IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA PHARMACEUTICALS LP, and ASTRAZENECA UK LIMITED, and IPR PHARMACEUTICALS, INC., and SHIONOGI SEIYAKU KABUSHIKI KAISHA,	)	
Plaintiffs,	)	C.A. No. 07-811-JJF
v.	)	
COBALT PHARMACEUTICALS INC., and COBALT LABORATORIES INC.,	)	
Defendants.	)	

DEFENDANTS' ANSWER, DEFENSES, AND COUNTERCLAIMS

Defendants, Cobalt Pharmaceuticals, Inc. and Cobalt Laboratories, Inc. (collectively, "Defendants"), hereby answer the Complaint filed by AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals, Inc., and Shionogi Seiyaku Kabushiki Kaisha (collectively "Plaintiffs"), as follows:

Nature of the Action

1. Defendants admit that the Complaint purports to state a civil action for infringement of U.S. Patent No. RE37,314 ("the '314 patent") under 35 U.S.C. § 271(e) and (a). Defendants admit that the Complaint purports to relate to Abbreviated New Drug Application ("ANDA") No. 79-167 filed by Cobalt. Defendants deny each and every remaining allegation contained in paragraph 1 of the Complaint.

Parties

2. Defendants lack sufficient information to form a belief as to the truth or falsity of the allegations contained in paragraph 2 of the Complaint and, therefore, deny each and every allegation in paragraph 2 on that basis.

3. Defendants lack sufficient information to form a belief as to the truth or falsity of the allegations contained in paragraph 3 of the Complaint and, therefore, deny each and every allegation in paragraph 3 on that basis.

4. Defendants lack sufficient information to form a belief as to the truth or falsity of the allegations contained in paragraph 4 of the Complaint and, therefore, deny each and every allegation in paragraph 4 on that basis.

5. Defendants lack sufficient information to form a belief as to the truth or falsity of the allegations contained in paragraph 5 of the Complaint and, therefore, deny each and every allegation in paragraph 5 on that basis.

6. Defendants admit the allegations contained in paragraph 6 of the Complaint.

7. Defendants admit that Cobalt Laboratories is a corporation operating and existing under the laws of Delaware with its principal place of business at 24840 South Tamiami Trail, Suite 1, Bonita Springs, Florida 34134 USA. Defendants deny all other allegations contained in paragraph 7 of the Complaint.

Background

8. Defendants lack sufficient information to form a belief as to the truth or falsity of the allegations contained in paragraph 8 of the Complaint and, therefore, deny each and every allegation in paragraph 8 on that basis.

9. Defendants admit that CRESTOR® is a prescription drug that contains rosuvastatin calcium and is approved by the FDA for at least one indication. Defendants lack sufficient information to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 9 of the Complaint and, therefore, deny each and every remaining allegation in paragraph 9 on that basis.

10. Defendants lack sufficient information to form a belief as to the truth or falsity of the allegations contained in paragraph 10 of the Complaint and, therefore, deny each and every allegation in paragraph 10 on that basis.

11. Defendants admit that Cobalt Pharmaceuticals filed with the FDA ANDA No. 79-167 seeking approval for sale in the United States of rosuvastatin calcium tablets, which meet the FDA's requirements for approval of therapeutical equivalents to plaintiffs' CRESTOR® tablets. Defendants deny each and every remaining allegation contained in paragraph 11 of the Complaint.

12. Defendants admit that by letter of October 29, 2007 (the "Notice Letter"), Cobalt Pharmaceuticals notified Plaintiffs that Cobalt had filed ANDA No. 79-167. Defendants admit that ANDA No. 79-167 seeks approval to market rosuvastatin calcium tablets in 5mg, 10mg, 20mg, and 40mg dosage strengths. Defendants admit that the Notice Letter indicated that it was providing information to Plaintiffs pursuant to section 505(j)(2)(B)(iv) and C.F.R. § 314.95. Defendants deny each and every remaining allegation contained in paragraph 12 of the Complaint.

13. Defendants admit that Cobalt Pharmaceuticals, Inc. manufactures certain generic prescription drug products, and that certain of these products are sold to Cobalt Laboratories, Inc. Defendants admit that certain generic prescription drug products manufactured by Cobalt Pharmaceuticals, Inc. are available for purchase in various states in the United States. Defendants admit that Cobalt Laboratories, Inc. is the owner of ANDA 79-167. Defendants deny each and every remaining allegation contained in paragraph 13 of the Complaint.

