IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ALLERGAN, INC.,

Plaintiff,

v.

SANDOZ, INC., ALCON LABORATORIES, INC., ALCON RESEARCH, LTD., FALCON PHARMACEUTICALS, LTD., APOTEX, INC., APOTEX CORP., AND WATSON LABORATORIES, INC.

Defendants.

Civil Action No. _____

Jury Trial Demanded

PLAINTIFF ALLERGAN, INC.'S COMPLAINT AGAINST SANDOZ, INC., ALCON RESEARCH, LTD., ALCON LABORATORIES, INC., FALCON PHARMACEUTICALS, LTD., APOTEX INC., APOTEX CORP., AND WATSON PHARMACEUTICALS, INC.

Plaintiff Allergan, Inc. ("Allergan" or "Plaintiff") by its attorneys, Stevens, Love, Hill, & Holt PLLC and Fish & Richardson P.C., for its complaint against Defendants Sandoz, Inc. ("Sandoz"); Alcon Research, Ltd., Alcon Laboratories, Inc., and Falcon Pharmaceuticals, Ltd. (collectively, "Alcon"); Apotex, Inc. and Apotex Corp. (collectively, "Apotex"); and Watson Laboratories, Inc. ("Watson," together with Sandoz, Alcon, and Apotex, "Defendants") alleges as follows:

The Nature of the Action

1. This is an action for infringement of United States Patents No. 8,133,890 (the "'890 patent") under 35 U.S.C. § 271 (e)(2) and for Declaratory Judgment of infringement under 28 U.S.C. §§ 2201-02 and 35 U.S.C. § 271(a), (b) and (c).

The Parties

2. Allergan is a corporation organized and existing under the laws of the State of Delaware, with a principal place of business at 2525 Dupont Drive, Irvine, California 92612.

3. On information and belief, defendant Sandoz, Inc. is a Colorado corporation with its principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540.

4. On information and belief, defendant Alcon Research, Ltd. is a corporation incorporated under the laws of the State of Delaware, having a principal place of business in Texas. On information and belief, defendant Alcon Laboratories, Inc. is a corporation incorporated under the laws of the State of Delaware, and is headquartered in Fort Worth, Texas. On information and belief, Falcon Pharmaceuticals, Ltd. is a corporation incorporated under the laws of the State of Texas, having a principal place of business in Texas.

5. On information and belief, defendant Apotex, Inc. is a Canadian corporation with a place of business at 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9. On information and belief, defendant Apotex Corp. is a Delaware corporation with its principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida, 33326.

6. On information and belief, defendant Watson Laboratories, Inc. is a Nevada corporation with a place of business at 400 Interpace Parkway, Parsippany, NJ 07054.

7. On information and belief, Defendants are in the business of manufacturing, distributing and selling generic drugs throughout the United States, including in this judicial jurisdiction.

Jurisdiction and Venue

8. This action arises under the patent laws of the United States of America, United States Code, Title 35, Section 1, *et seq* and the Declaratory Judgment Act. This Court has subject matter jurisdiction over the action under 28 U.S.C. §§ 1331, 1338, 2201, and 2202.

9. This Court has personal jurisdiction over Defendants by virtue of their systematic and continuous contacts with this jurisdiction, as alleged herein, as well as because of the injury to Allergan, and the cause of action Allergan has raised, as alleged herein.

10. This Court has personal jurisdiction over defendant Sandoz, Inc. because it, either directly or through an agent, regularly does or solicits business in this jurisdiction, engages in other persistent courses of conduct in this jurisdiction, and/or derives substantial revenue from services or things used or consumed in this jurisdiction.

11. On information and belief, Sandoz, Inc. is a licensed drug distributor in Texas.

12. On information and belief, drug products of Sandoz, Inc. are listed on the Texas prescription drug formulary.

13. On information and belief, Sandoz, Inc. markets and sells generic drugs manufactured by Sandoz, Inc. throughout the United States, including this judicial district. On information and belief, Sandoz, Inc. sold approximately $840 million of its products in Texas in 2008, with at least $50 million of those sales in this judicial district.

14. This Court has personal jurisdiction over defendants Apotex, Inc. and Apotex Corp. because they, either directly or through an agent, regularly do or solicit business in this jurisdiction, engage in other persistent courses of conduct in this jurisdiction, and/or derive substantial revenue from services or things used or consumed in this jurisdiction.

15. On information and belief, Apotex, Inc. and Apotex Corp. are agents of each other and/or work in active concert with respect to the development, regulatory approval, marketing, sale and distribution of pharmaceutical products, including the generic brimonidine tartrate/timolol maleate ophthalmic solution 0.2%/0.5% described in ANDA No. 91-442.

