 2.5 to 10 mg); (2) a fixed dose of atorvastatin (about 10 to 80 mg); or (3) the combination of the above doses of amlodipine and atorvastatin. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of atorvastatin calcium may be used in this invention. Calculation of the dosage amount for these other forms of atorvastatin calcium and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. Patients are kept on these doses and are asked to return in six to eight weeks so that the baseline evaluations can be repeated. At this time the new values are entered into the Framingham Risk equation to determine whether the subject has a lower, greater or no change in the risk of future cardiovascular event.

The above assays demonstrating the effectiveness of amodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof in the treatment of angina pectoris, atherosclerosis, hypertension and hyperlipidemia together, and the management of cardiac risk, also provide a means whereby the activities of the compounds of this invention can be compared between themselves and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

The following dosage amounts and other dosage amounts set forth elsewhere in the specification and in the appendant claims are for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine the dosage amount required for a subject whose weight falls outside the 65 kg to 70 kg range, based upon the medical history of the subject and the presence of diseases, e.g., diabetes, in the subject. All doses set forth herein, and in the appendant claims, are daily doses.

In general, in accordance with this invention, amlodipine besylate is generally administered in a dosage of about 2.5 mg to about 20 mg. Preferably, amlodipine besylate is administered in a dosage of about 5 mg to about 10 mg. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate may be used in this invention. Calculation of the dosage amount for these other forms of or the free base form or other salt forms of amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

In general, in accordance with this invention, atorvastatin is administered in a dosage of about 2.5 mg to about 160 mg. Preferably, atorvastatin is administered in a dosage of about 10 mg to about 80 mg. It will be recognized by a skilled person that the free base form or other salt forms of atorvastatin calcium may be used in this invention. Calculation of the dosage amount for these other forms of or the free base form or other salt forms of atorvastatin calcium is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable carrier or diluent. Thus, the compounds of this invention can be administered either individually or together in any conventional oral, parenteral or transdermal dosage form.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

The combination of this invention may also be administered in a controlled release formulation such as a slow release or a fast release formulation. Such controlled release dosage formulations of the combination of this invention may be prepared using methods well known to those skilled in the art. The method of preferred administration will be determined by the attendant physician or other person skilled in the art after an evaluation of the subject's condition and requirements. The generally preferred formulation of amlodipine is Norvasc®. The generally preferred formulation of atorvastatin is Lipitor®.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, see *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

Pharmaceutical compositions according to the invention may contain 0.1%–95% of the compound(s) of this

invention, preferably 1%–70%. In any event, the composition or formulation to be administered will contain a quantity of a compound(s) according to the invention in an amount effective to treat the condition or disease of the subject being treated.

Since the present invention relates to the treatment of diseases and conditions with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit includes two separate pharmaceutical compositions: amlodipine or a pharmaceutically acceptable acid addition salt thereof and atorvastatin or a pharmaceutically acceptable salt thereof. The kit includes container means for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically the kit includes directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

It should be understood that the invention is not limited to the particular embodiments described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

What is claimed is:

1. A method for treating a mammal suffering from combined hypertension and hyperlipidemia comprising administering to said mammal

(a) an amount of a first compound, said first compound being amlodipine or a pharmaceutically acceptable acid addition salt thereof; and

(b) an amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof;

wherein said first compound and said second compound are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

2. The method of claim **1** comprising amlodipine besylate.

3. The method of claim **2** comprising the hemicalcium salt of atorvastatin.

4. The method of claim **1** comprising the hemicalcium salt of atorvastatin.

5. A method of treating a mammal which has been diagnosed as suffering from hypertension and hyperlipidemia or the risk of hypertension and hyperlipidemia which would benefit from therapy by the combined administration of the active ingredients designated as (a) and (b) below, and therefore administration of both (a) and (b) has been prescribed, which comprises administering to said mammal so diagnosed and prescribed

(1) an amount of a first active ingredient (a), said first active ingredient (a) being amlodipine or a pharmaceutically acceptable acid addition salt thereof; and

(2) an amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof;

wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

6. The method of claim **5** wherein active ingredient (a) is amlodipine besylate.

7. The method of claim **6** wherein active ingredient (b) is the hemicalcium salt of atorvastatin.

8. The method of claim **5** wherein active ingredient (b) is the hemicalcium salt of atorvastatin.

9. A method of treating combined hypertension and hyperlipidemia in a mammal which has been examined for both hypertension and hyperlipidemia by a medical practitioner and diagnosed as in need of therapy for said hypertension and hyperlipidemia by the joint administration of the active ingredients designated as (a) and (b) below, which comprises administering to said mammal

(1) an amount of a first active ingredient (a), said first active ingredient (a) being amlodipine or a pharmaceutically acceptable acid addition salt thereof; and

(2) an amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof;

wherein said first active ingredient (a) and said second active ingredient (b) are administered together in single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

10. The method of claim **9** wherein active ingredient (a) is amlodipine besylate.

11. The method of claim **10** wherein active ingredient (b) is the hemicalcium salt of atorvastatin.

12. The method of claim **9** wherein active ingredient (b) is the hemicalcium salt of atorvastatin.

* * * * *

EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC, PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC and WARNER-LAMBERT EXPORT, LTD.,	)	
Plaintiffs,	)	
v.	)	**C.A. No. 03-209-JJF (Consolidated)**
RANBAXY LABORATORIES LIMITED, and RANBAXY PHARMACEUTICALS INCORPORATED,	)	
Defendants.	)	

FINAL JUDGMENT ORDER

This action having come to trial before the Court, Honorable Joseph J. Farnan, Jr., District Judge presiding; the issues having been heard and a decision having been rendered:

IT IS ORDERED AND ADJUDGED this 3rd day of January, 2006, for the reasons set forth in the Court's Memorandum Opinion dated December 16, 2005, that Judgment shall be entered in favor of plaintiffs Pfizer Inc, Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company LLC and Warner-Lambert Export, Ltd. (collectively "Pfizer") and against defendants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Incorporated (collectively "Ranbaxy") on Pfizer's claims that Ranbaxy has infringed claims 1-4, and 8-9 of United States Patent No. 4,681,893 (the "'893 Patent") and claim 6 of United States Patent No. 5,273,995 (the "'995 Patent"); and it is further,

ORDERED AND ADJUDGED that Judgment shall be entered in favor of Pfizer and against Ranbaxy on all counterclaims alleging noninfringement, invalidity, or unenforceability of the '893 Patent or its patent term extension; and it is further,

ORDERED AND ADJUDGED that Judgment shall be entered in favor of Pfizer and against Ranbaxy on all counterclaims alleging noninfringement, invalidity, or unenforceability of the '995 Patent; and it is further,

ORDERED that pursuant to 35 U.S.C. § 271 (e) (4) (A), the effective date of any approval of Ranbaxy's Abbreviated New Drug Application No. 76-477 shall be a date which is not earlier than the date of expiration of the '893 Patent and its patent term extension (September 24, 2009, with attached six months of pediatric exclusivity ending on March 24, 2010, to which Pfizer is entitled); and it is further,

ORDERED that pursuant to 35 U.S.C. § 271 (e) (4) (A), the effective date of any approval of Ranbaxy's Abbreviated New Drug Application No. 76-477 shall be a date which is not earlier than the date of expiration of the '995 Patent (December 28, 2010, with attached six months of pediatric exclusivity ending on June 28, 2011, to which Pfizer is entitled); and it is further,

ORDERED that pursuant to 35 U.S.C. § 271 (e) (4) (B), defendants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Incorporated, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them or either of them are permanently enjoined from engaging in the manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any product comprising atorvastatin calcium covered by, or the use of which is covered by claims 1-4 and 8-9 of the '893 Patent; and it is further,

ORDERED that pursuant to 35 U.S.C. § 271 (e) (4) (B), defendants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Incorporated, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them

or either of them are permanently enjoined from engaging in the manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any product comprising atorvastatin calcium covered by, or the use of which is covered by claim 6 of the '995 Patent.

Joseph J. Farnan, Jr.
United States District Judge

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

PFIZER INC., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC, and WARNER-LAMBERT EXPORT, LTD.,	:	
Plaintiffs,	:	
v.	:	Civil Action No. 03-209-JJF (Consolidated)
RANBAXY LABORATORIES LIMITED and RANBAXY PHARMACEUTICALS, INC.,	:	
Defendants.	:	

O R D E R

WHEREAS, the Court of Appeals for the Federal Circuit has issued its decision in the above-captioned appeal, affirming-in-part, reversing-in-part, and remanding this matter for modification of the permanent injunction; Pfizer Inc. v. Ranbaxy Laboratories Ltd., 457 F.3d 1284 (Fed. Cir. 2006);

WHEREAS, specifically, the Federal Circuit concluded that United States Patent No. 5,273,995 (the "'995 patent") was invalid for failure to comply with the requirements of 35 U.S.C. § 112, ¶ 4;

NOW THEREFORE, IT IS HEREBY ORDERED that, consistent with the Federal Circuit's decision, the last paragraph of the Final Judgment Order dated January 3, 2006, and entered by the Court on January 4, 2006, enjoining Defendants and others "from engaging in the manufacture, use, offer to sell, or sale within the United

States, or importation into the United States, of any product comprising atorvastatin calcium covered by, or the use of which is covered by claim 6 of the '995 Patent" is **STRICKEN**.

November 7, 2006
DATE

Joseph J. Farnan Jr.
UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

PFIZER INC., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC, and WARNER-LAMBERT EXPORT, LTD.,	:	
Plaintiffs,	:	
v.	:	Civil Action No. 03-209-JJF (Consolidated)
RANBAXY LABORATORIES LIMITED and RANBAXY PHARMACEUTICALS, INC.,	:	
Defendants.	:	

O R D E R

WHEREAS, by Order dated November 7, 2006, the Court modified the Final Judgment Order entered on January 4, 2006, in light of the decision by the Court of Appeals for the Federal Circuit that United States Patent No. 5, 273, 995 (the "'995 patent) is invalid;

WHEREAS, it has come to the Court's attention that further modification of the Final Judgment Order is required;

WHEREAS, because the '995 patent has been declared invalid, a basis no longer exists to support delaying the approval of Ranbaxy's Abbreviated New Drug Application No. 76-477 ("ANDA");

NOW THEREFORE, IT IS FURTHER ORDERED that the sixth paragraph of the Final Judgment Order delaying the effective date

of any approval of Ranbaxy's ANDA until a date not earlier than the expiration of the '995 patent is **STRICKEN**.

November 30 2006
DATE

Joseph J. Farnan Jr.
UNITED STATES DISTRICT JUDGE

EXHIBIT D

RANBAXY

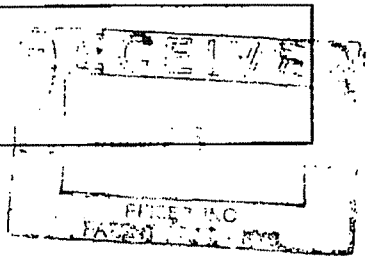
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FACSIMILE COVER SHEET

DATE: January 24, 2007

#OF PAGES: 56
(INCLUDING THIS COVER)

TO: Dr. Peter Richardson
Pfizer, Inc.
FAX NO.: (212) 573-1939



FROM: Jay R. Deshmukh, Esq.
Senior Vice President – Intellectual Property

Re: AMLODIPINE BESYLATE/ATORVASTATIN CALCIUM
ANDA received by the FDA on December 29, 2006
U.S. PATENT NOS.: 4,681,893; 5,273,995; 5,686,104; 5,969,156; 6,126,971; and 6,455,574

Please see attached.

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RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540, PHONE: (609) 720-9200 FAX: (609) 720-1155

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January 24, 2007

VIA FACSIMILE (212) 573-1939
CONFIRMATION VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. Peter Richardson
Senior Assistant General Counsel
and General Patent Counsel
Pfizer, Inc.
Legal Division
150 East 42nd Street, 5th Floor
New York, NY 10017-5755

Re: AMLODIPINE BESYLATE/ATORVASTATIN CALCIUM
ANDA received by the FDA on December 29, 2006
U.S. PATENT NOS.: 4,681,893; 5,273,995; 5,686,104; 5,969,156; 6,126,971; and 6,455,574

Dear Peter:

Pursuant to Section 505(j)(2)(B) of the Food, Drug and Cosmetic Act ("FDCA") and 21 C.F.R. 314.95, you are hereby notified as follows:

(1) Ranbaxy Laboratories Limited ("RLL") has previously submitted and the FDA has received an abbreviated new drug application ("ANDA") under FDCA Section 505(j)(2)(B)(ii) which contains bioavailability or bioequivalence data in order to obtain approval to engage in the commercial manufacture, use or sale of a drug product containing a combination of amlodipine besylate and atorvastatin calcium.

(2) RLL's ANDA referred to in paragraph (1) has not been assigned a number to date, but this will be supplied to you as it is available.

(3) The established name for the drug product is amlodipine besylate; atorvastatin calcium, and the name of the drug product as listed on page 3-26 of the 26th edition of the FDA publication entitled *Approved Drug Products With Therapeutic Equivalence Evaluations (2006)* (the "Orange Book") is Caduet®, equivalent to 2.5 mg, 5 mg and 10 mg of amlodipine

besylate, each of which may be combined with 10 mg, 20 mg, and 40 mg of atorvastatin calcium. Additionally, the 5 mg and 10 mg amlodipine besylate dosages can be combined with 80 mg of atorvastatin, to make 11 different combinations of strengths.

(4) RLL's proposed drug product is in the form of tablets (6 strengths, as follows), which contain the equivalent of 5 mg amlodipine/10 mg atorvastatin, 5 mg amlodipine/20 mg atorvastatin, 10 mg amlodipine/10 mg atorvastatin, 10 mg amlodipine/20 mg atorvastatin, 5 mg amlodipine/40 mg atorvastatin and 10 mg amlodipine/ 80 mg of atorvastatin as the active ingredient.

(5) RLL's ANDA received by the FDA on December 29, 2006 (hereinafter "Ranbaxy's ANDA" or "ANDA", contains a Paragraph III certification with respect to U.S. Patent Nos. 4,572,909 and 4,879,303, indicating that RLL will not launch its product prior to the expiry of these patents. RLL's ANDA also certifies under FDCA Section 505(j)(2)(A)(vii), paragraph IV ("Paragraph IV certification"), that in the opinion of RLL and to the best of its knowledge, U.S. Patent Nos. 4,681,893, 5,273,995, 5,686,104; 5,989,156, 6,126,971 and 6,455,574 are invalid or will not be infringed by the manufacture, use, sale, or offer to sell of the drug product for which RLL's ANDA has been submitted. A detailed statement of factual and legal bases for this opinion follows.

(6) With respect to the Paragraph IV certification made herein with respect to the Patent Term Extension ("PTE") for U.S. Patent No. 4,681,893 ("the '893 Patent"), Ranbaxy makes this certification contingent on the U.S. Supreme Court's acceptance of its petition for certiorari from the Federal Circuit's decision with respect to the PTE for the '893 Patent in Pfizer Inc. et al. v. Ranbaxy Laboratories Ltd., et al. (Fed. Cir. Docket No. 06-1179) decision of August 2, 2006 ("Ranbaxy's petition for cert.").

I. The Term Extension of U.S. 4,681,893 is Invalid Because Warner-Lambert did not Fulfill its Duty to Disclose Material Information

Under 35 U.S.C. §156(d)(4), a Patent Term Extension ("PTE") applicant is required to provide information to enable the Director to determine the eligibility of a patent for an extension. In connection with that requirement, the PTO has imposed a duty of candor and good faith on the applicant requiring the disclosure of information that is material to the grant of a PTE, 37 CFR §1.765. A PTE applicant's duty of disclosure is so critical to the determination of PTE eligibility that an extension will be denied even for a grossly negligent failure to disclose material information.