14. Defendants deny the allegations contained in paragraph 14 of the Complaint.

15. Defendants deny that facts "(1)", "(2)", and "(3)" alleged in paragraph 15 of the Complaint are evidence of Cobalt Laboratories, Inc.'s participation in the preparation and filing of ANDA No. 79-167. Defendants admit the truth of each of the alleged facts "(1)", "(2)", and "(3)" in paragraph 15 of the Complaint. Defendants deny each and every remaining allegation contained in paragraph 15 of the Complaint.

Jurisdiction and Venue

16. Paragraph 16 of the Complaint contains legal conclusions to which no answer is required. Defendants therefore deny each and every allegation in paragraph 16 of the Complaint, except to admit that this Court has subject matter jurisdiction over Count I of the Complaint, asserting infringement under 35 U.S.C. §271(e)(2). In particular, defendants maintain that the Court lacks subject matter jurisdiction over Count II of the Complaint, purporting to assert infringement under 35 U.S.C. §271(a).

17. Defendants deny the allegations of paragraph 17 of the complaint.

18. Defendants deny each and every allegation contained in paragraph 18 of the Complaint. Nonetheless, Cobalt Pharmaceuticals waives the defense of lack of personal jurisdiction by virtue of its filing this Answer, Defenses, and Counterclaims in this action.

19. Defendants admit that Cobalt Laboratories, Inc. is a Delaware corporation. Defendants deny each and every remaining allegation contained in paragraph 19 of the Complaint. Nonetheless, Cobalt Laboratories waives the defense of lack of personal jurisdiction by virtue of its filing this Answer, Defenses, and Counterclaims in this action.

20. Defendants deny each and every allegation contained in paragraph 20 of the Complaint. Nonetheless, Defendants waive the defense of improper venue by virtue of its filing this Answer, Defenses, and Counterclaims in this action.

Count I

21. Defendants incorporate by reference paragraphs 1-20 of this Answer as if fully set forth herein.

22. Defendants admit that U.S. Patent No. 5,260,440 was reissued on August 7, 2001 as U.S. Patent No. RE37,314. Defendants lack sufficient information to form a belief as to the truth or falsity of each and every remaining allegation contained in paragraph 22 of the Complaint, and therefore deny those allegations on that basis.

23. Defendants deny that Cobalt Laboratories made any of the alleged filings with the FDA. Defendants admit that Cobalt Pharmaceuticals filed ANDA No. 79-167 with the FDA, including a certification pursuant to 21 U.S.C.§355(j)(2)(A)(vii)(IV) that the '314 patent was not infringed, was invalid and/or unenforceable. Defendants deny the remaining allegations contained in paragraph 23 of the Complaint.

24. Paragraph 24 of the Complaint asserts legal conclusions and calls for legal contentions to which no answer is required. Defendants deny the allegations of paragraph 24 on that basis.

25. Defendants deny each and every allegation of paragraph 25.

26. Defendants deny each and every allegation contained in paragraph 26 of the Complaint.

Count II

27. Defendants incorporate by reference paragraphs 1-26 of this Answer as if fully set forth herein.

28. This and all other allegations in Count II are the subject of Defendants' Motion to Dismiss. Fed. R. Civ. P. 12. Accordingly, no answer is required. Nevertheless, Defendants deny each and every allegation contained in paragraph 28 of the Complaint.

29. This and all other allegations in Count II are the subject of Defendants' Motion to Dismiss. Fed. R. Civ. P. 12. Accordingly, no answer is required. Nevertheless, Defendants admit that Cobalt Pharmaceuticals filed ANDA 79-167 with the FDA for the purpose of seeking approval to market the proposed rosuvastatin calcium tablets described in the ANDA. Defendants deny each and every remaining allegation contained in paragraph 29 of the Complaint.

30. This and all other allegations in Count II are the subject of Defendants' Motion to Dismiss. Fed. R. Civ. P. 12. Accordingly, no answer is required. Nevertheless, Paragraph 30 of the Complaint asserts legal conclusions and calls for legal contentions to which no answer is required. Defendants deny each and every allegation of paragraph 30.

31. This and all other allegations in Count II are the subject of Defendants' Motion to Dismiss. Fed. R. Civ. P. 12. Accordingly, no answer is required. Nevertheless, Defendants deny each and every allegation contained in paragraph 31 of the Complaint.