16. On information and belief, defendant Apotex Corp. is a licensed drug distributor in Texas.

17. On information and belief, defendant Apotex, Inc.'s drug products are listed on the Texas prescription drug formulary.

18. On information and belief, defendant Apotex Corp. markets and sells numerous generic drugs, manufactured and supplied by Apotex, Inc., throughout the United States, including this judicial district. On information and belief, in 2009 Apotex Corp. sold nearly $700 million worth of Apotex, Inc. products in Texas, over $50 million of which were sold in this judicial district.

19. This Court has personal jurisdiction over defendant Watson Laboratories, Inc. because it, either directly or through an agent, regularly does or solicits business in this jurisdiction, engages in other persistent courses of conduct in this jurisdiction, and/or derives substantial revenue from services or things used or consumed in this jurisdiction.

20. On information and belief, drug products of Watson Laboratories, Inc. are listed on the Texas prescription drug formulary.

21. On information and belief, drug products of Watson Laboratories are marketed and sold throughout the United States, including this judicial district, by its agent Watson Pharma. On information and belief, Watson Pharma had over $825 million in sales in Texas alone, and at least $50 million of those sales were in this judicial district.

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

Background

23. The ’890 patent, entitled “Combination of brimonidine and timolol for topical ophthalmic use,” issued to Chin-Ming Chang, Gary J. Beck, Cynthia C. Pratt, and Amy L. Batoosingh on March 13, 2012. A copy of the ’890 patent is attached to this complaint as A.

24. Allergan, as assignee, owns the entire right, title, and interest in the ’890 patent.

25. Allegan is the holder of an approved New Drug Application (“NDA”) No. 21-398 for brimonidine tartrate/timolol maleate ophthalmic solution 0.2%/0.5%, sold under the Combigan® trademark.

26. In conjunction with that NDA, Allergan has listed with the United States Food and Drug Administration (“FDA”) five patents that cover the approved formulation or methods of using the approved formulation of Combigan®. The listed patents are U.S. Patent Nos. 7,030,149, 7,320,976, 7,323,463, 7,642,258, and the ’890 patent (collectively, “the Listed Patents”). The FDA has published these five patents in the Approved Drug Products with Therapeutic Equivalence Evaluations, commonly referred to as the “Orange Book.”

27. Combigan® or approved methods of using Combigan® are covered by at least one claim of each of the Listed Patents, including the ’890 patent.

28. On November 20, 2008, defendant Sandoz submitted its ANDA No. 91-087 to the FDA, seeking approval to commercially manufacture, use, offer for sale, or sell a generic version of Combigan®. Sandoz’s ANDA No. 91-087 received tentative approval from the FDA on May 11, 2011.

29. On May 27, 2009, Alcon submitted its Abbreviated New Drug Application No. 91-574 to the FDA, seeking approval to commercially manufacture, use, offer for sale, or sell a generic version of Combigan®. Alcon’s ANDA No. 91-574 received tentative approval from the FDA on August 3, 2010.

30. On January 29, 2010, defendant Apotex submitted its ANDA No. 91-442 to the FDA, seeing approval to commercially manufacture, use, offer for sale, or sell a generic version of Combigan®.

31. On May 7, 2010, defendant Watson submitted its ANDA No. 201949 to the FDA, seeing approval to commercially manufacture, use, offer for sale, or sell a generic version of Combigan®.

32. In an August 22, 2011 opinion, the District Court for the Eastern District of Texas found that Defendants' proposed generic versions of Combigan® infringed U.S. Patent Nos. 7,030,149, 7,320,976, 7,323,463, and 7,642,258, and that those patents were not invalid. The Court entered an injunction order on August 25, 2011 stating that Defendants were enjoined from manufacturing their proposed generic versions of Combigan® until the latest of the expiration dates of U.S. Patent Nos. 7,030,149, 7,320,976, 7,323,463, and 7,642,258.

33. In filing their ANDAs, Defendants have each requested the FDA's approval to market a generic version of Allergan's Combigan® product throughout the United States, including in Texas.

34. On information and belief, following FDA approval of ANDA Nos. 91-087, 91-574, 91-442, and 201949, each of the Defendants will sell the approved generic version of Allergan's Combigan® product throughout the United States, including in Texas.

Count I

(Infringement of the '890 Patent Under 35 U.S.C. § 271(e)(2) by Sandoz's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%)

35. Paragraphs 1 to 34 are incorporated herein as set forth above.

36. Sandoz submitted ANDA No. 91-087 to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use or sale of its proposed

Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% throughout the United States. By submitting this application, Sandoz has committed an act of infringement of the '890 patent under 35 U.S.C. § 271(e)(2)(A).