Charles Ashbrook was the Warner-Lambert attorney responsible for drafting and prosecuting the '893 PTE application. In that application, Mr. Ashbrook asserted that

"U.S. Patent No. 4,681,893 claims Lipitor (atorvastatin calcium)." In connection with that assertion, Mr. Ashbrook violated his duty of candor and good faith by failing to disclose material information.

In particular, to gain allowance of the '995 Patent over rejections based on the prior art '893 Patent, Warner-Lambert made numerous assertions about the '893 Patent, asserting that it neither teaches a person of ordinary skill how to make enantiomers, nor puts them in the possession of enantiomers. Warner-Lambert also candidly stated that the '893 Patent does not enable enantiomers. Such admissions are material *per se*. Additionally, Warner-Lambert distinguished the '893 Patent from atorvastatin calcium by asserting that atorvastatin calcium is not "even hinted at" in the '893 Patent. This emphatic and unconditional admission was clearly material to Mr. Ashbrook's later assertion that the '893 Patent *claims* atorvastatin calcium. Warner-Lambert also repeatedly told the PTO that the '893 Patent does not describe or disclose enantiomers. Moreover, the Board considered all of Warner-Lambert's admissions about the '893 Patent and concluded that the '893 Patent "at best, only describes the trans racemate." Again, Warner-Lambert's admissions and the Board's decision about the sufficiency of the '893 Patent's disclosure are directly relevant to a determination of what the '893 Patent "claims" under § 156.

At the time he filed the '893 PTE application, Mr. Ashbrook was aware of the foregoing admissions and the Board's decision about the '893 Patent, but failed to disclose them to the PTO. Further, Pfizer withheld from the Patent Office the very existence of the '995 patent, which specifically discloses and claims the enantiomer atorvastatin calcium.[1] At trial, Mr. Ashbrook argued that this information was not material because it had no bearing on the scope of the '893 Patent's claims and because the '893 and '995 Patents are not related by a common priority date. But Warner-Lambert's admissions and the Board's conclusion about the '893 Patent are material *per se*, and that the '893 and '995 Patents are not related by a common priority date is irrelevant. While such a distinction may play a role in construing claims for patent infringement purposes, it plays no role in determining what a patent claims or what information is considered to be material under the broad, inclusive duty of disclosure required of PTE applicants. At the very least, Mr. Ashbrook knew or should have known of the materiality of these admissions. Moreover, given the quantity of this information and his intimate awareness of it, Mr. Ashbrook's deliberate withholding of this material information supports a finding of both gross negligence and deceptive intent.

Thus, the '893 PTE is invalid pursuant to 35 U.S.C. §282.

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[1] It is undisputed that Mr. Ashbrook was aware of all of this information, but chose not to submit it in connection with the PTE application.

II. The '893 Patent is Invalid as Obvious in View of EP 179 559

U.S. Patent No. 4,681,893, entitled "TRANS-6-[2-(3- OR 4-CARBOXAMIDO-SUBSTITUTED PYRROLE-1-YL)ALKYL]-4-HYDROXYPYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS," issued on July 21, 1987 to Bruce D. Roth from application serial number 06/868,867 ("the '867 Application"), filed May 30, 1986. The '893 Patent does not claim priority to any foreign or domestic application. The '893 Patent was assigned to Warner-Lambert.

The European counterpart of the '893 Patent (EP 247 633, or "the '633 application") was filed May 29, 1987 and received a first examination report dated April 20, 1989. The Examiner found no inventive step for the claims of the '633 application over EP 179 559, a patent application filed by Warner Lambert listing as inventors Milton L. Hoefle, Bruce D. Roth, and Charlotte D. Stratton.[2] The European Examiner found, *inter alia*, that although the subject matter claimed in the '633 application met the novelty requirement, it was merely an obvious solution to the problem of provision of further 6(pyrrol-1-yl) alkyl pyran-2-one inhibitors of cholesterol synthesis in light of EP 179 559. As the Examiner noted, since EP 179 559 makes clear "that the 3- and 4-positions of the pyrazole [sic] ring can be substituted by a wide variety of substituents, including esters, without leading to a loss of the said pharmaceutical properties," the skilled artisan "would expect that the pyrazole [sic] was susceptible to further substitutions at the 3- and 4-position including other carboxy derivatives such as amides, without leading to a significant change in qualitative properties." The Examiner indicated that if data were presented demonstrating surprising effectiveness over the cited prior art (EP 179 559), the inventive step could be acknowledged.

In a response to this examination report, dated October 12, 1989, Warner-Lambert's representative stated that "[a]pplicants generally accept the Examining Division's arguments saying that a person skilled in the art would expect that the pyrazole [sic] ring was susceptible to further substitutions at the 3- and 4-position including other carboxy derivatives... without leading to a significant change in qualitative properties." Applicants sought to overcome this rejection by presenting "data clearly demonstrating a superior effect of compounds showing the substitution pattern of the present invention in the 3- and 4-positions of the pyrazole [sic] ring. It should be noted that both tested compounds are at least by the factor 10 more effective than the compounds according to EP-A-179 559. This effect is unexpected and was not to be forseen." (Warner-Lambert response of October 12, 1989 to EP examination report of April 20, 1989, emphasis in the original).

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[2] The inventorship of the U.S. Patent which issued from the same family as EP 179 559, U.S. Patent No. 4,647,576, was eventually changed, in August 2003, to list Bruce D. Roth as sole inventor.

The data referred to in the October 12, 1989 response is a comparison of CSI data[3] (presumably generated as set forth in the '633 application) generated from the sodium salts of compounds in the '633 application (compounds 1 and 3 from Table 1) with four hydroxy acid compounds of EP 179 559. However, the CSI data generated by Warner-Lambert with respect to at least the compounds of the '633 application is unreliable. The CSI assay is concentration based; that is, the IC_{50} values[4] used to measure the activity of the test compound in the system were calculated based on a concentration curve. As noted by expert witnesses for both Ranbaxy and Pfizer in litigations in a number of jurisdictions, it is not be possible to quantify the results of the CSI assay without knowing the concentration of the test compound in the assay solution.

When reviewed in its entirety, the CSI data has extensive variability. For example, experiments run three weeks apart had an eighty fold variation in activity for racemic atorvastatin calcium. This variability is so large it is not possible to draw scientifically valid conclusions from any of the CSI data. Thus, the CSI values for compound 1 of the '893 application (0.035 micromolar) presented in the specification, and for the same compound presented in the European prosecution history of the '633 application (0.001 micromolar) show a difference which is three and a half times more than the purported difference between that compound and the prior art compound of EP 179 559.

The '893 patent claims are invalid as obvious over the disclosure of EP 179 559.[5] Compounds disclosed in claim 1 of the '893 patent, as admitted by Warner-Lambert in the prosecution of the counterpart '633 application, do not show inventive step over EP 179 559. The data relied upon by Warner-Lambert to ultimately gain issuance of their EP patent is unreliable. Claim 2 of the '893 patent does not add any patentable subject matter, as EP 179 599 discloses a "first preferred subgeneric chemical compound aspect," with X as $-CH_2CH_2-$ Claim 3 of the '893 patent does not add any patentable subject matter, as EP 179 599 discloses a "second preferred subgeneric chemical compound aspect," with R_1 as claimed. Claim 4 of the '893 patent does not add any patentable subject matter, as EP 179 599 discloses that R_4, in a second preferred subgeneric chemical compounds aspect, is alkyl of from one to four carbon atoms or trifluoromethyl. The definition of one to four carbon atoms is within the claimed range of from one to six carbon atoms, and the claim is otherwise obvious for the reasons given above. Claim 5 of the '893 patent is again obvious over the disclosure of EP 179 559. Compound 1 disclosed in claim 5 of the '893 patent, as admitted by Warner-Lambert in the prosecution

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[3] Although the EP public record indicates that the data is COR data, in fact it is CSI data, as stipulated to by Pfizer in prior litigation (*Pfizer et al. v. Ranbaxy et al.*, in the U.S. District Court for the District of Delaware).

[4] IC_{50} value refers to the concentration of the test compound that produced fifty percent inhibition of the conversion of radiolabeled acetate to radioactive cholesterol.

[5] We further note that neither EP 179 559, nor any member of that application family was cited to the U.S. Examiner, so that the U.S. Examiner did not have an opportunity to review the patentability of claims to the '893 patent in light of the art confronted by Warner-Lambert in the European prosecution.

of the counterpart '633 application, does not show inventive step over EP 179 559. The data relied upon by Warner-Lambert to ultimately gain issuance of the claim to compound 1 in the EP prosecution is unreliable. Claim 6 of the '893 patent is again obvious over the disclosure of EP 179 559. Compound 2 disclosed in claim 6 of the '893 patent, as admitted by Warner-Lambert in the prosecution of the counterpart '633 application, does not show inventive step over EP 179 559. The data relied upon by Warner-Lambert to ultimately gain issuance of the claim to compound 2 in the EP prosecution is unreliable. Claim 7 of the '893 patent is again obvious over the disclosure of EP 179 559. Compound 3 disclosed in claim 7 of the '893 patent, as admitted by Warner-Lambert in the prosecution of the counterpart '633 application, does not show inventive step over EP 179 559. The data relied upon by Warner-Lambert to ultimately gain issuance of the claim to compound 3 in the EP prosecution is unreliable. Claim 8 of the '893 patent does not add any patentable subject matter, as EP 179 559 discloses the use of its compounds in pharmaceutical compositions, in hypercholesterolemic effective amounts. Claim 9 of the '893 patent does not add any patentable subject matter, as EP 179 559 discloses the use of its compounds in methods for inhibiting cholesterol biosynthesis through administration of pharmaceutical compositions, in hypercholesterolemic effective amounts.

Section 103 of the Patent Act focuses on differences between subject matter sought to be patented and the prior art. The Supreme Court's traditional approach looks to whether a person having ordinary skill in the art would have been capable of adapting extant technology to achieve a desired result, not whether such a person would have had motivation to adapt extant technology to achieve a desired result. *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1960). Under *Sakraida* and *Anderson's-Black*, where an alleged invention is "an assembly of old elements," the court's inquiry goes to whether the claimed invention "only unites old elements with no change in their respective functions," or whether there is some interaction of combined elements with each other to yield a "new or different function" or "an effect greater than the sum of the several effects taken separately." Sakraida, 425 U.S. at 282. If there is no such function or effect, the claimed invention is obvious under 35 U.S.C. §103, and no further analysis is needed. Analysis of the existence of some "teaching, suggestion or motivation" that would have led a person of ordinary skill in the art to combine the relevant teachings in the manner claimed has no basis in the text of Section 103 and conflicts with Supreme Court precedent.[6] Where the situation is vitally altered between the time of the first judgment and the second, the prior determination may not be conclusive. For example, a judicial declaration intervening between the two proceedings may so change the legal atmosphere as to render the rule of collateral estoppel inapplicable. *Wilson v. Turnage*, 791 F.2d 151 (Fed. Cir. 1986). For at least the last 25 years, the Court of Appeals for the Federal Circuit, and U.S. District Courts have consistently required an analysis of teaching, suggestion or motivation as part of the test for obviousness although it is not statutorily recognized as such. A change in

[6] This same position is argued by Petitioners in *KSR International Co. v. Teleflex Inc. et al.* (Supreme Court Docket No. 04-1350).

controlling precedent to reduce or eliminate the role of these factors would constitute a significant change in the legal atmosphere of obviousness in patent law.

Here, the use of a carboxamide group in compounds of EP 179 559 was well within the capability of a person of ordinary skill in the art, and was directed to achieving further effective HMG-CoA reductase inhibitors. EP 179 559 in fact itself contains compounds containing such linkages, a fact which was apparently not appreciated by the European Examiner. (Compound XLI, in Reaction Sequence 8, page 25). There is no indication that the carboxamido group employed in the compounds of the '633 patent has any function other than the functions that carboxamido groups are known to have.

Consequently, all claims of the '893 patent are invalid over EP 179 599.

III. All Claims of U.S. Patent No. 5,273,995 Are Invalid or are not infringed

The Claims of the '995 patent

The claims are set forth below.

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

(2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; or

pharmaceutically acceptable salts thereof.

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

3. A compound of claim 1 which is (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

4. The monosodium salt of the compound of claim 2.

5. The monopotassium salt of the compound of claim 2.

6. The hemicalcium salt of the compound of claim 2.

7. The N-methylglucamine salt of the compound of claim 2.

8. The hemimagnesium salt of the compound of claim 2.

9. The hemizinc salt of the compound of claim 2.

10. The 1-deoxy-1-(methylamino)-D-glucitol mixture with the compound of claim 2.

11. A pharmaceutical composition for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

12. A method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia comprising administering a compound of claim 1 in unit dosage form.

A. <u>All claims of the '995 patent are Invalid for Anticipation or are obvious Over U.S. 4,681,893 or are not infringed</u>

As construed by the Federal Circuit in *Pfizer Inc. et al. v. Ranbaxy Laboratories Ltd.*, et al., 457 F.3d 1284 (Fed. Cir. 2006), U.S. 4,681,893 ("the '893 Patent") discloses both the racemate and the enantiomers of atorvastatin. Specifically, the court held that claim 1 of the '893 patent is correctly construed to include the enantiomeric trans-forms of the compounds of structural formula I. Under the Federal Circuit's construction, Compound I of the '893 Patent discloses the three possible stereo-forms of atorvastatin: the racemate, the S-trans enantiomer, the R-trans enantiomer (atorvastatin lactone) and unequal mixtures of enantiomers. Furthermore, the '893 Patent discloses acid and salt forms of Formula I, and states that "acids may be converted to a corresponding pharmaceutically acceptable salt by conventional means, if desired..." Thus, the '893 Patent anticipates claim 6 of the '995 Patent, because it discloses atorvastatin in its hemicalcium salt form.

Other particular metal salt claims (claim 4, to the monosodium salt; claim 5, to the monopotassium salt; claim 8, to the hemimagnesium salt; and claim 9, to the hemizinc salt) are also invalid for the same reasons, by anticipating disclosure in the '893 Patent, but these are also not infringed by the Ranbaxy product, which does not contain such compounds. Claim 7 to the methylglucamine salt, a standard, well-known and readily available amine salt, is *prima facie* obvious. The '893 Patent discloses various pharmaceutically acceptable *amine* salts of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, including salts with ammonium and organic nitrogenous bases strong enough to form salts with carboxylic acids. Claim 7 is also not infringed by the Ranbaxy product as it does not contain such compounds. Claim 10, to a mixture with 1-deoxy-1-(methylamino)-D-glucitol, a standard, well-known and readily available amine derivative of sorbitol in admixture with the heptanoic acid form of the enantiomer of claim 1, is also *prima facie* obvious, for reasons similar to those presented for claim 7. Further, as Ranbaxy's proposed formulation does not include a mixture of any atorvastatin with a 1-

deoxy-1-(methylamino)-D-glucitol, Ranbaxy, additionally, does not infringe this claim of the '995 Patent.

Claim 11 of the '995 Patent, drawn to a pharmaceutical composition for treating hypercholesterolemia comprising an effective amount of either the lactone or the heptanoic acid form of the enantiomer of claim 1, is also anticipated. The '893 Patent discloses pharmaceutical compositions for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide and a pharmaceutically acceptable carrier. In view of the claim construction of the '893 Patent, the use of the enantiomer in such a composition is anticipated.

Claim 12 of the '995 Patent, drawn to a method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia by administering an effective amount of either the lactone or the heptanoic acid form of the enantiomer of claim 1, is also anticipated. The '893 Patent discloses methods for inhibiting cholesterol synthesis in humans suffering from hypercholesterolemia by administering the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide in unit dosage form. The use of the enantiomer in such a composition is anticipated.