32. This and all other allegations in Count II are the subject of Defendants' Motion to Dismiss. Fed. R. Civ. P. 12. Accordingly, no answer is required. Paragraph 32 of the Complaint asserts legal conclusions and calls for legal contentions to which no answer is required. Nevertheless, Defendants deny the allegations of paragraph 32.

Prayer for Relief

33. Defendants deny that Plaintiffs are entitled to the relief requested in paragraphs (1) through (8) in the Complaint.

DEFENSES

First Defense – Invalidity of the '314 Patent

1. One or more claims of the '314 patent are invalid for failure to comply with one or more of the requirements of 35 U.S.C. §§ 102, 103, 112 and/or 251.

Second Defense – Inequitable Conduct

2. The '314 patent is unenforceable for inequitable conduct.

3. United States Patent No. 5,260,440 (the "'440 patent") is the patent from which the '314 patent was reissued.

4. The application from which the '440 patent ultimately issued was filed on June 12, 1992.

5. European Patent Application 0 521 471 (the "'471 application"), is a European Patent Application corresponding to the '440 patent.

6. On October 10, 1992, a search report (the "Search Report") issued in connection with the prosecution of the '471 application.

7. The Search Report identified EP 895 and indicated that EP 895 was "particularly relevant" to claims 1, 7, 8, and 9.

8. EP 895 is prior art to the '314 patent.

9. Both the Search Report and EP 895 are documents highly material to claims in both the '440 patent and the '314 patent.

10. The applicants admitted during the '314 reissue proceeding that EP 895 anticipated some claims of the '440 patent.

11. Upon information and belief, individuals associated with the prosecution of the '440 patent knew of the existence of both the Search Report and EP 895 during the prosecution of the '440 patent.

12. Support for this belief is based in part on the similarity between the attorney docket number identified in the '440 prosecution on one hand, and the attorney docket number identified on a copy of EP 895 that was supplied to the Canadian Patent Office during the prosecution of the Canadian counterpart to the '440 patent, on the other hand. This is evidence that EP 895 was provided to someone associated with the prosecution of the '440 patent.

13. No one associated with prosecution of the '440 patent submitted either the Search Report or EP 895 to the United States Patent and Trademark Office ("PTO") during prosecution of the '440 patent.

14. The failure to disclose the Search Report or EP 895 to the United States Patent Office during prosecution of the '440 patent amounts to a material and misleading representation on the part of one or more persons who owed a duty of candor to the PTO.

15. Upon information and belief, the failure to disclose the Search Report and EP 895 was intentional and was intended to deceive or mislead the United States Patent Office.

16. Support for the allegations that the failure to disclose the Search Report and EP 895 was intentional and intended to deceive or mislead the PTO comes at least from the highly material nature of the Search Report and EP 895.

17. Further support for the allegations that the failure to disclose the search report and EP 895 was intentional and intended to deceive or mislead the PTO comes from comparing the

behavior of the '440 patent inventors and prosecuting law firm during the prosecution of the '440 patent, with their behavior during another prosecution.

18. Specifically, during prosecution of what became United States Patent No. 5,128,366 (the "'366 patent"), the attorneys disclosed a search report from a corresponding European Patent Application; this report cited certain references as background material.

19. During this prosecution, the attorneys also disclosed to the examiner the "background" references cited in that search report.

20. The failure of those same inventors and attorneys to disclose the October 10, 1992 Search Report or the EP 895 reference during the '440 patent prosecution suggests an intent to mislead the PTO, especially in light of the fact that the EP 895 reference was cited in the October 10, 1992 search report as "particularly relevant", as opposed to mere background material.

Third Defense – Lack of Subject Matter Jurisdiction

21. The Court lacks subject matter jurisdiction over Count II of the Complaint, purporting to allege future infringement under 35 U.S.C. § 271(a). The factual allegations of the Complaint (as opposed to the mere conclusions of law) fail to establish a basis for jurisdiction under the Declaratory Judgment Act. Among other things, those allegations fail to establish the requisite immediacy and reality for an Article III case or controversy under the Act.