37. The commercial manufacture, use, offer for sale, sale and/or importation of Sandoz's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will constitute an act of infringement of the '890 patent.

38. On information and belief, Sandoz became aware of the '890 patent no later than the date on which that patent was listed in the Orange Book.

39. On information and belief, Sandoz knows or should know that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively induce and contribute to the actual infringement of the '890 patent.

40. On information and belief, Sandoz knows or should know that its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will be especially made for or especially adapted for use in an infringement of the '890 patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use, and that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively contribute to the actual infringement of the '890 patent.

41. The commercial manufacture, use, offer for sale, sale and/or importation of Sandoz's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% in violation of Allergan's patent rights will cause harm to Allergan for which damages are inadequate.

Count II

(Declaratory Judgment of Infringement of the '890 Patent Under 35 U.S.C. § 271(a) by Sandoz)

42. Paragraphs 1 to 41 are incorporated herein as set forth above.

43. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

44. There is an actual case or controversy such that the Court may entertain Allergan's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

45. The commercial manufacture, use, offer for sale, sale, and/or importation of Sandoz's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will constitute an act of direct infringement of one or more claims of the '890 patent.

46. On information and belief, Sandoz will engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Sandoz's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% immediately and imminently upon approval of ANDA No. 91-087.

47. The foregoing actions by Sandoz will constitute infringement of the '890 patent.

48. Sandoz will commit those acts of infringement without license or authorization.

49. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Sandoz's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% by Sandoz will infringe the '890 patent.

50. Unless Sandoz is enjoined from infringing the '890 patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

51. On information and belief, Sandoz became aware of the '890 patent no later than the date on which that patent was listed in the Orange Book.

52. On information and belief, Sandoz has made, and will continue to make, substantial preparation in the United States to manufacture, sell, offer to sell, and/or import Sandoz's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%.

53. Sandoz's actions indicate a refusal to change the course of its actions in the face of acts by Allergan.

54. On information and belief, Sandoz has acted, and will continue to act, with full knowledge of the '890 patent and without a reasonable basis for believing that it would not be liable for infringing the '890 patent.

55. On information and belief, despite having actual notice of the '890 patent, Sandoz continues to willfully, wantonly, and deliberately prepare to infringe the '890 patent in disregard of Allergan's rights, making this case exceptional and entitling Allergan to reasonable attorneys' fees pursuant to 35 U.S.C. § 285.

Count III

(Declaratory Judgment of Infringement of the '890 Patent under 35 U.S.C. § 271(b) and (c) by Sandoz's Proposed Generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%)

56. Paragraphs 1 to 55 are incorporated herein as set forth above.

57. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

58. There is an actual case or controversy such that the Court may entertain Allergan's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

59. Sandoz has actual knowledge of the '890 patent.

60. On information and belief, Sandoz became aware of the ’890 patent no later than the date on which that patent was listed in the Orange Book.

61. On information and belief, Sandoz has acted with full knowledge of the ’890 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the ’890 patent.

62. The commercial manufacture, use, sale, offer for sale, and/or importation of Sandoz’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will induce the actual infringement of the ’890 patent.

63. On information and belief, Sandoz knows or should know that its commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively induce the actual infringement of the ’890 patent.

64. On information and belief, Sandoz will encourage another’s infringement of the ’890 patent by and through the commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, which is covered by certain claims of the ’890 patent.

65. Sandoz’s acts of infringement will be done with knowledge of the ’890 patent and with the intent to encourage infringement.

66. The foregoing actions by Sandoz will constitute active inducement of infringement of the ’890 patent.

67. On information and belief, Sandoz knows or should know that its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will be

especially made or especially adapted for use in an infringement of the ’890 patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use.

68. The commercial manufacture, use, sale, offer for sale, and/or importation of Sandoz’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will contribute to the actual infringement of the ’890 patent.

69. On information and belief, Sandoz knows or should know that its offer for sale, sale and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will contribute to the actual infringement of the ’890 patent.

70. The foregoing actions by Sandoz will constitute contributory infringement of the ’890 patent.

71. On information and belief, Sandoz intends to, and will, actively induce and contribute to the infringement of the ’890 patent when ANDA No. 91-087 is approved, and plan and intend to, and will, do so immediately and imminently upon approval.

72. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Sandoz’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% by Sandoz will induce and/or contribute to infringement of the ’890 patent.

73. The commercial manufacture, use, offer for sale, sale and/or importation of Sandoz’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, which will actively induce and/or contribute to infringement of the ’890 patent, in violation of Allergan’s patent rights, will cause harm to Allergan for which damages are inadequate.