B. <u>The '995 is Invalid for Double Patenting Over U.S. 5,003,080 in view of the '893 Patent</u>

Claims 12 and 14 of U.S. 5,003,080 ("the '080 Patent") define a process, as well as the products prepared by that process. The three claim construction issues regarding claims 12 and 14 are: (1) the identity of the lactones that fall within the scope of Formula Ia depicted in claim 12; (2) whether claim 14 incudes all of the process steps of claim 12, thereby producing atorvastatin lactone and its acid and salts; and (3) the meaning of the phrase "pharmaceutically acceptable salts."

Claim 12 of the '080 Patent recites, in part: "A process for the preparation of the compound of Formula Ia [structural depiction] and the hydroxy acid and pharmaceutically acceptable salts thereof, ..." Claim 12 also contains two lettered paragraphs delineated (a) and (b). Step (a) affords "the compound of Formula Ia," which is in the lactone form. Step (b) recites three substeps: (1) "and if desired, converting the resulting compound of Formula Ia to a hydroxy acid" by "conventional hydrolysis," (2) "and further, if desired, converting the hydroxy acid to a corresponding pharmaceutically acceptable salt by conventional means," and (3) "if so desired, converting the hydroxy acid to a compound of Formula Ia." When the lactone of Formula Ia is atorvastatin lactone, the process of claim 12 also produces atorvastatin acid and pharmaceutically acceptable salts of atorvastatin.

Claim 14, which depends from claim 12, recites, "A process according to claim 12 and for the preparation of [atorvastatin lactone]." This dependent claim incorporates all limitations of its antecedent claim, including process step (b) of claim 12. Thus, claim 14 is a process for preparing atorvastatin lactone, and if desired, atorvastatin acid and, if desired, its corresponding pharmaceutically acceptable salts. Construction of the phrase "pharmaceutically acceptable salts," as defined in the patent, means (1) metal salts formed with sodium, potassium, calcium, magnesium, aluminum, iron and zinc ions, and (2) amine salts formed with ammonia and organic nitrogenous bases. Therefore, claim 14 as properly construed, expressly recites the atorvastatin calcium salt (among other salts). Further, since the '893 Patent teaches that each of the lactone compounds of Formula I may be converted to pharmaceutically acceptable salts, and names calcium as one such suitable metal salt for such conversion, there is no patentable distinction between claims of the '995 Patent and claim 14 of the '080 patent, in view of the '893 Patent disclosure.

Thus, claims 1-3 of the '995 Patent are obvious in light of the express recitation of the process to make the subject matter of each of claims 1-3, in claims 12 and 14 of the '080 Patent. Also, claims 4-9 of the '995 Patent, which recite various salts of compounds, are all obvious in light of the express recitation of the processes to make the subject matter of each of claims 4-9, in claims 12 and 14 of the '080 Patent. Claim 10, to the mixture of 1-deoxy-1-(methylamino)-D-glucitol and the compound of claim 2 is not infringed by Ranbaxy's proposed atorvastatin/amlodipine tablets.

Claim 11 of the '995 Patent, drawn to a pharmaceutical composition for treating hypercholesterolemia comprising an effective amount of either the lactone or the heptanoic acid form of the enantiomer of claim 1, is also invalid for double patenting over the '080 Patent in light of the disclosure of the '893 Patent. The '893 Patent discloses pharmaceutical compositions for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide and a pharmaceutically acceptable carrier. In view of the claim construction of the '893 Patent, the use of the enantiomer in such a composition is obvious from the process of making the material in claims 12 and 14 of the '080 Patent.

Claim 12 of the '995 Patent, drawn to a method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia by administering an effective amount of either the lactone or the heptanoic acid form of the enantiomer of claim 1, is also invalid for double patenting over the '080 Patent in light of the disclosure of the '893 Patent. The '893 Patent discloses methods for inhibiting cholesterol synthesis in humans suffering from hypercholesterolemia by administering the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide in unit dosage form. The use of the enantiomer in such a method of therapy is obvious from the process of making the material in claims 12 and 14 of the '080 Patent.

C. The '995 is Unenforceable for Inequitable Conduct

During prosecution of the application for the '995 Patent, Warner-Lambert withheld highly material information concerning its own earlier patents and their subject matter and misrepresented the cholesterol inhibition activity of the compounds at issue. The inequitable conduct determination is a two-step analysis. First the court must determine whether the accused conduct (1) concerns information that satisfies a threshold level of materiality and (2) involves culpability that satisfies a threshold level of intent to mislead. Second, once the threshold levels of materiality and intent have been established, the trial court is required to weigh materiality and intent.

1. Warner-Lambert Improperly Withheld Activity Data from the Patent Office

Warner-Lambert withheld highly material activity data from the Patent Office with deceptive intent. This activity data falls into two categories: (1) results from in vivo experiments ("AICS data"), and (2) results from in vitro experiments ("CSI data").

The AICS data were material, not cumulative, and contained results that directly refuted assertions made for patentability of the compounds claimed in the '995 Patent. Warner-Lambert has argued repeatedly that the R isomer of atorvastatin claimed in the '995 Patent has ten times the activity of the prior art compounds of the earlier '893 Patent. The AICS data show precisely the opposite of Warner-Lambert's arguments, that the activity level of the R isomer was, in fact, two times that of the racemic mixture, just as a chemist would have expected. Warner-Lambert's own internal documents, prepared before and after the filing of the '995 application, demonstrate that Warner-Lambert and the '995 inventor, Dr. Roth, believed that the AICS data were correct in showing only a two-fold difference. The deceptive intent is clearly inferable from the fact that Dr. Roth withheld the AICS data and made an argument for patentability which could not have been made had the information been disclosed. Also, his conscious misrepresentation of the data as "surprising and unexpected" when he had used the AICS data in memoranda bearing his signature to draw the opposite conclusion, constituted clear and convincing evidence of an intentional misrepresentation.

The CSI data were material, not cumulative, and contained results that directly refuted assertions made for patentability of the compounds claimed in the '995 Patent. The undisclosed CSI data directly refute Warner-Lambert's repeated assertions of an "unexpected" "ten times" difference in activity between the R isomer of atorvastatin and the racemic compounds. But even the disclosed CSI data had to be carefully manipulated to support those assertions. Dr. Roth admitted that a Warner-Lambert Vice President directed him to search for data showing the R isomer to have surprising and unexpected data over the racemate. Dr. Roth then searched his personal binder and selected data to show surprising and unexpected activity. Dr. Roth withheld other CSI data inconsistent with that activity. This behavior constitutes clear and convincing evidence that Dr. Roth intended to mislead and deceive the Patent Office.

Based on the same information referred to above, Justice Young of the Federal Court of Australia, on December 20, 2006, revoked Australian Patent No. 628198 (analogous to the '995 patent and having essentially the same specification), having reached the following conclusions:

"(a) The statements in the specification for the Enantiomer Patent that represented that Warner-Lambert had found that the R-trans enantiomer achieved surprising and unexpected inhibition of the biosynthesis of cholesterol in the order of a ten-fold increase above the activity levels of the racemate were false and misleading.

(b) The representation in the specification for the Enantiomer Patent that the results in the CSI table reflected all of the CSI data available to Warner-Lambert for the relevant compounds, and that the data as a whole provided reasonable grounds for the findings set forth in the CSI Table, were false and misleading.

(c) The representation by Warner-Lambert to the Patent office in its patent attorney's letter of 26 June 1992 that the R-trans isomer was ten times more active than its racemic mixture was false and misleading."

In reaching the above Conclusions, Justice Young found that:

> "Dr. Roth's evidence that the CSI data was perfectly fine and he saw no problems with it is not credible. I reject it. I carefully observed Dr. Roth in the course of his evidence. I formed the opinion that in relation to the CSI Table he was defending his own choice of data and, in effect, arguing Warner-Lambert's case rather than giving frank evidence. Moreover, the evidence he gave was not consistent with Warner-Lambert's own internal records, as detailed below."

Ranbaxy's position in regards to unenforceability due to withholding data has been fully vindicated by the Australian decision as is clear from the quotations above.

2. <u>Warner-Lambert Improperly Withheld All Information About the '080 Patent</u>

Before Warner-Lambert filed the application for the '995 Patent, it had already applied for the '080 Patent, and a CIP application. The CIP application expressly claimed processes for making enantiomers identical to those Warner-Lambert later claimed in the '995 patent application. No information of record disclosed the enantiomers, and thus the CIP application was not cumulative. The claims presented in the CIP application undeniably teach one of ordinary skill in the art to use the recited process to make the recited enantiomers. Thus, those claims render obvious the '995 patent application's claims to the same enantiomers. Moreover, when two co-pending patent applications have

overlapping content in their specifications and claims, then the earlier is highly material to the prosecution of the latter because it could conceivably serve as the basis for a double-patenting rejection. Because the CIP application and the '080 patent were highly material, deceptive intent may properly be inferred from commensurately less circumstantial evidence. However, overwhelming evidence shows that Drs. Roth and Daignault (Warner-Lambert's in-house patent attorney) knew of the CIP application and the '080 patent while prosecuting the '995 application, and knew or should have known of their materiality.

D. Claim 6 of the '995 Patent has been Held Invalid Under 35 U.S.C. §112, ¶4.

As held by the Court of Appeals for the Federal Circuit in *Pfizer Inc. et al. v. Ranbaxy Laboratories Ltd.*, et al. (Fed. Cir. Docket No. 06-1179) decision of August 2, 2006, claim 6 of the '995 Patent is invalid for failure to comply with 35 U.S.C. §112, ¶4, as an improperly dependent claim. Accordingly, there can be no infringement of this claim.

For the same reason that claim 6 was held invalid, claims 4, 5 and 7-9 are also invalid.

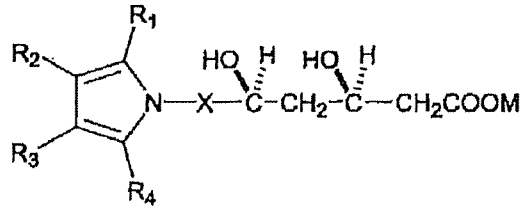
IV. U.S. Patent No. 5,686,104 Is Not Infringed

U.S. Patent No. 5,686,104 ("the '104 patent") entitled "Stable Oral CI-981 Formulation and Process of Preparing Same" issued on November 11, 1997. This patent contains a total of 22 claims, of which claims 1, 14, 15, and 21 are independent, while claims 2-5, 7-13, 16-20 and 22 are dependent claims. Claims 2-13 depend directly or indirectly from claim 1, claims 16-20 depend from claim 15, and claim 22 depends from claim 21.

The Claims

Claims 1, 14, 15 and 21 are reproduced below.

> 1. A pharmaceutical composition for the peroral treatment of hypercholesterolemia or hyperlipidemia characterized by improved stability comprising in a mixture, a compound as active ingredient of structural formula I



wherein X is —CH_2—, —CH_2CH_2—, —$CH_2CH_2CH_2$— or —$CH_2CH(CH_3)$;

R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl, norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with flourine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoylalkoxy of from two to eight carbon atoms;

either R_2 or R_3 is --$CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

R_4 is alkyl of from one to six carbon atoms, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or trifluoromethyl;

M is a pharmaceutically acceptable metal salt;

at least one stabilizing pharmaceutically acceptable alkaline earth metal salt additive;

and comprising by weight of the total solid composition at least one binder selected from the group consisting of methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol, starch, and hydroxymethylcellulose comprising by weight between about 0.5% and about 6%;

at least one diluent selected from the group consisting of microcrystalline cellulose, hydrous lactose, cornstarch, sucrose, and silicic anhydride comprising by weight between about 1% and about 80%;

at least one disintegrant selected from the group consisting of carboxymethylcellulose, croscarmellose and starch comprising by weight between about 1% and about 15%;

at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer comprising by weight between about 0.1% and about 4%;

at least one lubricant selected from the group consisting of magnesium stearate, stearic acid, palmitic acid, and talc comprising by weight between about 0.25% and about 2%;

and optionally at least one antioxidant selected from the group consisting of butylated hydroxanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, and ascorbic acid comprising by weight up to about 3%. (emphasis added to analyzed claim terms)

14. A stabilized solid pharmaceutical composition for peroral treatment of hypercholesterolemia or hyperlipidemia comprising in solid unit dosage form an active ingredient R-(R*,R*)-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)- 3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt and *a stabilizer selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide* and comprising by weight of the total solid composition at least one binder selected from the group consisting of methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol, starch, and hydroxymethylcellulose comprising by weight between about 0.5% and about 6%;

at least one diluent selected from the group consisting of microcrystalline cellulose, hydrous lactose, cornstarch, sucrose, and silicic anhydride comprising by weight between about 1% and about 80%;

at least one disintegrant selected from the group consisting of carboxymethylcellulose, croscarmellose and starch comprising by weight between about 1% and about 15%;

at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer comprising by weight between about 0.1% and about 4%;

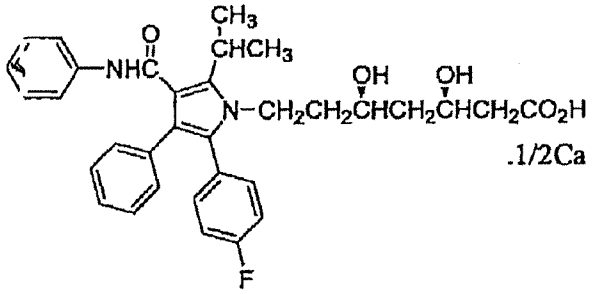
at least one lubricant selected from the group consisting of magnesium stearate, stearic acid, palmitic acid, and talc comprising by weight between about 0.25% and about 2%;

and optionally at least one antioxidant selected from the group consisting of butylated hydroxanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, and

ascorbic acid comprising by weight up to about 3%. (emphasis added to analyzed claim terms)

15. A method for preparing a stabilized pharmaceutical composition formulated for peroral therapy of hypercholesterolemia or hyperlipidemia comprising:

(a) milling an excess of the drug, Cl-981 Hemi-Calcium of the formula IA:



(b) *dissolving at least one binder additive in aqueous surfactant solution*;

(c) blending the milled drug with *at least one drug-stabilizing alkaline earth metal salt additive* and at least one diluent additive ingredient with the drug-stabilizing additive and one half of a disintegrant additive in a rotary mixing vessel equipped with a chopping device;

(d) granulating the blended drug mixture of step (c) with the surfactant/binder solution of step (b) in gradual increments in the chopper equipped mixing vessel;

(e) drying the granulated drug mixture overnight at about 50° C.;

(f) sieving the dried granulated drug mixture;

(g) tumble blending the sieved drug mixture with the remaining amount of the disintegrant additive;

(h) mixing separately an aliquot of the step (g) drug mixture with magnesium stearate, sieving same, and returning same to the drug mixture of step (g) and tumble blending the entire drug mixture; and compressing aliquots of the step (h) drug mixture into tablets. (emphasis added to analyzed claim terms)

21. A peroral pharmaceutical composition for treating hypercholesterolemia comprising an effective, cholesterol synthesis inhibitory amount of the enantiomer R-(R*,R*)-2(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3- phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, hemicalcium salt; *stabilized by calcium carbonate*, and comprising by weight of the total solid composition at least one binder selected from the group consisting of methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol, starch, and hydroxymethylcellulose comprising by weight between about 0.5% and about 6%;

at least one diluent selected from the group consisting of microcrystalline cellulose, hydrous lactose, cornstarch, sucrose, and silicic anhydride comprising by weight between about 1% and about 80%;

at least one disintegrant selected from the group consisting of carboxymethylcellulose, croscarmellose and starch comprising by weight between about 1% and about 15%;

at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer comprising by weight between about 0.1% and about 4%;

at least one lubricant selected from the group consisting of magnesium stearate, stearic acid, palmitic acid, and talc comprising by weight between about 0.25% and about 2%;

and optionally at least one antioxidant selected from the group consisting of butylated hydroxanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, and ascorbic acid comprising by weight up to about 3%, in a dosage of solid enantiomer ranging from about 0.1 to about 8.0 mg/kg body weight per day. (emphasis added to analyzed claim terms)

RLL's Formulation

RLL has developed a specific formulation of tablets containing amorphous atorvastatin calcium and amlodipine besylate, having approximately 5 mg amlodipine besylate combined with 10 mg, 20 mg and 40 mg of atorvastatin calcium; and approximately 10 mg, amlodipine besylate combined with 10 mg, 20 mg and 80 mg of atorvastatin calcium.