Fourth Defense – Failure to State a Claim

22. Count II of the Complaint fails to state a claim upon which relief can be granted.

COUNTERCLAIMS

Defendant/Counterclaim-Plaintiffs Cobalt Pharmaceuticals, Inc. and Cobalt Laboratories, Inc. for their counterclaims against Plaintiffs/Counterclaim-Defendants Astrazeneca Pharmaceuticals LP, Astrazeneca UK Limited, IPR Pharmaceuticals, Inc., and Shionogi Seiyaku Kabushiki Kaisha, allege as follows:

The Parties

1. Defendant/Counterclaim-Plaintiff Cobalt Pharmaceuticals is a corporation duly organized and existing under the laws of Canada, having its principal place of business at 6500 Kitimat Road, Mississauga, Ontario, Canada, L5N 2B8.

2. Defendant/Counterclaim-Plaintiff Cobalt Laboratories is a corporation operating and existing under the laws of Delaware with its principal place of business at 24840 South Tamiami Trail, Suite 1, Bonita Springs, Florida 34134 USA.

3. According to the Complaint, Plaintiff/Counterclaim-Defendant IPR Pharmaceuticals, Inc. ("IPR") is a corporation operating and existing under the laws of Puerto Rico with its principal place of business at Carr 188 Lote 17, San Isidro industrial Park, Canovanas, Puerto Rico 00729.

4. According to the Complaint, Plaintiff/Counterclaim-Defendant AstraZeneca Pharmaceuticals LP is a corporation operating and existing under the laws of Delaware with its principal place of business at 1800 Concord Pike, Wilmington, Delaware 19803 USA.

5. According to the Complaint, Plaintiff/Counterclaim-Defendant AstraZeneca UK is a corporation operating and existing under the laws of the United Kingdom with its principal place of business at 15 Stanhop Gate, London W1K 1LN, England.

Jurisdiction & Venue

Case or Controversy

6. Defendants/Counterclaim-Plaintiffs are entitled to bring and maintain the instant counterclaims for declaratory judgment of non-infringement, patent invalidity and unenforceability under, *inter alia*, 21 U.S.C. § 355(c)(3)(C)(D)(i)-(ii), 35 U.S.C. § 271(e)(5), and 28 U.S.C. § 2201.

7. On information and belief, IPR, AstraZeneca Pharmaceuticals LP, and AstraZeneca UK hold all substantial rights in United States Patent No. RE37,314 ("the '314 patent"), including the right to sue for infringement thereof.

8. According to the Complaint, AstraZeneca is the United States Agent for IPR.

9. On information and belief, Plaintiffs/Counterclaim-Defendant IPR and AstraZeneca hold all substantial rights in U.S. Patent No. 6,316,460 ("the '460 patent," attached hereto as Exhibit 1), including the right to sue for infringement thereof.

10. One or more Plaintiffs/Counterclaim-Defendants caused the '314 and '460 patents to be listed in the FDA's "Orange Book," in association with Crestor® Rosuvastatin calcium tablets.

11. As a consequence of listing the '314 and '460 patents in the FDA's "Orange Book," Plaintiffs/Counterclaim-Defendants were and are representing to the world that the '314 and '460 patents claim the approved drug product, and that patent infringement actions relating to each of these Orange Book patents could reasonably be expected to be brought against unlicensed filers of New Drug Applications for which patent certification would be required.

12. On information and belief, Plaintiffs/Counterclaim-Defendants have enforced and continue to enforce vigorously their alleged intellectual property rights by filing patent infringement actions, including the infringement action purportedly alleged in the Complaint.

13. Cobalt Pharmaceuticals submitted Abbreviated New Drug Application ("ANDA") No. 79-167 to the United States Food and Drug Administration ("FDA").

14. Cobalt Pharmaceuticals certified to the FDA in its ANDA No. 79-167 that its proposed rosuvastatin calcium product will not infringe any valid and enforceable claim contained in the '314, and '460 patents, and that the claims of the '314 and '460 patents were not infringed, were invalid, and/or were not enforceable.

15. Defendants/Counterclaim-Plaintiffs notified Plaintiffs/Counterclaim-Defendants of the factual and legal bases for Cobalt Pharmaceutical's certifications with respect to the '314 and '460 patents in a letter of October 29, 2007 (the "Notice Letter").

16. The Notice Letter included an offer of confidential disclosure pursuant to 21 U.S.C. § 355(c)(3)(D)(i)(III).

17. By submitting certifications to the listed '314 and '460 patents in its ANDA No. 79-167, and notifying Plaintiffs/Counterclaim-Defendants of same, Cobalt Pharmaceuticals has created a case or controversy under Article III of the Constitution regarding the infringement, validity and/or unenforceability of these three patents.