74. Unless Sandoz is enjoined from actively inducing and contributing to the infringement of the '890 patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

75. On information and belief, despite having actual notice of the '890 patent, Sandoz continues to willfully, wantonly, and deliberately prepare to actively induce and/or contribute to infringement of the '890 patent in disregard of Allergan's rights, making this case exceptional and entitling Allergan to reasonable attorneys' fees pursuant to 35 U.S.C. § 285.

Count IV

(Infringement of the '890 Patent Under 35 U.S.C. § 271(e)(2) by Alcon's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%)

76. Paragraphs 1 to 75 are incorporated herein as set forth above.

77. Alcon submitted ANDA No. 91-574 to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use or sale of its proposed Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% throughout the United States. By submitting this application, Alcon has committed an act of infringement of the '890 patent under 35 U.S.C. § 271(e)(2)(A).

78. The commercial manufacture, use, offer for sale, sale and/or importation of Alcon's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will constitute an act of infringement of the '890 patent.

79. On information and belief, Alcon became aware of the '890 patent no later than the date on which that patent was listed in the Orange Book.

80. On information and belief, Alcon knows or should know that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Brimonidine

Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively induce and contribute to the actual infringement of the '890 patent.

81. On information and belief, Alcon knows or should know that its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will be especially made for or especially adapted for use in an infringement of the '890 patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use, and that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively contribute to the actual infringement of the '890 patent.

82. The commercial manufacture, use, offer for sale, sale and/or importation of Alcon's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% in violation of Allergan's patent rights will cause harm to Allergan for which damages are inadequate.

Count V

(Declaratory Judgment of Infringement of the '890 Patent Under 35 U.S.C. § 271(a) by Alcon)

83. Paragraphs 1 to 82 are incorporated herein as set forth above.

84. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

85. There is an actual case or controversy such that the Court may entertain Allergan's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

86. The commercial manufacture, use, offer for sale, sale, and/or importation of Alcon's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will constitute an act of direct infringement of one or more claims of the '890 patent.

87. On information and belief, Alcon will engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Alcon's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% immediately and imminently upon approval of ANDA No. 91-574.

88. The foregoing actions by Alcon will constitute infringement of the '890 patent.

89. Alcon will commit those acts of infringement without license or authorization.

90. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Alcon's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% by Alcon will infringe the '890 patent.

91. Unless Alcon is enjoined from infringing the '890 patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

92. On information and belief, Alcon became aware of the '890 patent no later than the date on which that patent was listed in the Orange Book.

93. On information and belief, Alcon has made, and will continue to make, substantial preparation in the United States to manufacture, sell, offer to sell, and/or import Alcon's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%.

94. Alcon's actions indicate a refusal to change the course of its actions in the face of acts by Allergan.

95. On information and belief, Alcon has acted, and will continue to act, with full knowledge of the ’890 patent and without a reasonable basis for believing that it would not be liable for infringing the ’890 patent.

96. On information and belief, despite having actual notice of the ’890 patent, Alcon continues to willfully, wantonly, and deliberately prepare to infringe the ’890 patent in disregard of Allergan’s rights, making this case exceptional and entitling Allergan to reasonable attorneys’ fees pursuant to 35 U.S.C. § 285.

Count VI

(Declaratory Judgment of Infringement of the ’890 Patent under 35 U.S.C. § 271(b) and (c) by Alcon’s Proposed Generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%)

97. Paragraphs 1 to 96 are incorporated herein as set forth above.

98. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

99. There is an actual case or controversy such that the Court may entertain Allergan’s request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

100. Alcon has actual knowledge of the ’890 patent.

101. On information and belief, Alcon became aware of the ’890 patent no later than the date on which that patent was listed in the Orange Book.

102. On information and belief, Alcon has acted with full knowledge of the ’890 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the ’890 patent.

103. The commercial manufacture, use, sale, offer for sale, and/or importation of Alcon’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will induce the actual infringement of the ’890 patent.

104. On information and belief, Alcon knows or should know that its commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively induce the actual infringement of the ’890 patent.

105. On information and belief, Alcon will encourage another’s infringement of the ’890 patent by and through the commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, which is covered by certain claims of the ’890 patent.

106. Alcon’s acts of infringement will be done with knowledge of the ’890 patent and with the intent to encourage infringement.

107. The foregoing actions by Alcon will constitute active inducement of infringement of the ’890 patent.

108. On information and belief, Alcon knows or should know that its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will be especially made or especially adapted for use in an infringement of the ’890 patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use.

109. The commercial manufacture, use, sale, offer for sale, and/or importation of Alcon’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will contribute to the actual infringement of the ’890 patent.

110. On information and belief, Alcon knows or should know that its offer for sale, sale and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will contribute to the actual infringement of the ’890 patent.