Non-Infringement Analysis

RLL does not literally infringe any claim of the '104 Patent because RLL's proposed formulation does not employ an "alkaline earth metal salt additive." Claims 1-13 and 15-20 of the 104 patent require a stabilized pharmaceutical composition or a method for preparing a stabilized pharmaceutical composition where the composition contains a "stabilizing alkaline earth metal salt additive" or a more specific such additive. The only alkaline earth metal salt additive proposed for use by RLL is magnesium stearate. However, magnesium stearate is specifically defined in the '104 patent as a lubricant and, therefore, cannot be an "alkaline earth metal salt additive."

More specifically, each of the ingredients of the core of the RLL tablets can be readily accounted for in the '104 patent, with the exception of mannitol, sodium carbonate, colloidal silicon dioxide, and sodium laurel sulfate. The mannitol serves as a diluent, colloidal silicon dioxide serves as a disintegrant while the sodium lauryl sulfate serves as a surfactant.

The sodium carbonate and sodium lauryl sulfate, as used in RLL's formulation, are sodium salts. Sodium an alkali metal and is located in Group I of the Periodic Table of the Elements; it is therefore monovalent. Sodium is not an alkaline earth metal. Alkaline earth metals are in Group II of the Periodic Table of the Elements and are divalent. Thus, RLL's proposed formulation cannot be considered to contain an "alkaline earth metal salt additive" as required by claims 1-13 and 15-20 of the '104 patent. Therefore, it does not literally infringe any of claims 1-13 or 15-20 of the '104 patent.

As noted above, claim 14 of the '104 patent is limited to a stabilized pharmaceutical composition having a stabilizer "selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide." RLL's proposed formulation does not include any of these stabilizers, which are all alkaline earth metal salts. Thus, RLL's proposed formulation does not literally infringe claim 14 of the '104 patent.

As noted above, claim 21 is limited to a stabilized pharmaceutical composition stabilized by "calcium carbonate," and claim 22 is limited to a method of treatment comprising a dosage of the pharmaceutical composition of claim 21. RLL's proposed formulation does not include calcium carbonate, which is an alkaline earth metal salt. Thus, RLL's proposed formulation does not literally infringe claims 21 or 22 of the '104 patent.

Further, RLL's proposed formulation does not infringe claims 1-14, 17 or 21-22 of the '104 Patent because it does not employ the surfactant polyoxyethylene sorbitan or the polyoxyethylene-polyoxypropylene copolymer. Claims 1-14, 17 and 21-22 of the '104 patent are limited to a stabilized pharmaceutical composition or a method for preparing a

stabilized pharmaceutical composition where the composition contains at least one surfactant selected from the group consisting of polyoxyethylene sorbitan [Tween 80] and polyoxyethylene-polyoxypropylene copolymer. RLL's proposed formulation does not include either of these surfactants. Thus, RLL's proposed formulation does not literally infringe any of claims 1-14, 17 or 21-22 of the '104 patent.

RLL's proposed formulation does not infringe claims 15-20 of the '104 Patent because it does not employ aqueous surfactant solutions. Claims 15-20 of the '104 patent recite a method of preparing a stabilized pharmaceutical composition and require the steps of "dissolving at least one binder additive in aqueous surfactant solution." RLL's proposed process does not involve dissolving a binder, or any other additive, in an aqueous surfactant solution. RLL's proposed process for manufacturing atorvastatin calcium/amlodipine besylate tablets does not literally infringe claims 15-20 of the '104 patent.

Doctrine of Equivalents

RLL's proposed process and formulation for atorvastatin calcium/amlodipine besylate tablets does not infringe any claim of the '104 patent under the doctrine of equivalents. The scope of the claims of the '104 patent may not be broadened under the doctrine of equivalents to cover the use of sodium carbonate, or the use of a known alternative surfactant such as sodium lauryl sulfate.

The patentee is estopped from asserting that sodium carbonate is an equivalent metal salt additive. Originally filed claim 1 described a pharmaceutical composition containing "at least one stabilizing pharmaceutically acceptable metal salt additive." In response to a Section 112, first paragraph, rejection of claim 1, the applicants for the '104 Patent clearly narrowed claim 1 so that it recited "at least one stabilizing pharmaceutically acceptable *alkaline earth* metal salt additive."

Originally filed claim 16 (issued claim 15) described a method for preparing a stabilized pharmaceutical composition that required the step of "blending the milled drug with at least one drug-stabilizing additive." In response to a Section 112, first paragraph, rejection of claim 16, the applicants for the '104 Patent clearly narrowed claim 16 so that it recited "blending the milled drug with at least one drug-stabilizing *alkaline earth metal salt* additive."

The scope of original claims 1 and 16 may have covered sodium carbonate as a "metal salt additive" as recited in original claim 1 or as an "additive" as recited in original claim 16.[7] However, in response to a rejection of claims 1 and 16, the applicants for the

[7] However, there is no support in the '104 patent to provide written description or enablement of sodium carbonate as a 'stabilizing" additive. Furthermore, there is no evidence to suggest that sodium carbonate exhibits the ability to "stabilize" atorvastatin.

'104 Patent voluntarily narrowed their claims to cover only an "alkaline earth metal salt additive." Thus, the patentee has surrendered coverage of sodium carbonate as an equivalent of an "alkaline earth metal salt additive."

Furthermore, the patentee cannot overcome this presumption of surrender. The patentee is estopped because the use of sodium carbonate in a solid pharmaceutical dosage form was well known as of the filing date of the '919 application. For example, U.S. Patent No. 4,976,949 to Mayer et al. describes the use of sodium carbonate in a solid pharmaceutical dosage form.

The patentee is also estopped from asserting that sodium lauryl sulfate is an equivalent surfactant. In response to a § 103 rejection, applicants for the '104 Patent narrowed originally filed claims 1, 13 and 20 (issued as claims 1, 14 and 21) by amending them to require "*at least one surfactant.*" These claims, as first amended, may have covered the use of sodium lauryl sulfate as a surfactant. However, the Examiner maintained the rejection of these claims in the second Office Action, and in response, applicants for the '104 Patent further narrowed claims 1, 13, and 20 so that they recited "at least one surfactant *selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer.*" Thus, the patentee has surrendered coverage of sodium lauryl sulfate as an equivalent of a "surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer."

Furthermore, the patentee cannot overcome this presumption. The patentee is estopped because the use of sodium lauryl sulfate as a surfactant in a solid pharmaceutical dosage form was well known as of the filing date of the '919 application. For example, U.S. Patent No. 4,963,509 to Radebaugh et al. describes the use of sodium laurel sulfate in a solid pharmaceutical dosage form.

Accordingly, the doctrine of prosecution history estoppel prevents the patentee from proving that RLL's proposed formulation of amorphous atorvastatin calcium/amlodipine besylate tablets or RLL's proposed method for manufacturing amorphous atorvastatin calcium/amlodipine besylate tablets infringe any claim of the '104 patent under the doctrine of equivalents.

Accordingly, the drug product for which RLL is seeking approval to market in the ANDA received by the FDA on December 29, 2006 does not infringe any claim of the '104 Patent.

V. U.S. Patent No. 5,969,156 Is Not Infringed

U.S. Patent No. 5,969,156 ("the '156 patent") entitled "Crystalline [R-(R*,R*)]-2-(4-difluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Atorvastatin)," issued on October 19, 1999. This patent contains a total of 44 claims, of which claims 1-9, and 28-44 are

independent, while claims 10-27 are dependent claims. Claims 10 and 11 depend from claim 1, claims 12 and 13 depend from claim 2, claims 14 and 15 depend from claim 3, claims 16 and 17 depend from claim 4, claims 18 and 19 depend from claim 5, claims 20 and 21 depend from claim 6, claims 22 and 23 depend from claim 7, claims 24 and 25 depend from claim 8, and claims 26 and 27 depend from claim 9.

The Independent Claims

Claims 1–5 are independent claims directed to crystalline Form I atorvastatin hydrate characterized by its X-ray powder diffraction spectral characteristics. These claims recite:

> 1. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 11.9 or 22.0.
>
> 2. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 11.9, 21.6 and 22.0.
>
> 3. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 17.1, 19.5 and 21.6.
>
> 4. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 9.2, 9.5, 10.3, 10.6, 11.9, 12.2, 17.1, 19.5, 21.6, 22.0, 22.7, 23.3, 23.7, 24.4, 28.9 and 29.2.
>
> 5. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 9.150, 9.470, 10.266, 10.560, 11.853, 12.195, 17.075, 19.485, 21.626, 21.960, 22.748, 23.335, 23.734, 24.438, 28.915 and 29.234.

Claims 6–9 are independent claims directed to crystalline Form I atorvastatin hydrate characterized by its solid-state ^{13}C NMR spectral characteristics. These claims recite:

> 6. A crystalline Form I atorvastatin hydrate characterized by solid state ^{13}C nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 5.1 or 51.8.
>
> 7. A crystalline Form I atorvastatin hydrate characterized by solid state ^{13}C nuclear magnetic resonance and having the following

chemical shift differences between the lowest ppm resonance and other resonances: 3.9, 5.1, 43.6, 46.8, 49.2 and 51.8.

8. A crystalline Form I atorvastatin hydrate characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 3.9, 5.1, 18.9, 20.6, 26.1, 43.6, 46.8, 49.2, 51.8, 92.5, 96.9, 99.6, 102.2, 106.3, 108.2, 109.8, 113.6, 115.7, 138.0, 145.4, 157.1 and 161.5.

9. A crystalline Form I atorvastatin hydrate characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3. 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.

Claims 28–31 are independent claims claiming crystalline Form II atorvastatin hydrate characterized by X-ray powder diffraction and recite:

28. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 9.0 and 20.5.

29. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 8.5 and 9.0.

30. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 5.6, 7.4, 8.5, 9.0, 12.4 (broad), 15.8 (broad), 17.1–17.4 (broad), 19.5, 20.5, 22.7–23.2 (broad), 25.7 (broad) and 29.5.

31. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 5.582, 7.384, 8.533, 9.040, 12.440 (broad), 15.771 (broad), 17.120-17.360 (broad), 19.490, 20.502, 22.706–23.159 (broad), 25.697 (broad) and 29.504.

Claims 32–35 are independent claims directed to crystalline Form II atorvastatin hydrate characterized by its solid-state ^{13}C NMR spectral characteristics. These claims recite:

32. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid state ^{13}C nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 4.7 or 47.8.

33. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 4.7, 44.5, 45.2, 46.2 and 47.8.

34. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 4.7, 17.4, 18.9, 19.5, 20.6, 44.5, 45.2, 46.2, 47.8, 91.9, 92.9, 94.3, 96.2, 97.5, 98.6, 100.1, 106.2, 110.5, 112.0, 117.7, 138.2, 140.2 and 158.2.

35. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 22.8 (broad), 27.5, 40.2, 41.7, 42.3, 43.4, 67.3, 68.0, 69.0, 70.6, 114.7, 115.7, 117.1, 119.0, 120.3, 121.4, 122.9, 129.0, 133.3, 134.8, 140.5, 161 (broad), 163 (broad) and 181 (broad).

Claims 36–40 are independent claims directed to crystalline Form IV atorvastatin hydrate characterized by its X-ray powder diffraction spectral characteristics. These claims recite:

36. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 8.0 or 9.7.

37. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 4.9, 8.0 and 9.7.

38. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 8.0, 9.7 and 19.6.

39. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 4.9, 5.4, 5.9, 8.0, 9.7, 10.4, 12.4, 17.7, 18.4, 19.2, 19.6, 21.7, 23.0, 23.7 and 24.1.

40. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 4.889, 5.424, 5.940, 7.997, 9.680, 10.416, 12.355, 17.662, 18.367, 19.200, 19.569, 21.723, 23.021, 23.651 and 24.143.

Claims 41–44 are independent claims directed to crystalline Form IV atorvastatin hydrate characterized by its solid-state ^{13}C NMR spectral characteristics. These claims recite:

> 41. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid state ^{13}C nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 3.0 or 53.6.
>
> 42. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 1.5, 2.4, 8.0, 45.6, 48.4, 50.0 and 53.6.
>
> 43. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 1.5, 2.4, 8.0, 22.1, 24.2, 25.5, 28.2, 45.6, 48.4, 50.0, 53.6, 97.8, 101.9, 104.8, 109.2, 111.3, 116.8, 120.2, 141.1, 148.2, 161.4, 163.5, 167.0 and 168.5.
>
> 44. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 17.9, 19.4, 20.3, 25.9, 40.0, 42.1, 43.4, 46.1, 63.5, 66.3, 67.9, 71.5, 115.7, 119.8, 122.7, 127.1,129.2, 134.7, 138.1 (broad), 159.0 (broad), 166.1 (broad), 179.3, 181.4, 184.9 and 186.4.

The written description of the '156 Patent provides X-ray powder diffraction and solid-state CP-MAS ^{13}C-NMR data for crystalline Forms I, II, and IV of atorvastatin calcium, as well as experimental procedures for producing atorvastatin calcium in each of these three crystalline forms. The written description emphasizes the distinctions between amorphous atorvastatin, admittedly disclosed in several prior art U.S. patents, and crystalline Form I atorvastatin.

During prosecution of the '156 Patent, the applicants distinguished the claimed crystalline forms of atorvastatin from amorphous atorvastatin on the ground that in diffractograms of amorphous atorvastatin there was the absence of any distinct x-ray powder diffraction lines. Applicants also asserted that the claimed chemical shift combinations are unique for each of the crystal forms. Declarations presented to the Patent Office used x-ray powder diffraction data, observations regarding tablet preparations, and stability determinations to further distinguish the claimed crystalline forms of atorvastatin from amorphous atorvastatin.

Non-Infringement Analysis

X-ray powder diffraction spectra of RLL's amorphous atorvastatin calcium are presented as Exhibit A. For these measurements, the powder was filled into an aluminum holder by the side-drift method and exposed to CuKα radiation (45 kV x 40 mA) in a wide-angle X-ray powder diffractometer (Model D5005), Siemens). The instrument was operated in the step-scan mode, in increments of 0.05°2Θ. The angular range was 5 to 40°2Θ and counts were accumulated for 1 sec at each step. The data collection program used was JADE 5.0. The resulting powder patterns of amorphous atorvastatin calcium indicate that the samples are amorphous

Thus, a straightforward comparison between RLL's amorphous atorvastatin and the subject matter of the independent claims of the '156 Patent reveals that RLL's amorphous atorvastatin is not crystalline, i.e., it does not fall within the literal meaning of the independent claims of the '156 Patent.

Doctrine of Equivalents

RLL's amorphous atorvastatin also does not infringe any claim of the '156 Patent under the doctrine of equivalents. Based on the arguments advanced by applicants during prosecution of the '156 Patent, RLL's amorphous atorvastatin could not infringe this patent under the doctrine of equivalents. This conclusion is based on determinations that the scope of the claims of the '156 Patent may not effectively be broadened under the doctrine of equivalents to cover material in the prior art.