18. This case or controversy provided subject matter for Plaintiffs/Counterclaim-Defendants to bring and maintain a suit alleging infringement of the '314 patent.

19. It has been more than 45 days since Plaintiffs/Counterclaim-Defendants received Cobalt's October 29, 2007 letter. Plaintiffs/Counterclaim-Defendants have not alleged infringement of the '460 patent.

20. Plaintiffs/Counterclaim-Defendants have sued Defendants/Counterclaim-Plaintiffs for infringement of the '314 patent, and have not provided a covenant not to sue Defendants/Counterclaim-Plaintiffs for alleged infringement of the '460 patent.

21. Cobalt Pharmaceutical's certifications to the FDA provided the necessary case or controversy and subject matter jurisdiction for Defendants/Counterclaim-Plaintiffs to bring and maintain the instant counterclaims for non-infringement, invalidity, and/or unenforceability of the '314 and '460 patents.

22. There is an actual, substantial and continuing justiciable case and controversy between Defendants/Counterclaim-Plaintiffs and Plaintiffs/Counterclaim-Defendants regarding infringement, invalidity, and unenforceability of the '314 and '460 patents, over which this Court can and should exercise jurisdiction and declare the rights of the parties.

Subject Matter Jurisdiction and Venue

23. This action arises under, *inter alia*, the Patent Laws of the United States, 35 U.S.C. §§ 1 *et seq.*; 28 U.S.C. §§ 2201 and 2202; 21 U.S.C. § 355(c)(3)(D)(i)-(ii) and 35 U.S.C. § 271(e)(5).

24. This Court has original jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a), because it involves substantial claims arising under the United States Patent Act, 35 U.S.C. §§ 1 *et seq.*; under 28 U.S.C. §§ 2201 and 2202 because it is an actual controversy concerning the infringement, validity and/or enforceability of the '314 and '460 patents; and under 21 U.S.C. § 355(c)(3)(D)(i)-(ii) and 35 U.S.C. § 271(e)(5) because Congress has directed that district courts maintain and exercise jurisdiction in such cases.

25. This Court can and should declare the rights and legal relations of the parties regarding the '314 and '460 patents pursuant to, *inter alia*, 28 U.S.C. §§ 2201 and 2202 and 21 U.S.C. § 355(c)(3)(D)(i)-(ii) and 35 U.S.C. § 271(e)(5).

26. This Court has personal jurisdiction over Plaintiffs/Counterclaim-Defendants because each conducts substantial business in, and has regular and systematic contact with, this District, including conduct related to the marketing, distribution and/or sale of its pharmaceutical products in this District.

27. This Court also has jurisdiction over Plaintiffs/Counterclaim-Defendants because they have availed themselves of the rights and privileges of this forum by filing numerous lawsuits in this District.

28. This Court also has personal jurisdiction over Plaintiffs/Counterclaim-Defendants because each Plaintiff has consented to jurisdiction by bringing in this District an action against Cobalt which arises from the same events as these Counterclaims.

29. Venue is proper in this District under 28 U.S.C. §§ 1391(b) and 1400(b).

First Claim for Relief: Declaratory Judgment of Invalidity of the '314 Patent

30. Defendants/Counterclaim-Plaintiffs assert and reallege paragraphs 1 through 29 of the instant Counterclaims as if fully set forth herein.

31. One or more claims of the '314 patent would have been obvious to one of skill in the relevant art in light of the prior art at the time the application from which the '314 patent issued was filed.

32. Defendants/Counterclaim-Plaintiffs are entitled to a judicial declaration that one or more claims of the '314 patent are invalid under at least one of 35 U.S.C. §§ 102, 103, 112, and/or 251.

Second Claim for Relief: Declaratory Judgment of Invalidity of the '314 Patent

33. Defendants/Counterclaim-Plaintiffs assert and reallege paragraphs 1 through 32 of the instant Counterclaims as if fully set forth herein.

34. The '314 patent is a reissue of United States Patent No. 5,260,440 (the "'440 patent").

35. One or more claims of the '314 patent are broader than the claims of the '440 patent.

36. One or more claims of the '314 patent were added more than two years after the issuance of the '440 patent.

37. Defendants/Counterclaim-Plaintiffs are entitled to a judicial declaration that one or more claims of the '314 patent are invalid under 35 U.S.C. § 251.