111. The foregoing actions by Alcon will constitute contributory infringement of the ’890 patent.

112. On information and belief, Alcon intends to, and will, actively induce and contribute to the infringement of the ’890 patent when ANDA No. 91-574 is approved, and plan and intend to, and will, do so immediately and imminently upon approval.

113. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Alcon’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% by Alcon will induce and/or contribute to infringement of the ’890 patent.

114. The commercial manufacture, use, offer for sale, sale and/or importation of Alcon’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, which will actively induce and/or contribute to infringement of the ’890 patent, in violation of Allergan’s patent rights, will cause harm to Allergan for which damages are inadequate.

115. Unless Alcon is enjoined from actively inducing and contributing to the infringement of the ’890 patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

116. On information and belief, despite having actual notice of the ’890 patent, Alcon continues to willfully, wantonly, and deliberately prepare to actively induce and/or contribute to infringement of the ’890 patent in disregard of Allergan’s rights, making this case exceptional and entitling Allergan to reasonable attorneys’ fees pursuant to 35 U.S.C. § 285.

Count VII

(Infringement of the ’890 Patent Under 35 U.S.C. § 271(e)(2) by Apotex’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%)

117. Paragraphs 1 to 116 are incorporated herein as set forth above.

118. Apotex submitted ANDA No. 91-442 to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use or sale of its proposed Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% throughout the United States. By submitting this application, Apotex has committed an act of infringement of the '890 patent under 35 U.S.C. § 271(e)(2)(A).

119. The commercial manufacture, use, offer for sale, sale and/or importation of Apotex's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will constitute an act of infringement of the '890 patent.

120. On information and belief, Apotex became aware of the '890 patent no later than the date on which that patent was listed in the Orange Book.

121. On information and belief, Apotex knows or should know that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively induce and contribute to the actual infringement of the '890 patent.

122. On information and belief, Apotex knows or should know that its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will be especially made for or especially adapted for use in an infringement of the '890 patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use, and that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively contribute to the actual infringement of the '890 patent.

123. The commercial manufacture, use, offer for sale, sale and/or importation of Apotex's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% in violation of Allergan's patent rights will cause harm to Allergan for which damages are inadequate.

Count VIII

(Declaratory Judgment of Infringement of the '890 Patent Under 35 U.S.C. § 271(a) by Apotex)

124. Paragraphs 1 to 123 are incorporated herein as set forth above.

125. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

126. There is an actual case or controversy such that the Court may entertain Allergan's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

127. The commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will constitute an act of direct infringement of one or more claims of the '890 patent.

128. On information and belief, Apotex will engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% immediately and imminently upon approval of ANDA No. 91-442.

129. The foregoing actions by Apotex will constitute infringement of the '890 patent.

130. Apotex will commit those acts of infringement without license or authorization.

131. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's proposed generic

Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% by Apotex will infringe the '890 patent.

132. Unless Apotex is enjoined from infringing the '890 patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

133. On information and belief, Apotex became aware of the '890 patent no later than the date on which that patent was listed in the Orange Book.

134. On information and belief, Apotex has made, and will continue to make, substantial preparation in the United States to manufacture, sell, offer to sell, and/or import Apotex's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%.

135. Apotex's actions indicate a refusal to change the course of its actions in the face of acts by Allergan.

136. On information and belief, Apotex has acted, and will continue to act, with full knowledge of the '890 patent and without a reasonable basis for believing that it would not be liable for infringing the '890 patent.

137. On information and belief, despite having actual notice of the '890 patent, Apotex continues to willfully, wantonly, and deliberately prepare to infringe the '890 patent in disregard of Allergan's rights, making this case exceptional and entitling Allergan to reasonable attorneys' fees pursuant to 35 U.S.C. § 285.

Count IX

(Declaratory Judgment of Infringement of the '890 Patent under 35 U.S.C. § 271(b) and (c) by Apotex's Proposed Generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%)

138. Paragraphs 1 to 137 are incorporated herein as set forth above.

139. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

140. There is an actual case or controversy such that the Court may entertain Allergan's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

141. Apotex has actual knowledge of the '890 patent.

142. On information and belief, Apotex became aware of the '890 patent no later than the date on which that patent was listed in the Orange Book.

143. On information and belief, Apotex has acted with full knowledge of the '890 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '890 patent.

144. The commercial manufacture, use, sale, offer for sale, and/or importation of Apotex's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will induce the actual infringement of the '890 patent.

145. On information and belief, Apotex knows or should know that its commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively induce the actual infringement of the '890 patent.

146. On information and belief, Apotex will encourage another's infringement of the '890 patent by and through the commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, which is covered by certain claims of the '890 patent.