Accordingly, the drug product for which RLL is seeking approval to market in the ANDA received by the FDA on December 29, 2006 does not infringe any claim of the '156 Patent.

VI. U.S. Patent No. 6,126,971 Is Not Infringed

U.S. Patent No. 6,126,971 ("the '971 patent") entitled "Stable Oral CI-981 Formulation and Process for Preparing Same" issued on October 3, 2000. This patent contains a total of 19 claims, of which claims 1, 4, 7, 8, 13, 16, and 17 are independent, while claims 2-3, 5-6, 9-12, 14-15 and 18-19 are dependent claims. Claims 2-3 depend directly or indirectly from claim 1, claims 5-6 depend directly or indirectly from claim 4, claims 9-12 depend directly from claim 8, claims 14-15 depend directly or indirectly from claim 13, and claims 18-19 depend directly from claim 17.

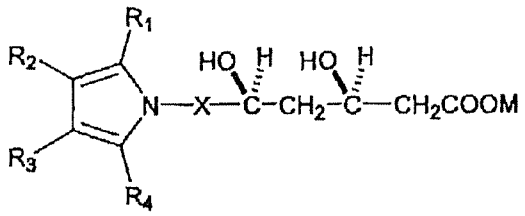
The Independent Claims

Independent claim 1 of the '971 patent recites a composition, as follows:

1. A pharmaceutical composition for the peroral treatment of hypercholesterolemia or hyperlipidemia characterized by improved stability comprising

in a mixture, about 1% to about 50% by weight of the composition of a compound as active ingredient of structural formula I

formula I



wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2\ CH(CH_3)$[;]

R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl, norbornenyl; 2-,3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoylalkoxy of from two to eight carbon atoms;

either R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-,3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

R_4 is alkyl of from one to six carbon atoms, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or trifluoromethyl;

M is a pharmaceutically acceptable metal salt; and

about 5% to about 75% by weight of the composition of calcium carbonate to stabilize the composition.

Claim 1 therefore requires, *inter alia*, that the pharmaceutical composition comprise about 5% to about 75% by weight of the specific salt calcium carbonate.

Independent claim 4 of the '971 patent recites a composition, as follows:

4. A pharmaceutical composition characterized by improved stability comprising in a mixture, about 1% to about 50% by weight of the composition of a pharmaceutically acceptable metal salt of [R-R*,R*)]-2-

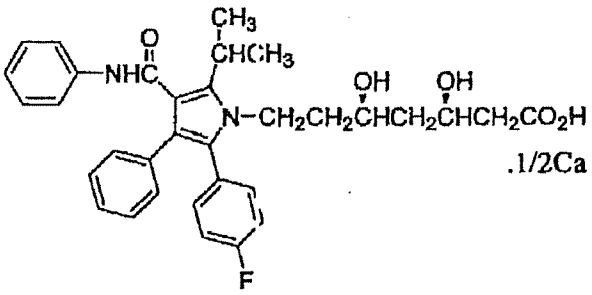
(4-fluorophenyl-β, Λ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid; *and about 5% to about 75% by weight of the composition of calcium carbonate* to stabilize the composition.

Claim 4, like claim 1, therefore requires, *inter alia*, that the pharmaceutical composition comprise about 5% to about 75% by weight of the specific salt calcium carbonate.

Independent claim 7 of the '971 patent recites a composition, as follows:

7. A pharmaceutical composition characterized by improved stability comprising in a mixture, the Hemi-Calcium of Formula (IA):

(IA)



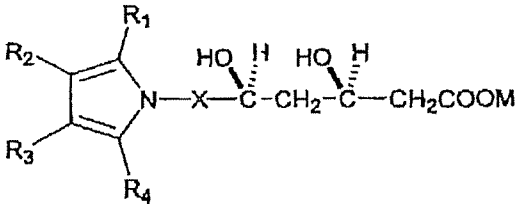
and an effective amount of calcium carbonate.

Claim 7, like claims 1 and 4, therefore requires, *inter alia*, that the pharmaceutical composition comprise the salt calcium carbonate. However, unlike claims 1 and 4, claim 7 requires "an effective amount" of calcium carbonate rather than a specific weight percent.

Independent claim 8 of the '971 patent recites a method of improving stability of a composition, as follows:

8. A method of improving the stability of a pharmaceutical composition comprising as an active ingredient a compound having the structural formula I

formula I



wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2\ CH(CH_3)$;

R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl, norbornenyl; 2-,3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoylalkoxy of from two to eight carbon atoms;

either R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-3- or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

R_4 is alkyl of from one to six carbon atoms, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or trifluoromethyl;

M is a pharmaceutically acceptable metal salt;

by adding an effective amount of an alkaline earth metal salt to the composition.

Claim 8 therefore requires a step of adding an amount of an alkaline earth metal salt sufficient to enhance the stability of the pharmaceutical composition.

Independent claim 13 of the '971 patent also recites a method of improving stability of a composition, as follows:

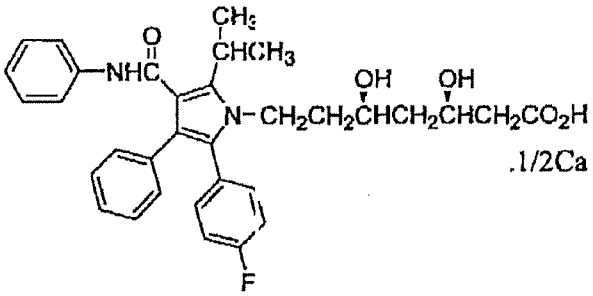
> 13. *A method* of improving the stability of a pharmaceutical composition by adding *an effective amount of calcium carbonate* to a composition comprising a pharmaceutically acceptable metal salt of [R-R*,R*)]-2-(4-fluorophenyl-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1 heptanoic acid.

Claim 13 therefore requires a step of adding an amount of the specific salt calcium carbonate sufficient to enhance the stability of the pharmaceutical composition.

Independent claim 16 of the '971 patent also recites a method of improving stability of a composition, as follows:

> 16. *A method* of improving the stability of a pharmaceutical composition by *adding an effective amount of calcium carbonate* to a composition comprising the Hemi-Calcium of Formula (IA):

(IA)

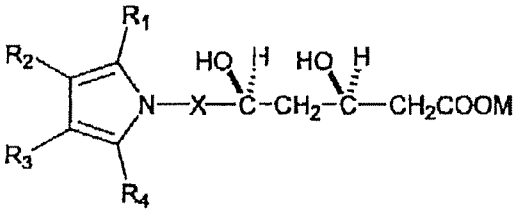


Claim 16, like claim 13, therefore requires a step of adding an amount of the specific salt calcium carbonate sufficient to enhance the stability of the pharmaceutical composition.

Independent claim 17 of the '971 patent recites a composition, as follows:

> 17. A pharmaceutical composition for the peroral treatment of hypercholesterolemia or hyperlipidemia characterized by improved stability comprising in a mixture, about 1% to about 50% by weight of the composition of a compound as active ingredient of structural formula I

formula I



wherein X is --CH_2--, --CH_2CH_2--, --$CH_2CH_2CH_2$-- or --$CH_2CH(CH_3)$[;]

> R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl, norbornenyl; 2-,3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine,

hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoylalkoxy of from two to eight carbon atoms;

either R_2 or R_3 is --$CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-,3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

R_4 is alkyl of from one to six carbon atoms, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or trifluoromethyl;

M is a pharmaceutically acceptable metal salt; and

about 5% to about 75% by weight of the composition of at least one stabilizing pharmaceutically acceptable calcium or lithium salt additive.

Claim 17 therefore requires, *inter alia*, that the pharmaceutical composition comprise about 5% to about 75% by weight of the a stabilizing pharmaceutically acceptable salt that is either a calcium salt or a lithium salt.

In sum, as noted above, each of these independent claims requires the inclusion or the use of either the specific salt calcium carbonate (claims 1, 4, 7, 13 and 16), a calcium or lithium salt (claim 17), or a "alkaline earth metal salt" (claim 8).

Non-Infringement Analysis

RLL's proposed formulation does not literally infringe any claim of the '971 Patent because it does not employ an "alkaline earth metal salt additive," a "calcium or lithium salt additive," or the specific salt "calcium carbonate."

Claim 8 of the '971 patent require the step of adding "an alkaline earth metal salt." The only alkaline earth metal salt additive proposed for use by RLL is magnesium stearate. However, magnesium stearate is specifically defined in the '971 patent as a lubricant and, therefore, cannot be an "alkaline earth metal salt additive." *See*, '104 patent, col. 13, lines 6-9 ("Magnesium stearate can be selected from a group including other substances such as stearic acid, palmitic acid, talc or similar lubricating compounds.").

More specifically, each of the ingredients of the core of the RLL tablets can be readily accounted for in the '971 patent, with the exception of mannitol, sodium carbonate, colloidal silicon dioxide, and *sodium* lauryl sulfate. The mannitol serves as a diluent, colloidal silicon dioxide serves as a disintegrant while the sodium lauryl sulfate serves as a surfactant.

The sodium carbonate and sodium lauryl sulfate, as used in RLL's formulation, are sodium salts. Sodium an alkali metal and is located in Group I of the Periodic Table of the Elements; it is therefore monovalent. Sodium is not an alkaline earth metal, which are in Group II of the Periodic Table of the Elements and are divalent. Thus, RLL's proposed formulation cannot be considered to contain an "alkaline earth metal salt additive" as required by claims 1-13 and 15-20 of the '104 patent. Therefore, it does not literally infringe claim 8 or the claims that depend from it (claims 9 and 10).

As noted above, claim 17 of the '971 patent is limited to a pharmaceutical composition at least one "stabilizing pharmaceutically acceptable calcium or lithium salt." RLL's proposed formulation does not include any of such salt. Thus, RLL's proposed formulation does not literally infringe claim 17 or those claims that depend from it (claims 18 and 19).

As also noted above, claims 1, 4, 7, 13 and 16 are each limited to the inclusion or use of "calcium carbonate." RLL's proposed formulation does not include calcium carbonate, which is a specific alkaline earth metal salt. Thus, RLL's proposed formulation does not literally infringe claims 1, 4, 7, 13 or 16 of the '104 patent, or those claims that depend from any of them.

Doctrine of Equivalents

RLL's proposed process and formulation for atorvastatin calcium/amlodipine besylate tables does not infringe any claim of the '104 patent under the doctrine of equivalents. The scope of the claims of the '104 patent may not effectively be broadened under the doctrine of equivalents to cover the use of sodium carbonate, the use of a known alternative surfactant such as sodium lauryl sulfate, or a wholly solid-phase formulation method.

The patentee is estopped from asserting that sodium carbonate is an equivalent metal salt additive. As originally filed in the parent '919 application, claim 1 described a pharmaceutical composition containing "at least one stabilizing pharmaceutically acceptable metal salt additive." In response to a Section 112, first paragraph, rejection of claim 1, Mills et al. clearly narrowed claim 1 so that it recited "at least one stabilizing pharmaceutically acceptable *alkaline earth* metal salt additive."

Claim 16, as originally filed in the parent '919 application, described a method for preparing a stabilized pharmaceutical composition that required the step of "blending the milled drug with at least one drug-stabilizing additive." In response to a Section 112, first

paragraph, rejection of claim 16, Mills et al. clearly narrowed claim 16 so that it recited "blending the milled drug with at least one drug-stabilizing *alkaline earth metal salt* additive."

The scope of original claims 1 and 16 may have covered sodium carbonate as a "metal salt additive" as recited in original claim 1 or as an "additive" as recited in original claim 16.[8] However, in response to a rejection of claims 1 and 16, Mills et al. voluntarily narrowed their claims to cover only an "alkaline earth metal salt additive." Thus, under *Festo*, the patentee would be presumed to have surrendered coverage of sodium carbonate as an equivalent of an "alkaline earth metal salt additive." Moreover, while literal coverage of a "pharmaceutically acceptable . . . lithium salt additive" was regained in the child '982 application by virtue of claim 17, no such literal coverage was obtained for sodium salts such a sodium carbonate.

Furthermore, the patentee cannot overcome this presumption of surrender. The patentee is estopped because the use of sodium carbonate in a solid pharmaceutical dosage form was well known as of the filing date of the '919 application. For example, U.S. Patent No. 4,976,949 to Mayer et al. (entitled "Controlled Release Dosage Form" and issued December 11, 1990) describes the use of sodium carbonate in a solid pharmaceutical dosage form. Accordingly, the patentee will not be able to prove that the RLL compound infringes any claim of the '971 patent under the doctrine of equivalents.

Accordingly, the drug product for which RLL is seeking approval to market in the ANDA received by the FDA on December 29, 2006 does not infringe any claim of the '971 Patent.

VIII. U.S. Patent No. 6,455,574 is Invalid

The '574 Patent discloses methods of treating hypertension and hyperlipidemia by administering a single pharmaceutical composition comprising amlodipine and atorvastatin. The '574 Patent contains a total of 12 claims. Claims 1, 5 and 9 are independent.

Claim 1 is directed to a method for treating a mammal suffering from combined hypertension and hyperlipidemia. Claim 1 of the '872 Patent recites:

> 1. A method for treating a mammal suffering from combined hypertension and hyperlipidemia comprising administering to said mammal
>
> (a) an amount of a first compound, said first compound being

[8] However, there is no support in the '104 patent to provide written description or enablement of sodium carbonate as a "stabilizing" additive. Furthermore, there is no evidence to suggest that sodium carbonate exhibits the ability to "stabilize" atorvastatin.

amlodipine or a pharmaceutically acceptable acid addition salt thereof; and

(b) an amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof

wherein said first compound and said second compound are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Claim 5 is directed to a method of treating a mammal which has been diagnosed as suffering from hypertension and hyperlipidemia or the risk of hypertension and hyperlipidemia. Claim 5 of the '574 Patent recites:

5. A method of treating a mammal which has been diagnosed as suffering from hypertension and hyperlipidemia or the risk of hypertension and hyperlipidemia which would benefit from therapy by the combined administration of the active ingredients designated as (a) and (b) below, and therefore administration of (a) and (b) has been prescribed, which comprises administering to said mammal so diagnosed and prescribed an amount of a first active ingredient

(a), said first active ingredient (a) being amlodipine or a pharmaceutically acceptable acid addition salt thereof; and an amount of a second active ingredient

(b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof;

wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Claim 9 is directed to a method of treating combined hypertension and hyperlipidemia in a mammal which has been examined for both hypertension and hyperlipidemia. Claim 9 of the '574 Patent recites:

9. A method of treating combined hypertension and hyperlipidemia in a mammal which has been examined for both hypertension and hyperlipidemia by a medical practitioner and diagnosed as in need of therapy for said hypertension and hyperlipidemia by the joint administration of the active ingredients designated as (a) and (b) below, which comprises administering to said mammal

(1)an amount of a first active ingredient (a), said first active ingredient

(a) being amlodipine or a pharmaceutically acceptable acid addition salt thereof; and

(2) an amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof;

wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Claims 2 and 4 depend from claim 1. Claims 2 and 4 recite:

2. The method of claim 1, comprising amlodipine besylate.

4. The method of claim 1, comprising the hemicalcium salt of atorvastatin.

Claim 3 depends from claim 2, and recites:

3. The method of claim 2 comprising the hemicalcium salt of atorvastatin.

Dependent claims 6, 8 and 10 and 12 are identical to dependent claims 2 and 4 except that they depend from claim 5 and 9, respectively, instead of from claim 1. Likewise, dependent claims 7 and 11 are identical to dependent claim 3 except that they depend from claims 5 and 10 instead of from claim 2. Dependent claims 2-4, 6-8, and 10-12 specifically limit the compounds to amlodipine besylate or the hemicalcium salt of atorvastatin.