Third Claim for Relief: Declaratory Judgment of Unenforceability of the '314 Patent

38. Defendants/Counterclaim-Plaintiffs assert and reallege paragraphs 1 through 37 of the instant Counterclaims as if fully set forth herein.

39. Defendants/Counterclaim-Plaintiffs assert and reallege each and every allegation of its Second Defense as if fully set forth herein.

40. Defendants/Counterclaim-Plaintiffs are entitled to a judicial declaration that the '314 patent is unenforceable for inequitable conduct.

Fourth Claim for Relief:
Declaratory Judgment of Noninfringement or Invalidity of the '460 Patent

41. Defendants/Counterclaim-Plaintiffs assert and reallege paragraphs 1 through 40 of the instant Counterclaims as if fully set forth herein.

42. Defendants/Counterclaim-Plaintiffs are entitled to a judicial declaration that the manufacture, sale, offer for sale, use, or importation of Defendants/Counterclaim-Plaintiffs

proposed rosuvastatin calcium product that is the subject of NDA No. 79-167 does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid and enforceable claim of the '460 patent.

43. If any claim of the '460 patent is expanded under the doctrine of equivalents to include Defendants/Counterclaim-Plaintiffs proposed rosuvastatin calcium product, Defendants/Counterclaim-Plaintiffs are entitled to a judicial declaration that any such claim is invalid under 35 U.S.C. § 103.

Prayer

WHEREFORE, Defendants/Counterclaim-Plaintiffs pray for the following relief:

A. That it be adjudged and decreed that Defendants/Counterclaim-Plaintiffs proposed rosuvastatin calcium product described in NDA No. 79-167 does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), upon any valid, enforceable claim of U.S. Patent No. RE37,314.

B. That it be adjudged and decreed that Defendants/Counterclaim-Plaintiffs proposed rosuvastatin calcium product described in NDA No. 79-167 does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), upon any valid, enforceable claim of U.S. Patent No. 6,316,460

C. That it be adjudged and decreed that this is an exceptional case;

D. That Defendants/Counterclaim-Plaintiffs be awarded their attorneys' fees under 35 U.S.C. § 285;

E. That Defendants/Counterclaim-Plaintiffs be awarded costs and expenses in this action; and

F. That such other and further relief and damages be granted to Defendants/Counterclaim-Plaintiffs as the Court may deem justice and equity to require.

POTTER ANDERSON & CORROON LLP

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Dated: January 31, 2008
845902 / 32588

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, Richard L. Horwitz, hereby certify that on January 31, 2008, the attached document was electronically filed with the Clerk of the Court using CM/ECF which will send notification to the registered attorney(s) of record that the document has been filed and is available for viewing and downloading.

I further certify that on January 31, 2008, the attached document was Electronically Mailed the document to the following person(s):

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EXHIBIT 1



US006316460B1

(12) **United States Patent**
Creekmore et al.

(10) **Patent No.: US 6,316,460 B1**
(45) **Date of Patent: Nov. 13, 2001**

(54) **PHARMACEUTICAL COMPOSITIONS**

(75) Inventors: **Joseph R Creekmore; Norman A. Wiggins**, both of Wilmington, DE (US)

(73) Assignee: **Astrazeneca AB**, Sodertalje (SE)

(*) 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.: **09/633,064**

(22) Filed: **Aug. 4, 2000**

(30) **Foreign Application Priority Data**

Jan. 26, 2000 (GB) 0001621

(51) **Int. Cl.**[7] **A61K 31/505**; A61K 31/19
(52) **U.S. Cl.** **514/275**; 514/256; 514/557
(58) **Field of Search** 514/557, 256, 514/275

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,743,450	5/1988	Harris et al. .
5,260,440	11/1993	Hirai et al. .
5,356,896	10/1994	Kabadi et al. .
5,665,881	9/1997	Inoue et al. .
5,686,104	11/1997	Mills et al. .
6,150,410	11/2000	Engh et al. .