147. Apotex's acts of infringement will be done with knowledge of the '890 patent and with the intent to encourage infringement.

148. The foregoing actions by Apotex will constitute active inducement of infringement of the ’890 patent.

149. On information and belief, Apotex knows or should know that its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will be especially made or especially adapted for use in an infringement of the ’890 patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use.

150. The commercial manufacture, use, sale, offer for sale, and/or importation of Apotex’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will contribute to the actual infringement of the ’890 patent.

151. On information and belief, Apotex knows or should know that its offer for sale, sale and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will contribute to the actual infringement of the ’890 patent.

152. The foregoing actions by Apotex will constitute contributory infringement of the ’890 patent.

153. On information and belief, Apotex intends to, and will, actively induce and contribute to the infringement of the ’890 patent when ANDA No. 91-442 is approved, and plan and intend to, and will, do so immediately and imminently upon approval.

154. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Apotex’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% by Apotex will induce and/or contribute to infringement of the ’890 patent.

155. The commercial manufacture, use, offer for sale, sale and/or importation of Apotex’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution,

0.2%/0.5%, which will actively induce and/or contribute to infringement of the '890 patent, in violation of Allergan's patent rights, will cause harm to Allergan for which damages are inadequate.

156. Unless Apotex is enjoined from actively inducing and contributing to the infringement of the '890 patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

157. On information and belief, despite having actual notice of the '890 patent, Apotex continues to willfully, wantonly, and deliberately prepare to actively induce and/or contribute to infringement of the '890 patent in disregard of Allergan's rights, making this case exceptional and entitling Allergan to reasonable attorneys' fees pursuant to 35 U.S.C. § 285.

Count X

(Infringement of the '890 Patent Under 35 U.S.C. § 271(e)(2) by Watson's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%)

158. Paragraphs 1 to 157 are incorporated herein as set forth above.

159. Watson submitted ANDA No. 201949 to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use or sale of its proposed Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% throughout the United States. By submitting this application, Watson has committed an act of infringement of the '890 patent under 35 U.S.C. § 271(e)(2)(A).

160. The commercial manufacture, use, offer for sale, sale and/or importation of Watson's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will constitute an act of infringement of the '890 patent.

161. On information and belief, Watson became aware of the '890 patent no later than the date on which that patent was listed in the Orange Book.

162. On information and belief, Watson knows or should know that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively induce and contribute to the actual infringement of the '890 patent.

163. On information and belief, Watson knows or should know that its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will be especially made for or especially adapted for use in an infringement of the '890 patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use, and that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively contribute to the actual infringement of the '890 patent.

164. The commercial manufacture, use, offer for sale, sale and/or importation of Watson's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% in violation of Allergan's patent rights will cause harm to Allergan for which damages are inadequate.

Count XI

(Declaratory Judgment of Infringement of the '890 Patent Under 35 U.S.C. § 271(a) by Watson)

165. Paragraphs 1 to 164 are incorporated herein as set forth above.

166. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

167. There is an actual case or controversy such that the Court may entertain Allergan's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

168. The commercial manufacture, use, offer for sale, sale, and/or importation of Watson's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will constitute an act of direct infringement of one or more claims of the '890 patent.

169. On information and belief, Watson will engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Watson's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% immediately and imminently upon approval of ANDA No. 201949.

170. The foregoing actions by Watson will constitute infringement of the '890 patent.

171. Watson will commit those acts of infringement without license or authorization.

172. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Watson's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% by Watson will infringe the '890 patent.

173. Unless Watson is enjoined from infringing the '890 patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

174. On information and belief, Watson became aware of the '890 patent no later than the date on which that patent was listed in the Orange Book.

175. On information and belief, Watson has made, and will continue to make, substantial preparation in the United States to manufacture, sell, offer to sell, and/or import Watson's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%.

176. Watson's actions indicate a refusal to change the course of its actions in the face of acts by Allergan.

177. On information and belief, Watson has acted, and will continue to act, with full knowledge of the ’890 patent and without a reasonable basis for believing that it would not be liable for infringing the ’890 patent.

178. On information and belief, despite having actual notice of the ’890 patent, Watson continues to willfully, wantonly, and deliberately prepare to infringe the ’890 patent in disregard of Allergan’s rights, making this case exceptional and entitling Allergan to reasonable attorneys’ fees pursuant to 35 U.S.C. § 285.

Count XII

(Declaratory Judgment of Infringement of the ’890 Patent under 35 U.S.C. § 271(b) and (c) by Watson’s Proposed Generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%)

179. Paragraphs 1 to 178 are incorporated herein as set forth above.

180. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

181. There is an actual case or controversy such that the Court may entertain Allergan’s request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

182. Watson has actual knowledge of the ’890 patent.

183. On information and belief, Watson became aware of the ’890 patent no later than the date on which that patent was listed in the Orange Book.