The '574 Patent states that hypertension and hyperlipidemia "frequently coexist" and may share a common mechanism. Without referencing a particular source, the '574 Patent continues, stating that patient compliance with hypertension therapies is generally better than with hyperlipidemia therapies, and concludes that "[i]t would therefore be advantageous for patients to have a single therapy which treats both of these conditions."

The '574 Patent issued from U.S. Application No. 09/512,914 (the '914 Application), filed February 25, 2000, which is a continuation of Application No. PCT/IB98/01225, filed August 11, 1998, which claims priority to U.S. Provisional Application No. 60/057,275 (the '275 Application) filed August 29, 1997.

Applicants responded to a Restriction Requirement on February 5, 2001, electing claims drawn to generic methods of treatment. Applicants also elected claims drawn to methods of treating hypertension and hyperlipidemia with traverse, and cancelled

nonelected claims. Applicants added independent claims which notably, unlike the originally filed method claims, left out the limitation that the composition produces an effect greater than the effect achieved when either compound is administered separately.

Applicants filed a Supplemental Information Disclosure Statement ("IDS") on March 26, 2001. Applicants revealed that an ongoing study of cardiovascular morbidity/mortality, funded by Pfizer ("the ASCOT study"), had been "underway from some years but the final results [were not] expected for several more years." According to Applicants, the study involved "the administration of amlodipine and atorvastatin." ASCOT was being conducted in foreign countries.

Applicants also revealed that in May 1997, Dr. Peter Sever presented posters describing the ASOCT trial at the WHO/ISH Blood Pressure Lowering Trialists' Collaboration Symposium in France. Applicants submitted these posters with the IDS. One poster described the evaluation of synergistic effects on total coronary or cardiovascular events from the use of atorvastatin and amlodipine. Applicants also submitted a press kit by Pfizer dated May 1997, that formally announced the ASCOT Trial. Applicants noted that the May 1997 activities were less than one year prior to the effective filing date of August 29, 1997, of the '914 Application.

Applicants further disclosed a July 3, 1996 letter from Peter Sever sent to all members of the British Hypertension Society ("BHS"). According to Applicants, the letter generally described a presentation by Sever during which he would formally announce the ASCOT study. The actual presentation was held on September 16, 1996. Applicants argued that although the presentation likely included a description of the evaluation of the use of atorvastatin and amlodipine in the ASCOT study, Sever's presentation did not occur in the U.S., nor was it more than a year prior to Applicants' August 29, 1997 claimed priority date.

Applicants argued that none of the above activities affected the patentability of the claims, since they did not describe the work of another. Specifically, Applicants asserted that the ASCOT study was funded by Pfizer and the art describing the ASCOT studies described the inventions of Jan Buch and Robert Scott, the named inventors on the '914 Application.

Applicants proceeded to describe the results of an investigation into the origination of the combination of amlodipine and atorvastatin for use in ASCOT. Applicants stated that Pfizer employees, with several organizations in the UK and Sweden, "proposed studies to assess the long term effects on coronary heart disease of different antihypertensive regimens, cholesterol lowering agents and antiplatelet therapy." According to Applicants, a December 3, 1993 proposal by BHS suggested evaluation of a "statin (unspecified) and a calcium channel blocker (e.g. amlodipine)." Applicants also noted that the use of amlodipine in combination with a statin, *e.g.*, lovastatin and simvastatin, for antiatherosclerotic effects had also been proposed.

Although Applicants' response did not discuss any dates, Applicants discussed the organization of the ASCOT trial, including the choice of atorvastatin and amlodipine as the compounds to be used in the trial. According to Applicants, the suggestion of atorvastatin was first recorded in notes and minutes of a study meeting attended by Dr. Buch and Dr. Sever, among others. One of the documents listed in Applicants' IDS was a letter from Dr. Sever and Professor Dahlof of ASCOT, neither of whom are named inventors on the '914 application, dated March 4, 1996. The letter was addressed to Robin Kingswell at Parke-Davis and enclosed details of the ASCOT trial, and indicated that the use of atorvastatin in ASCOT was originally proposed by the British Hypertension Society. Applicants stated that they had "investigated the true origin of this proposal and...concluded that the suggestion actually was based on the information and proposal provided to Dr. Sever by Dr. Jan Buch." Thus, Applicants urged that the letter and presentation did not describe the work of another, and was not available as prior art under 35 U.S.C. §102(a) or (b).

In response to an Office Action of October 25, 2001, in "Amendments to the Present claims," Applicants disclosed that prior to Applicants' earliest filing date, Warner-Lambert had conducted clinical trials to test the safety and efficacy of atorvastatin as a hypolipidemic agent. Applicants noted some patients in the clinical trial may have been taking amlodipine for hypertension, and that it was possible that atorvastatin may have been administered to these patients. Applicants stressed that some individuals that were not hypertensive may have been taking amlodipine, and also that some individuals may have been hypertensive and taking anti-hypertensive therapeutics other than amlodipine. Applicants urged that if individuals had taken atorvastatin at the same time as amlodipine, the "administration [was] not prescribed by anyone with knowledge of the present invention or by anyone intending to take advantage of the benefits discovered by applicants." Applicants argued that in contrast to the situation where "some patients in the United States may by chance have ingested separate doses of both amlodipine and atorvastatin within a given span of time, this was accidental and not prescribed pursuant to any diagnosis made by a medical practitioner specifically aware of the advantages of joint administration of the two specific drugs. . .as taught in the present application and seeking to provide those advantages to the patient."

Applicants then addressed the availability of the Warner-Lambert atorvastatin trial as prior art. Without addressing the possibility that the Warner Lambert trial expressly meets each and every limitation of Applicants' claims, Applicants insisted that assuming that there was no confidentiality agreement regarding the trials, the trials should be analyzed under the theory of anticipation by inherency. Applicants argued that in establishing anticipation by inherency, the Examiner's burden of establishing that the characteristic as to which the prior art is silent must necessarily, inevitably and always be present is very high. According to Applicants, any chance separate administration of amlodipine was not inevitably and always practiced in the trial. Thus, Applicants urged, chance administration of atorvastatin to individuals who were taking amlodipine does not constitute anticipatory activity with respect to claims requiring awareness of the

advantages of joint administration of atorvastatin and amlodipine. Applicants argued that amended claims "now recite either that amlodipine and atorvastatin are administered together in a single dosage form and/or that administration whether in single or in separate doses is pursuant to recognition and with knowledge (and in some instances specific diagnosis and prescription by a medical practitioner) of the benefits of joint treatment with amlodipine and atorvastatin," which literally distinguishes them over any co-administration in the Warner-Lambert trial.

Applicants argued that in addition to not meeting the requirements to establish anticipation by inherency, the "inherent but unintended and unappreciated" administration of atorvastatin to individuals taking amlodipine in the Warner-Lambert atorvastatin trial could not be combined with other prior art in an obviousness-type rejection. According to Applicants, motivation to combine and a reasonable expectation of success cannot be established where the art does not intend or recognize a particular event, even though the event may have occurred.

According to Applicants, in the October 24, 2001 Interview, the Examiner appreciated that claims limited to the administration of atorvastatin and amlodipine in a single dose is distinguishable over the Warner-Lambert trials. Applicants also argued that claims reciting methods for treating a mammal in need of therapy by the joint administration of amlodipine and atorvastatin, require that "the benefits of the instant invention [are] recognized and understood," although the Examiner did not make a decision regarding whether this rendered the distinguishable over the Warner-Lambert trials.

Applicants proceeded to discuss two U.S. Patent Applications submitted in the IDS that accompanied the Amendment and Response. The applications, which name Mason as the inventor, teach combinations of amlodipine and atorvastatin, and their use in the treatment of various cardiovascular diseases. According to Applicants, Mason had begun a contractual relationship with Pfizer. Applicants asserted that the priority date of the '914 Application preceded the earliest claimed priority date in either disclosed application. Applicants asserted that they had reviewed the documents reflecting the work of Mason, and concluded that although Mason disclosed the concept of an atorvastatin/amlodipine combination and its possible synergism to one of the inventors named in the '914 application, at that time the inventors '914 Application had already begun reducing this concept to practice. Applicants also disclosed that Mason conducted experiments with both atorvastatin and its metabolite, alone and in combination with amlodipine. Applicants alleged that while experiments with an atorvastatin metabolite in combination with amlodipine suggested a benefit for the combination, experiments with atorvastatin itself did not reveal the advantages for the atorvastatin/amlodipine combination.

In traversing an obviousness rejection, Applicants stressed the existence of a vast array of available compounds in the various classes of drugs (specifically calcium channel blockers and lipid-lowering drugs). Applicants urged that the cited art provides no teaching that the particular compounds claimed should be selected, or reasonable

expectation of success of the claimed method were that to be done. Applicants argued that "generalized teachings about combining classes of drugs, and specific combinations of individual drugs (which do not include the specific combination claimed) cannot provide the required suggestion or motivation in the art necessary to meet the legal standard of *prima facie* obviousness..." Applicants emphasized that at best, the art renders the claimed combination "obvious to try". Applicants argued that combining known elements for the same purpose disclosed in the prior art is not sufficient to establish *prima facie* obviousness.

Applicants noted that neither Messerli and Nawrocki mention combination therapy. Applicants characterized the Examiner's assertion that it is *prima facie* obvious to combine known active agents useful into the same method into a single composition for the same purpose as erroneous. Applicants argued that the Examiner improperly used hindsight and Applicants' own disclosure by stating as a general proposition that it would have been obvious to combine the known active agents useful in the same method into a single composition for the same purpose. Applicants argued that at the time of Applicants' invention, the totality of the art, including the references relied upon the Examiner would not lead one of skill in the art to select and concentrate on amlodipine and atorvastatin from the "broad drug classes involved." Furthermore, Applicants argued that the references relied upon by the Examiner do not suggest combination therapy of any kind. Applicants reiterated their argument that the Examiner's rejection of the claims based on the fact that atorvastatin and amlodipine were previously used separately for the same purpose as the claimed composition was improper.

Applicants also argued that the Examiner's finding that Sever *et al.* provided motivation for the claimed method was erroneous. Specifically, Applicants cited language in Sever *et al.* regarding the necessity of evaluation of combinations of drugs, and that states that further trials are being planned or are in progress. Further, Applicants argued that Sever *et al.* does not teach a combination of atorvastatin and amlodipine thereby evidencing that the art at best provides motivation to try the combination. Applicants concluded by reiterating that the Examiner cannot rely on a general proposition that each drug is known *per se* or event that one or both were known to be particularly effective.

Applicants filed a Supplemental Amendment, amending claims by removing the phrase "optionally and independently" from the claims. According to Applicants, removal of this language was discussed during an interview. Applicants maintained that the "optionally and independently" language "was intended to encompass both fixed combinations of [atorvastatin and amlodipine] (in a single dosage form) or free combinations ((a) and (b) in separate dosage forms)," and that the amended claims were similar in scope. Applicants also alerted the Examiner to the fact that atorvastatin was commercialized in February 1997, and that as with the Warner Lambert trials, "chance events" in which individuals took both atorvastatin and amlodipine may have occurred, but that these events fell outside of the scope of Applicants' claims.

On March 12, 2002, the Examiner sent a Notice of Allowability, accompanied by a Statement of Reasons for Allowance. U.S. Patent No. 6,455,574 issued on September 24, 2002.

Invalidity of the 574 Patent

The following description provides a summary of prior art references that are relevant to the validity of the claims of the '574 Patent.

U.S. Patent No. 4,572,909

U.S. Patent No. 4,572,909 ("the '909 Patent") lists the assignee as Pfizer, Inc. and the inventors as Simon F. Campbell, Peter E. Cross and John K. Stubbs. The '909 Patent was filed on February 3, 1984. The '909 Patent is listed as a reference that was cited during the prosecution of the '574 Patent. The '909 Patent is prior art to the '574 Patent under 35 U.S.C. § 102(b); it was patented February 25, 1986, that is more than a year prior to the earliest domestic priority date for the '574 Patent.

The '909 Patent describes the invention as relating to "certain 1,4, dihydropyridines having a substituted-amino containing group attached to the 2-postion, which have utility as anti-ischaemic and antihypertensive agents." The '909 Patent describes amlodipine. The '909 Patent goes on to state that:

> [f]or administration to man in the curative or prophylactic treatment of cardiac conditions and hypertension, oral dosages of the compounds will be in the range of from 2-50 mg daily for an average adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules are likely to contain from 1 to 10 mg of active compound . . .

'909 Patent at Col. 8, lines 8-15.

United States Patent No. 5,273,995

U.S. Patent No. 5,273,995 ("the '995 Patent") lists Bruce Roth as the inventor and Warner-Lambert Co. as the assignee. The '995 Patent was filed on February 26, 1991 and issued on December 28, 1993. The '995 Patent is listed as a reference that was cited during the prosecution of the '574 Patent. The '995 Patent is prior art to the '574 Patent under 35 U.S.C. § 102(b) since it was patented November 7, 1989, that is more than a year prior to the earliest priority date for the '574 Patent.

The '995 Patent discloses atorvastatin and pharmaceutically acceptable salts thereof. The '995 Patent states that [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, provides surprising inhibition of the biosynthesis of cholesterol, useful as hypolipidemic and hypocholesterolemic agents. The '995 patent teaches that:

> The compounds of the present invention utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from 10 to 500 mg per day . . . The dosages may be preferably from 0.5 to 1.0 mg/kg/day . . . The unit dosage form for oral or parenteral use may be varied or adjusted from 10 to 500 mg.

'995 Patent at Col. 9, lines 14-25.

Verispan Physician Drug & Diagnosis Audit, Drug Occurrences by Concomitant Product and Daily Dose January 1, 1997 to June 30 1997

The Verispan Physician Drug & Diagnosis Audit teaches that there were approximately 13,000 joint prescriptions (in the form of a single prescription by a single physician) of amlodipine and atorvastatin by physicians in the United States between January 1, 1997 and June 30, 1997. Because the joint prescription data reflects prescriptions prior to August 7, 1997, the data are prior art to the '574 patent under 35 U.S.C. §102(a). The Verispan Data was not considered by the Examiner during the prosecution of the '914 Application. A copy of the Verispan Data is attached hereto as Exhibit B.

U.S. Patent No. 5,208,225

U.S. Patent No. 5,208,255 ("the '255 Patent") lists Roger Boissonneault and Henry Miller as the inventors and Warner-Lambert Co. as the assignee. The '255 Patent was filed on October 22, 1991 and issued on May 4, 1993. The '255 Patent was not considered by the Examiner during the prosecution of the '574 Patent. The '225 Patent is prior art to the '574 Patent under 35 U.S.C. § 102(b) since it was patented May 4, 1993, that is more than a year prior to the earliest priority date for the '574 Patent.

The '225 Patent discloses a single pharmaceutical composition to deliver a combination of active ingredients, *i.e.*, a synthetic estrogenic agent and a synthetic progestogenic agent. The '225 patent teaches that the following are advantages of using a single dosage form to deliver a combination of active ingredients:

> ADVANTAGES - The compositions and processes of the invention have several advantages over those already known in the art. Principal among their advantages are:
>
> 1. The compositions are fixed, *i.e.*, constant or unitary, quantities of both the estrogenic and progestogenic agents. This simplifies manufacturing, storage, and packaging.

2. The use of a continuously dosed product minimizes patient compliance problems associated with an alternating sequence of dual therapies.

***

7. The use of the new and improved process for preparing low tablet dosage forms involving the combination of two drugs in one solution eliminates any error that may occur with distribution of one drug more than the other.

8. The new process also provides for processing to be carried out in one piece of equipment, *e.g.*, a P-K solids processor, from blending to addition of lubricant, thereby eliminating the need for transfer and drying.