FOREIGN PATENT DOCUMENTS

0 336 298	3/1988	(EP) .
0 380 021	8/1990	(EP) .
0 475 482 A1	3/1992	(EP) .
0 521 471	1/1993	(EP) .
2 262 229	6/1993	(GB) .
WO 97/23200	7/1997	(WO) .
WO 99/62560	12/1999	(WO) .
WO 00/35425	6/2000	(WO) .
WO 00/42024	7/2000	(WO) .
WO 00/45817	8/2000	(WO) .
WO 00/45818	8/2000	(WO) .
WO 00/45819	8/2000	(WO) .

OTHER PUBLICATIONS

Remington's Pharmaceutical Sciences, 13th Ed., 1965, left –hand column, lines 25–27.

Primary Examiner—Zohreh Fay
Assistant Examiner—Brian-Yong Kwon
(74) *Attorney, Agent, or Firm*—Pillsbury Winthrop LLP

(57) **ABSTRACT**

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

18 Claims, No Drawings

PHARMACEUTICAL COMPOSITIONS

CROSS-REFERENCES TO RELATED APPLICATIONS

Not Applicable

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not Applicable.

BACKGROUND OF THE INVENTION

1. Field of the Invention

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

2. Description of the Related Art

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

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

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

Pharmaceutical formulations of certain 7-substituted-3,5-dihydroxy-6-heptenoic acid salts, which are HMG CoA reductase inhibitors, are disclosed in UK Patent 2262229.

These formulations require the presence of an alkaline medium (such as a carbonate or bicarbonate) capable of imparting a pH of at least 8 to an aqueous solution or dispersion of the composition.

BRIEF SUMMARY OF THE INVENTION

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Preferred compositions of the invention include, for example, those comprising the Agent, tribasic calcium phosphate and excipients selected from lactose, mannitol, microcrystalline cellulose, povidone, crospovidone, sodium starch glycollate and magnesium stearate. Preferred independent compositions of the invention include, for example, compositions comprising the Agent, tribasic calcium phosphate, microcrystalline cellulose, lactose, sodium starch glycollate, butylated hydroxytoluene and magnesium stearate; compositions comprising the Agent, povidone, tribasic calcium phosphate, microcrystalline cellulose, mannitol, sodium starch glycollate, butylated hydroxytoluene and magnesium stearate; compositions comprising the Agent, tribasic calcium phosphate, crospovidone, microcrystalline cellulose, lactose and magnesium stearate, and compositions comprising the Agent, povidone, tribasic calcium phosphate, microcrystalline cellulose, lactose, sodium starch glycollate, magnesium stearate and butylated hydroxytoluene. Where lactose and microcrystalline cellulose are used, these are preferably present in the ratio of about 1:1 to 3:1 by weight.

Compositions of the invention which are of particular interest include, for example, the specific embodiments set out hereinafter in the accompanying Examples.

The pharmaceutical composition of the invention may be prepared, using standard techniques and manufacturing processes generally known in the art, for example by dry blending the components. For example, the Agent, the tribasic phosphate salt (for example tribasic calcium phosphate), one or more fillers, one or more binders and one or more disintegrates, as well as other additional excipients if desired are blended together. The components of the blend prior to blending, or the blend itself, may be passed through a mesh screen, for example a 400–700 um mesh screen. A lubricant, which may also be screened, is then added to the blend and blending continued until a homogeneous mixture is obtained. The mixture is then compressed into tablets. Alternatively, a wet granulation technique can be employed. For example, the Agent, the tribasic phosphate salt, one or more fillers, one or more binders and a portion of a disintegrant, as well as other additional excipients if desired, are blended together, for example by using a granulator, and the powder blend is granulated with a small volume of purified water. The granulate is dried and passed though a mill. The remainder of the disintegrant and a lubricant are added to the milled granulation and after blending the resultant homogeneous mixture is compressed into tablets. It will be appreciated that modifications of the dry blending and wet granulation techniques, including the order of addition of the components and their screening and blending prior to compression into tablets, may be carried out according to principles well known in the art.

A tablet coating may then be applied, for example by spray-coating. With a water-based film coating formulation.

The coating may comprise, for example, lactose, hydroxypropyl methylcellulose, triacetin, titanium dioxide and ferric oxides. Coating ingredient combinations are commercially available, such as those described in the Examples hereinafter. The coating may comprise, for example, 0.5 to 10% by weight of the tablet composition, particularly 1 to 6%, and preferably 2 to 3%. Coatings containing ferric oxides are especially preferred as they reduce the rate of formation of photodegradation products of the Agent.