184. On information and belief, Watson has acted with full knowledge of the ’890 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the ’890 patent.

185. The commercial manufacture, use, sale, offer for sale, and/or importation of Watson’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will induce the actual infringement of the ’890 patent.

186. On information and belief, Watson knows or should know that its commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will actively induce the actual infringement of the ’890 patent.

187. On information and belief, Watson will encourage another’s infringement of the ’890 patent by and through the commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, which is covered by certain claims of the ’890 patent.

188. Watson’s acts of infringement will be done with knowledge of the ’890 patent and with the intent to encourage infringement.

189. The foregoing actions by Watson will constitute active inducement of infringement of the ’890 patent.

190. On information and belief, Watson knows or should know that its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will be especially made or especially adapted for use in an infringement of the ’890 patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use.

191. The commercial manufacture, use, sale, offer for sale, and/or importation of Watson’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will contribute to the actual infringement of the ’890 patent.

192. On information and belief, Watson knows or should know that its offer for sale, sale and/or importation of its proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% will contribute to the actual infringement of the ’890 patent.

193. The foregoing actions by Watson will constitute contributory infringement of the ’890 patent.

194. On information and belief, Watson intends to, and will, actively induce and contribute to the infringement of the ’890 patent when ANDA No. 201949 is approved, and plan and intend to, and will, do so immediately and imminently upon approval.

195. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Watson’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% by Watson will induce and/or contribute to infringement of the ’890 patent.

196. The commercial manufacture, use, offer for sale, sale and/or importation of Watson’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, which will actively induce and/or contribute to infringement of the ’890 patent, in violation of Allergan’s patent rights, will cause harm to Allergan for which damages are inadequate.

197. Unless Watson is enjoined from actively inducing and contributing to the infringement of the ’890 patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

198. On information and belief, despite having actual notice of the ’890 patent, Watson continues to willfully, wantonly, and deliberately prepare to actively induce and/or contribute to infringement of the ’890 patent in disregard of Allergan’s rights, making this case exceptional and entitling Allergan to reasonable attorneys’ fees pursuant to 35 U.S.C. § 285.

Jury Trial Demand

Pursuant to Federal Rule of Civil Procedure 38(b), Allergan hereby demands a trial by jury of all issues so triable.

Prayer for Relief

Plaintiffs respectfully pray for the following relief:

a. That judgment be entered that Sandoz has infringed the '890 patent under 35 U.S.C. § 271(e)(2)(A) by submitting an ANDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, sale and/or importation of Sandoz's proposed Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% product will constitute an act of infringement of the '890 patent;

b. That an order be issued under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of Sandoz's ANDA shall be a date which is not earlier than the expiration date of the '890 patent, as extended by any applicable period of exclusivity;

c. Than an injunction be issued under 35 U.S.C. § 271(e)(4)(B) permanently enjoining Sandoz, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with it or acting on its behalf, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product covered by the '890 patent;

d. If Sandoz attempts to engage in the commercial manufacture, use, offer to sell, sale or importation of Sandoz's generic product disclosed in its ANDA prior to the expiration of the '890 patent, as extended by any applicable period of exclusivity, a preliminary injunction be entered enjoining such conduct;

e. If Sandoz attempts to engage in the commercial manufacture, use, offer to sell, sale or importation of Sandoz's generic product disclosed in its ANDA prior to the expiration of the '890 patents, as extended by any applicable period of exclusivity, judgment awarding Allergan damages resulting from such infringement under 35 U.S.C. § 271(e)(4)(C), increased to treble the amount found or assessed together with interest pursuant to 35 U.S.C. § 284;

f. That a declaration be issued under 28 U.S.C. § 2201 that if Sandoz, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf engage in the commercial manufacture, use, offer for sale, sale and/or importation of Sandoz's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, it will constitute an act of infringement of the '890 patent;

g. That judgment be entered that Alcon has infringed the '890 patent under 35 U.S.C. § 271(e)(2)(A) by submitting an ANDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, sale and/or importation of Alcon's proposed Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% product will constitute an act of infringement of the '890 patent;

h. That an order be issued under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of Alcon's ANDA shall be a date which is not earlier than the expiration date of the '890 patent, as extended by any applicable period of exclusivity;

i. Than an injunction be issued under 35 U.S.C. § 271(e)(4)(B) permanently enjoining Alcon, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with it or acting on its behalf, from engaging in the commercial manufacture, use, offer to sell, or sale