Claims 1-12 of the '574 Patent are invalid under 35 U.S.C. § 103(a) as obvious over the '909 Patent and the '995 Patent, in view of the '225 Patent, and in further view of the Verispan Data.

Claim 1 recites "[a] method for treating a mammal suffering from combined hypertension and hyperlipidemia comprising administering to said mammal (a) an amount of a first compound, said first compound being amlodipine or a pharmaceutically acceptable acid addition salt thereof; and (b) an amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof; wherein said first compound and said second compound are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent." Claims 5 and 9 differ from claim 1 only in their preambles, which recite "A method of treating a mammal which has been diagnosed as suffering from hypertension and hyperlipidemia or the risk of hypertension and hyperlipidemia which would benefit from therapy by the combined administration of the active ingredients listed as (a) and (b) below, and therefore administration of both (a) and (b) has been prescribed, which comprises administering to said mammal so diagnosed and prescribed" and "A method of treating combined hypertension and hyperlipidemia in a mammal which has been examined for both hypertension and hyperlipidemia by a medical practitioner and diagnosed as in need of therapy for said hypertension and hyperlipidemia by the joint administration of the active ingredients designated as (a) and (b) below."

Claims 2-4, 6-8 and 10-12 depend from claims 1, 5, and 9, respectively, and specify that that the pharmaceutical compositions comprise amlodipine besylate, and/or the hemicalcium salt of atorvastatin.

Under 35 U.S.C. § 103(a), an invention may be unpatentable "if the differences between the subject matter sought to be patented and the prior art are such that the subject

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

As discussed below, the prior art either expressly or inherently discloses each and every limitation of claims 1-12 of the '574 patent except that atorvastatin and amlodipine were administered in a single pharmaceutical composition.

The concurrence of hypertension and hyperlipidemia as recited in claims 1, 5, and 9 was well known prior to the claimed priority date for the '574 patent. This fact is evidenced by the specification of the '574 Patent itself, which teaches that "hypertension frequently exists with hyperlipidemia."

This is further evidenced by the Verispan data, which indicates that over a six month time period, medical doctors prescribed atorvastatin and amlodipine in a single prescription to more than 13,000 individuals. Amlodipine and atorvastatin are labeled for the treatment of hypertension and hyperlipidemia. The prescribing physicians determined that the individuals "suffer[ed] from combined hypertension and hyperlipidemia" as recited in claim 1, "diagnosed [the individuals] as suffering from hypertension or hyperlipidemia or the risk of hypertension or hyperlipidemia which would benefit from therapy by the combined administration of atorvastatin and amlodipine", as recited in claim 5, and "examined [the individuals] for both hypertension and hyperlipidemia. . . and diagnosed [the individuals] as in need of therapy for said hypertension and hyperlipidemia by joint administration" of amlodipine and atorvastatin" as recited in claim 9.

Both atorvastatin and amlodipine were well known compounds used in the treatment of hypertension and hyperlipidemia, respectively, as evidenced by the teachings of the '909 Patent and the '995 patent. The '909 teaches amlodipine compounds and states that the compounds are "useful as anithypertensive agents." The '909 Patent describes preferred dosages of amlodipine for prophylaxis and treatment of hypertension and cardiac conditions. The '995 Patent teaches atorvastatin compounds, and states that the compounds are useful as hypolipidemic and antihypercholesterolemic agents. The '995 Patent provides preferred dosages of atorvastatin for the treatment of hyperlipidemia or hypercholesterolemia.

As to the limitation that the amlodipine and atorvastatin compounds are "administered together in a single pharmaceutical composition, the well-known benefits of combining two agents into a single dosage form are illustrated," for example in the teachings of the '225 Patent. Benefits of the combined pharmaceutical outlined in the '225 Patent include simplification of manufacturing, storage and packaging and minimization of patient compliance problems. In fact, the patentees recite these very same factors as the motivation to combine atorvastatin and amlodipine. Specifically, the '574 Patent specification states that "it would. . . be advantageous for patients [who suffer from hypertension and hyperlipidemia] to have a single therapy which treats both of these conditions."

One of skill in the art at the time of filing of the '872 Patent would have had a reasonable likelihood of success in combining the amlodipine and atorvastatin compounds into a single composition. Because the '909 and '995 Patents disclose the amlodipine and atorvastatin compounds for treatment of hypertension and hyperlipidemia, respectively, and it would have been obvious to one of skill in the art to combine the two compounds into a single pharmaceutical composition, claims 1-12 of the '574 Patent are obvious.

The Applicants overcame an obviousness rejection during the prosecution of the '574 Patent by arguing that the Examiner's position that merely combining elements to achieve known effects is *prima facie* obvious was erroneous. Although the '574 Patent states that the combination provides synergistic results with the claimed combination, the '574 lacks any data to support the statements regarding synergy in the Summary of the Invention, and Applicants did not argue that the combination produced unexpected, synergistic results.

In the absence of data demonstrating unexpected results, Applicants cannot overcome the obviousness argument articulated above since it is well-established that the combination of ingredients into a single form based on the prior art is obvious under 35 U.S.C. § 103(a). *Richardson-Vicks*, 122 F.3d, 1483-1484. Applicants' combination is analogous to the facts decided in *Richardson-Vicks*. In *Richardson-Vicks*, the claims at issue related to a cough and cold medication comprising ibuprofen and pseudoephedrine in combinatory immixture. Pseudoephedrine and ibuprofen were known decongestants and analgesics, respectively, and doctors had prescribed the two compounds, albeit not in a single combination. As such, the only difference between the Appellants' claimed invention and the prior art was that the two compounds were not in a single dosage form. During the prosecution of Appellants' Application, Appellants' presented evidence to the Patent and Trademark Office of unexpected, synergistic results of the combination of pseudoephedrine and ibuprofen. The court noted that "the Examiner placed singular reliance on the evidence of synergy to allow the claims." *Id.* at 1482. Nevertheless, the court held that even in view of Appellants' evidence of unexpected results, the district court's decision that Appellants' claims were obvious was correct. *Id.* at 1483.

In view of the above holding, claims 1-12 of the '574 Patent are invalid under 35 U.S.C. § 103(a). As with *Richardson-Vicks*, the individual compounds of the combined therapeutic were both known in the prior art to be effective at treating the claimed conditions, *i.e.*, hypertension and hyperlipidemia. This fact is evident by the teachings of the '574 Patent, which states that "atorvastatin is a potent lipid lowering compound" and that "amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers" that are useful anti-hypertensive agents." '574 Patent at Col. 1, line 64, Col. 2, lines 27-31. Medical doctors had co-prescribed amlodipine and atorvastatin, although not in a single composition, as was the case in *Richardson-Vicks*. Unlike the case in *Richardson-Vicks*, however, the '574 Patentees did not provide evidence demonstrating that the combination of amlodipine and atorvastatin is synergistically effective at treating the claimed conditions. Rather, the Examiner relied upon the fact that the claims "are

limited to administration of amlodipine and atorvastatin together in a single pharmaceutical composition in methods for treating combined hypertension and hyperlipidemia.

The recitation of methods for treating a mammal "in need of therapy by the joint administration of amlodipine and atorvastatin" or the recitation that an individual has been diagnosed by a medical practitioner do not render the claims non-obvious over the prior art. Applicants' argued that these limitations require that "the benefits of the combination were recognized and understood," and also argued that the "narrower" claims reciting methods wherein an individual has been diagnosed as suffering from hypertension and hyperlipidemia or wherein medical practitioner has diagnosed an individual and co-prescribed atorvastatin and amlodipine "present even clearer method steps of the recognition of the benefits of the present invention." The Court of Appeals for the Federal Circuit has specifically held that these types of limitations are insufficient to overcome an obviousness rejection of a claimed combination that was known in the prior art.

In *In re Baxter Travenol Laboratories*, the court held that:

> Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) (citations omitted).

Further, Section 103 of the Patent Act focuses on differences between subject matter sought to be patented and the prior art. The Supreme Court's traditional approach looks to whether a person having ordinary skill in the art would have been capable of adapting extant technology to achieve a desired result, not whether such a person would have had motivation to adapt extant technology to achieve a desired result. *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1960). Under Sakraida and Anderson's-Black, where an alleged invention is "an assembly of old elements," the court's inquiry goes to whether the claimed invention "only unites old elements with no change in their respective functions," or whether there is some interaction of combined elements with each other to yield a "new or different function" or "an effect greater than the sum of the several effects taken separately." Sakraida, 425 U.S. at 282. If there is no such function or effect, the claimed invention is obvious under 35 U.S.C. §103, and no further analysis is needed. Analysis of the existence of some "teaching, suggestion or motivation" that would have led a person of ordinary skill in the art to combine the relevant teachings in the manner claimed has no basis in the text of Section 103 and conflicts with Supreme Court precedent.[9]

Here, the combination of known atorvastatin calcium and known amlodipine besylate does not result in any "new or different function" for either component.

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[9] This same position is argued by Petitioners in *KSR International Co. v. Teleflex Inc. et al.* (Supreme Court Docket No. 04-1350).

In conclusion, claims 1-12 of the '574 Patent are unpatentable as obvious over the '909 and '995 Patents, alone or in light of either the '225 Patent or the Verispan Data, or a combination of the two.

OFFER OF CONFIDENTIAL ACCESS TO APPLICATION

Ranbaxy hereby extends an offer of confidential access to relevant portions of RLL's ANDA that is in the custody of Ranbaxy. The conditions for confidential access are provided in the attached Confidential Disclosure Agreement ("CDA"). This offer and CDA are provided solely for the purpose of allowing Pfizer Inc. to evaluate whether an action under 35 USC 271(e)(2)(A) should be brought for the filing of RLL's ANDA. This offer and the CDA contains restrictions as to persons entitled to access relevant portions of the ANDA, and on the use and disposition of any information accessed, as would apply if a protective order was entered for the purpose of protecting trade secrets and other confidential business information. Under section 505 of the Food, Drug and Cosmetic Act, a request for access to an application under an offer of confidential access is considered to be acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract.

Very truly yours,

Jay Deshmukh by WDH

Jay R. Deshmukh
Senior Vice President – Intellectual Property

Offer of Confidential Access to Application

WHEREAS Ranbaxy Laboratories Ltd. ("Ranbaxy") and Pfizer, Inc. ("Pfizer") compete in the pharmaceutical industry and this Offer of Confidential Access to Application may involve the disclosure of certain documents, things and information in the possession, custody or control of Ranbaxy that constitute or contain trade secrets or other confidential research, development or commercial information within the meaning of Rule 26(c)(7) of the Federal Rules of Civil Procedure; and

WHEREAS such confidential information must be protected in order to preserve the legitimate business interests of Ranbaxy;

THEREFORE, for good cause shown, pursuant to Rule 26(c), all documents and other materials provided by Ranbaxy to Pfizer shall be provided subject to the following conditions:

1. This Offer of Confidential Access to Application shall apply to all documents, things, or information that are owned or controlled by Ranbaxy and contain its trade secrets or other confidential research, development, or commercial information, including without limitation documents and things ("Confidential Material").

2. Ranbaxy shall have the right to designate as Confidential Material and subject to this Offer of Confidential Access to Application any or all of the ANDA and/or Drug Master File(s) referenced in the paragraph IV notification letter. The duty of Pfizer as bound by this Offer of Confidentia Access to Application to maintain the confidentiality of Confidential Material so designated shall commence with such notice.

3. Ranbaxy hereby designates as Confidential Material all documents and things provided in response to acceptance of this Offer of Confidential Access to Application.

4. Pfizer and all other persons bound by the terms of this Offer of Confidential Access to Application shall use any Confidential Material for the sole purpose of evaluating whether to bring a civil action under 35 USC 271(e)(2)(A) and shall not use any Confidential

Material for any other purpose. The attorneys of record for Pfizer shall exercise reasonable care to insure that the information and documents governed by this Offer of Confidential Access to Application are (a) used only for the purpose specified herein, and (b) disclosed only to authorized persons.

5. Confidential Material shall be retained by attorneys of record for Pfizer and may be disclosed only to:

(a) Outside Counsel retained by Pfizer;

(b) Outside experts and consultants retained by Pfizer or its Outside Counsel to assist in evaluating whether to bring an action under 35 USC 271(e)(2)(A) (and the expert's or consultant's staff, stenographic, and clerical employees whose duties and responsibilities require access to such materials), who are not past or present full-time employees of Pfizer, as provided in Paragraph 6., below; and

(c) Any other person agreed to by Ranbaxy and Pfizer.

6. Before Outside counsel for Pfizer may disclose Confidential Material to a person described in Paragraph 5.b., above, that counsel shall give advance notice as follows: Counsel for Pfizer seeking to make the disclosure shall provide written notice (by facsimile followed by a hard copy sent next business day courier) to counsel for Ranbaxy, of the name, address, business affiliation and curriculum vitae of the person(s) to whom the Confidential Material is to be disclosed, as well as an executed copy of the Offer of Confidential Access to Application. Ranbaxy shall have seven (7) business days after receiving that notification within which to object to the proposed disclosure; such disclosure shall not occur before the time for any objection by Ranbaxy expires, and, if any such objection is made, before that objection is resolved. Any such objection shall be made in writing (by facsimile followed by a hard copy sent next business day courier) to the outside counsel for Pfizer seeking to make the disclosure. If the parties are unable to resolve the objection, the Confidential Material shall not be disclosed.

7. In no event shall the Confidential Material be disclosed to any person allowed access under Paragraphs 5.a, 5.b, or 5.c until such person has been shown a copy of and executed this Offer of Confidential Access to Application acknowledging and agreeing to be bound by the

terms of this Offer of Confidential Access to Application. The Confidential Material shall not be disclosed to any person who refuses to execute the Offer of Confidential Access to Application.

8. Upon reaching 45 days after receipt of the paragraph IV notification from Ranbaxy, unless otherwise agreed to in writing by Ranbaxy, Pfizer and its experts, consultants and outside counsel shall within thirty (30) days assemble and return all Confidential Material, including all copies, extracts, and summaries thereof, to Ranbaxy, except that any such materials that contain or constitute attorney work product may be destroyed rather than returned. All counsel of or for Pfizer shall make certification of compliance herewith and shall deliver the same to Ranbaxy not more than thirty (30) days after the running of the 45 day period mentioned above. In the event that litigation is initiated within the 45-day period, the provision regarding the return or destruction of Confidential Material shall be waived.

9. No part of the restrictions imposed by this Offer of Confidential Access to Application may be terminated, except by written agreement executed by Ranbaxy.

10. Notices under this Offer of Confidential Access to Application shall be to Ranbaxy and Pfizer at the addresses indicted below, unless this provision is modified by the parties in writing:

(a) notice to Ranbaxy shall be to George E. Heibel, Ranbaxy Inc., Suite 2100, College Road East, Princeton NJ 08540, facsimile (609) 514-9779, and

(b) notice to Pfizer shall be to

_____

_____

11. Any violation of this Offer of Confidential Access to Application may constitute unlawful disclosure of trade secrets and/or confidential commercial information and may cause me to be potentially liable in a civil action for damages by Ranbaxy, and may subject Pfizer to such additional and further remedies as may be available to Ranbaxy.

_____ _____

George E. Heibel
Senior Counsel –Intellectual Property

Date

CONFIDENTIALITY UNDERTAKING

I, _____, being duly sworn, state that:

(a) My present residential address is _____ _____.

(b) My present employer is _____ _____ and the address of my present employer is _____.

(c) My present occupation or job description is _____ _____.

(d) I have received and carefully read the Offer of Confidential Access to Application. I certify that I understand the terms of that Offer of Confidential Access to Application, recognize that I am bound by the terms of that Offer, and agree to comply with those terms. Further, I understand that unauthorized disclosure of any Confidential Material, or its substance, may constitute unlawful disclosure of trade secrets and/or confidential commercial information and may cause me to be potentially liable in a civil action for damages by Ranbaxy.