A further aspect of the present invention comprises a method of preparing a stabilised pharmaceutical composition which comprises admixing the Agent with a tribasic phosphate salt in which the cation is multivalent. A further aspect of the present invention comprises a method of producing a stabilised pharmaceutical composition which comprises incorporating a tribasic phosphate salt in which the cation is multivalent in a pharmaceutical composition containing the Agent.

The following pharmaceutical compositions, wherein the Agent is the calcium salt of formula I, are intended to illustrate the invention without being limitative in any way.

EXAMPLE 1

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

The Agent, microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, tribasic calcium phosphate, and butylated hydroxytoluene were blended together for 10 minutes. Magnesium stearate was screened through a #40 mesh (425 um) screen and added to the blend and blending continued for a further three minutes. The resulting homogeneous mixture was compressed into tablets.

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

EXAMPLE 2

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

The Agent, povidone, mannitol, microcrystalline cellulose, butylated hydroxytoluene, tribasic calcium phosphate and sodium starch glycollate (in the amounts given above) were blended for 5 to 60 minutes. Magnesium stearate was screened through a #40 mesh (425 um) screen

and added to the blend and blending continued for a further three minutes. The resulting homogeneous mixture was compressed into tablets. The compressed tablets were coated by spraying with a mixture of hydroxypropyl methylcellulose, polyethylene glycol 400, titanium dioxide and ferric oxide (sold as Spectrablend by Warner-Jenkinson) and water in a coating pan. The weight gain provided by the coating was 1 to 6% w/w, and preferably 2 to 3% w/w.

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

EXAMPLE 3

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

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

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

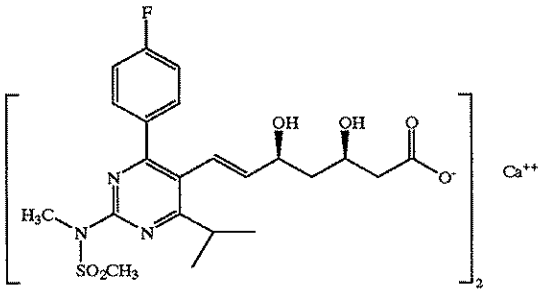
EXAMPLE 4

The Agent	2.50 mg
Povidone	2.50 mg
Tribasic calcium phosphate	20.0 mg
Microcrystalline cellulose	34.5 mg
Lactose monohydrate	34.0 mg
Sodium starch glycollate	6.00 mg
Magnesium stearate	1.00 mg
Butylated hydroxytoluene	0.05 mg

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

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

Formula 1



What we claim is:

1. A pharmaceutical composition comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof as the active ingredient and a tribasic phosphate salt in which the cation is multivalent.

2. The pharmaceutical composition as claimed in claim **1** wherein the tribasic phosphate salt in which the cation is multivalent is selected from the group consisting of tribasic calcium phosphate, tribasic magnesium phosphate and tribasic aluminum phosphate.

3. The pharmaceutical composition as claimed in claim **1** or **2** wherein the tribasic phosphate salt in which the cation is multivalent is tribasic calcium phosphate.

4. The pharmaceutical composition as claimed in claim **1** or **2** wherein the ratio of the tribasic phosphate salt to the active ingredient is in the range of 1:80 to 50:1 by weight.

5. The pharmaceutical composition as claimed in claim **1** or **2** additionally comprising one or more fillers, binders, disintegrates or lubricants.

6. A pharmaceutical composition for oral administration comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof as the active ingredient, one or more fillers, one or more binders, one or more disintegrants, one or more lubricants and a tribasic phosphate salt in which the cation is multivalent.

7. The pharmaceutical composition as claimed in claim **6** wherein the active ingredient is present in an amount 1 to 80% by weight of the composition.

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

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

10. The pharmaceutical composition as claimed in claim 6 or 7 wherein the binder is present in an amount 2 to 90% by weight of the composition.

11. The pharmaceutical composition as claimed in claim 6 or 7 wherein the disintegrant is present in an amount 2 to 10% by weight of the composition.

12. The pharmaceutical composition as claimed in claim 6 or 7 wherein the lubricant is present in an amount 0.5 to 3% by weight.

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

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

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

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

17. The pharmaceutical composition as claimed in claim 1, 2, 6, 13, 14, 15 or 16 wherein the active ingredient is the calcium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5- dihydroxyhept-6-enoic acid.

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

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