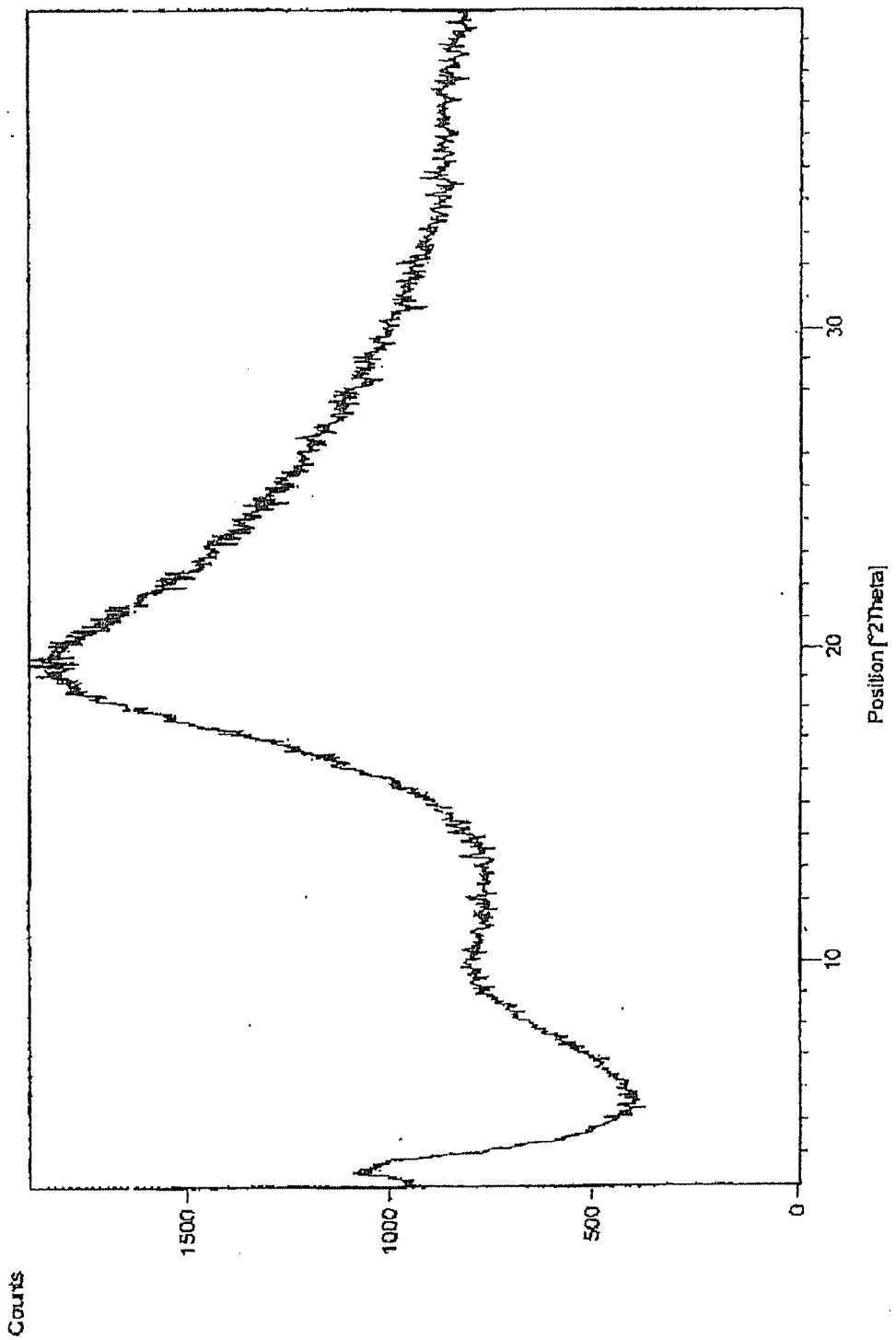
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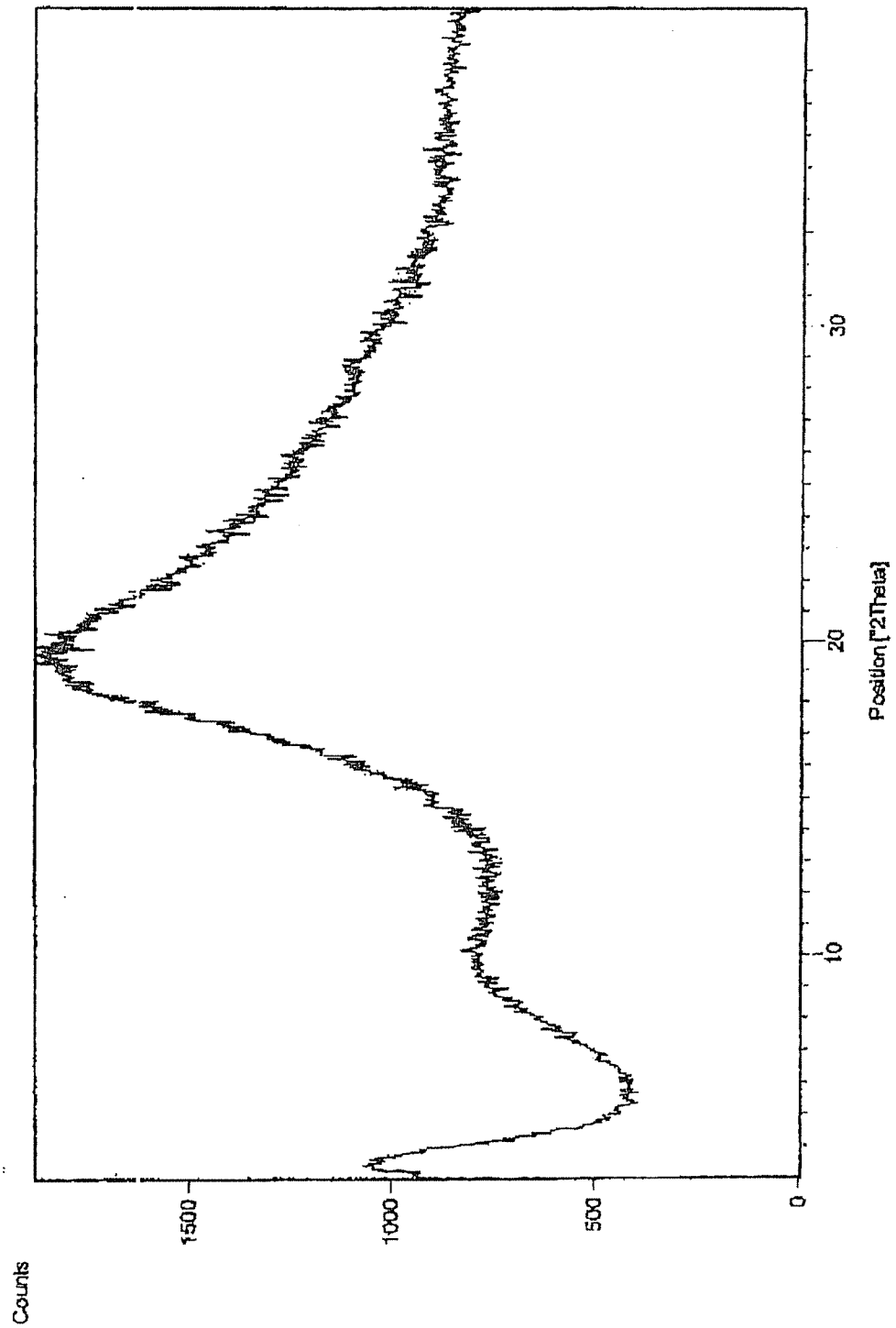
SUBSCRIBED and SWORN to before me
this _____ day of _____, 200___.

_____

Notary Public
My Commission Expires _____

EXHIBIT A


Counts
1500
1000
500
0
10
20
30
Position [°2Theta]


Counts
1500
1000
500
0
10
20
30
Position [°2Theta]

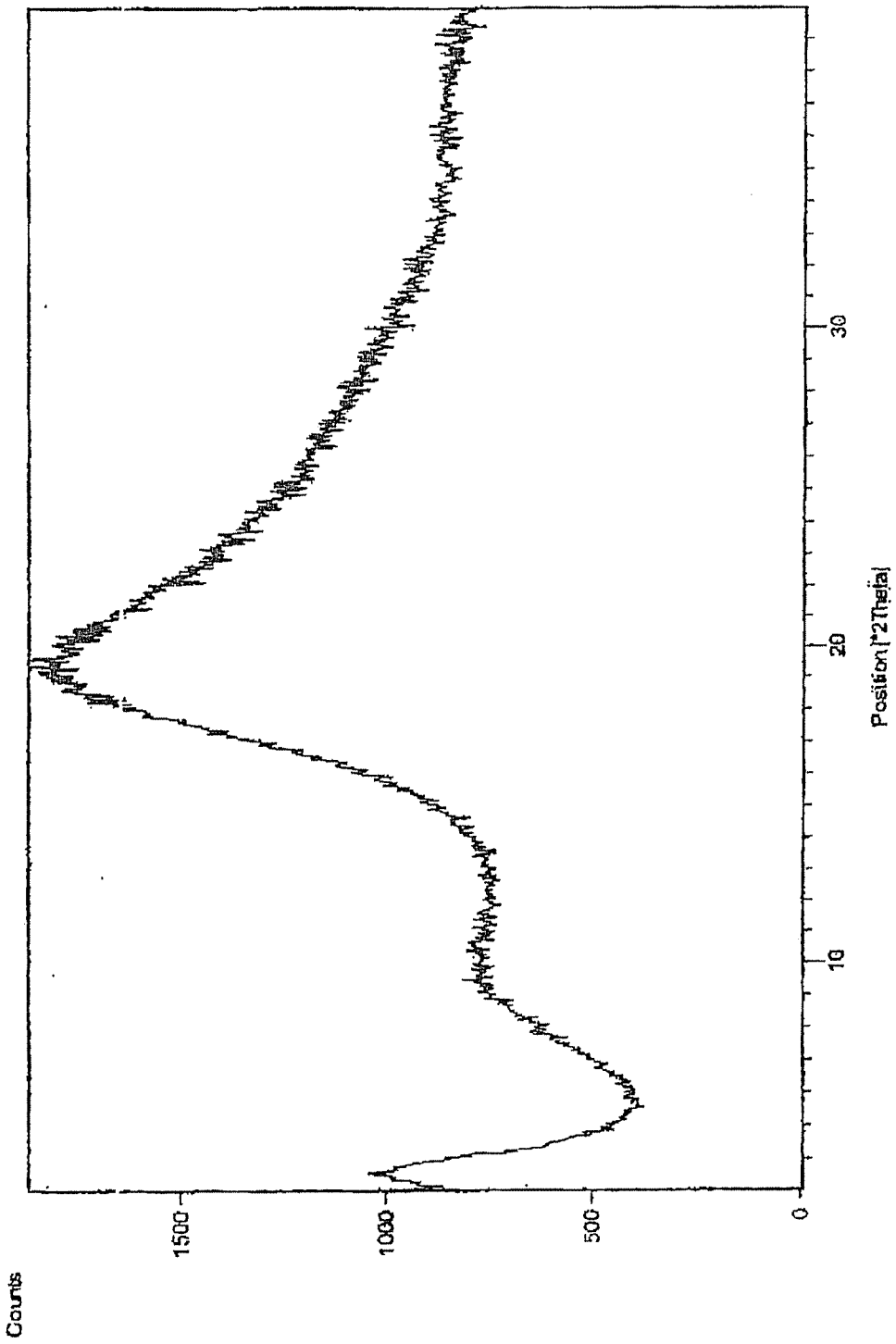

Counts
1500
1000
500
0
10
20
30
Position [°2Theta]

EXHIBIT B

Lipitor Norvasc Concom.txt

	----YTD/JUN/1997--- Occur (000)	Share %
Lipitor	1065	100.0
Used Alone	955	89.7
Colestid	20	1.8
Aspirin	19	1.7
Niacin	15	1.4
Lopid	14	1.3
Norvasc	13	1.2
Tenormin	11	1.0
Bumex Non-Inj	9	0.8
Verapamil SR	6	0.5
Nifedipine XL	6	0.5
Normodyne	6	0.5
Pravachol	5	0.5
Hyzaar	5	0.5
Antioxidant	5	0.5
Trental	5	0.5
Questran Light	5	0.4
Vitamin E Oral	4	0.4
Lozol	4	0.4
Prinivil	4	0.4
Calan SR	4	0.4
Aspirin,Enteric-Coat	4	0.4
Lopressor HCT	4	0.4
Imdur	4	0.4
Gemfibrozil	3	0.3
Ecotrin Adlt Low Str	3	0.3
Garlic	3	0.3
Climara	3	0.3
Lanoxin	3	0.3
Cardene	3	0.3
Metamucil	1	0.1
Glynase Prestab	1	0.1
Atorvastatin	44	100.0
Used Alone	26	58.9
Aspirin	8	18.6
Metoprolol Tartrate	6	13.3
Lopid	4	9.3
Estradiol Oral	4	9.3
Premarin Tabs	4	9.3
Vitamin E Oral	4	9.3
Norvasc	4	9.2

SOURCE: Verispan, PDUA

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
PFIZER INC, PFIZER PHARMACEUTICALS, LLC, PFIZER LIMITED, C.P. PHARMACEUTICALS INTERNATIONAL C.V., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC and WARNER-LAMBERT EXPORT, LTD.

(b) County Of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) ATTORNEYS (FIRM NAME, ADDRESS AND TELEPHONE NUMBER)
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DEFENDANTS
RANBAXY LABORATORIES LIMITED, and RANBAXY INC.

County Of Residence Of First Listed Defendant: _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (Place an "X" In One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☒ 1	☐ 1	Incorporated *or* Principal Place of Business in This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business in Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" In One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault. Libel & Slander
- ☐ 330 Federal Employers Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities – Employment
- ☐ 446 Amer. w/Disabilities – Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

HABEAS CORPUS:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt Relations
- ☐ 730 Labor/Mgmt Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced ar Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/ Commodities Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (PLACE AN "X" IN ONE BOX ONLY)

☒ 1 Original Proceeding | ☐ 2 Removed from State Court | ☐ 3 Remanded from Appellate Court | ☐ 4 Reinstated or Reopened | ☐ 5 Transferred from another district (specify) | ☐ 6 Multidistrict Litigation | ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity):**
35 U.S.C. § 271
Brief description of cause:
Patent infringement.

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23 **DEMAND:** CHECK YES only if demanded in complaint: **JURY DEMAND:** ☐ YES ☒ NO

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE DOCKET NUMBER
Pfizer Inc. et al. v. Ranbaxy, Farnan, J., Civil Action No. 03-209-JJF

DATE SIGNATURE OF ATTORNEY OF RECORD
March 9, 2007

FOR OFFICE USE ONLY
RECEIPT # AMOUNT APPLYING IFP JUDGE MAG. JUDGE

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS–44

Authority For Civil Cover Sheet

The JS–44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. **(a) Plaintiffs – Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. **Jurisdiction.** The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below: federal question actions take precedence over diversity cases.)

III. **Residence (citizenship) of Principal Parties.** This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. **Nature of Suit.** Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. **Origin.** Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C. Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VI. **Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statues unless diversity.** Example: U.S. Civil Statute: 47 USC 553
Brief Description: Unauthorized reception of cable service.

VII. **Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. **Related Cases.** This section of the JS 44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 1 3 8

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 5 COPIES OF AO FORM 85.

3/9/07
(Date forms issued)

Patrick Boyer
(Signature of Party or their Representative)

Patrick Boyer
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action