within the United States, or importation into the United States, of any drug product covered by the ’890 patent;

j. If Alcon attempts to engage in the commercial manufacture, use, offer to sell, sale or importation of Alcon’s generic product disclosed in its ANDA prior to the expiration of the ’890 patents, as extended by any applicable period of exclusivity, a preliminary injunction be entered enjoining such conduct;

k. If Alcon attempts to engage in the commercial manufacture, use, offer to sell, sale or importation of Alcon’s generic product disclosed in its ANDA prior to the expiration of the ’890 patents, as extended by any applicable period of exclusivity, judgment awarding Allergan damages resulting from such infringement under 35 U.S.C. § 271(e)(4)(C), increased to treble the amount found or assessed together with interest pursuant to 35 U.S.C. § 284;

l. That a declaration be issued under 28 U.S.C. § 2201 that if Alcon, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf engage in the commercial manufacture, use, offer for sale, sale and/or importation of Alcon’s proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, it will constitute an act of infringement of the ’890 patent;

m. That judgment be entered that Apotex has infringed the ’890 patent under 35 U.S.C. § 271(e)(2)(A) by submitting an ANDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, sale and/or importation of Apotex’s proposed Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% product will constitute an act of infringement of the ’890 patent;

n. That an order be issued under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of Apotex's ANDA shall be a date which is not earlier than the expiration date of the '890 patent, as extended by any applicable period of exclusivity;

o. Than an injunction be issued under 35 U.S.C. § 271(e)(4)(B) permanently enjoining Apotex, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with it or acting on its behalf, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product covered by the '890 patent;

p. If Apotex attempts to engage in the commercial manufacture, use, offer to sell, sale or importation of Apotex's generic product disclosed in its ANDA prior to the expiration of the '890 patents, as extended by any applicable period of exclusivity, a preliminary injunction be entered enjoining such conduct;

q. If Apotex attempts to engage in the commercial manufacture, use, offer to sell, sale or importation of Apotex's generic product disclosed in its ANDA prior to the expiration of the '890 patents, as extended by any applicable period of exclusivity, judgment awarding Allergan damages resulting from such infringement under 35 U.S.C. § 271(e)(4)(C), increased to treble the amount found or assessed together with interest pursuant to 35 U.S.C. § 284;

r. That a declaration be issued under 28 U.S.C. § 2201 that if Apotex, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf engage in the commercial manufacture, use, offer for sale, sale and/or importation of Apotex's

proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, it will constitute an act of infringement of the ’890 patent;

s. That judgment be entered that Watson has infringed the ’890 patent under 35 U.S.C. § 271(e)(2)(A) by submitting an ANDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, sale and/or importation of Watson’s proposed Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5% product will constitute an act of infringement of the ’890 patent;

t. That an order be issued under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of Watson’s ANDA shall be a date which is not earlier than the expiration date of the ’890 patent, as extended by any applicable period of exclusivity;

u. Than an injunction be issued under 35 U.S.C. § 271(e)(4)(B) permanently enjoining Watson, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with it or acting on its behalf, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product covered by the ’890 patent;

v. If Watson attempts to engage in the commercial manufacture, use, offer to sell, sale or importation of Watson’s generic product disclosed in its ANDA prior to the expiration of the ’890 patents, as extended by any applicable period of exclusivity, a preliminary injunction be entered enjoining such conduct;

w. If Watson attempts to engage in the commercial manufacture, use, offer to sell, sale or importation of Watson’s generic product disclosed in its ANDA prior to the expiration of the ’890 patents, as extended by any applicable period of exclusivity, judgment awarding

Allergan damages resulting from such infringement under 35 U.S.C. § 271(e)(4)(C), increased to treble the amount found or assessed together with interest pursuant to 35 U.S.C. § 284;

x. That a declaration be issued under 28 U.S.C. § 2201 that if Watson, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf engage in the commercial manufacture, use, offer for sale, sale and/or importation of Watson's proposed generic Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%, it will constitute an act of infringement of the '890 patent;

y. That this is an exceptional case under 35 U.S.C. § 285, and that Allergan be awarded reasonable attorneys' fees and costs;

z. An accounting for infringing sales not presented at trial and an award by the court of additional damages for any such infringing sales; and

aa. That this Court award such other and further relief as it may deem just and proper.

Dated: April 13, 2012

Respectfully submitted,

By: /s/ *Gregory P. Love*

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EXHIBIT A

US008133890B2

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

(10) **Patent No.: US 8,133,890 B2**
(45) **Date of Patent: *Mar. 13, 2012**

(54) **COMBINATION OF BRIMONIDINE AND TIMOLOL FOR TOPICAL OPHTHALMIC USE**

(75) Inventors: **Chin-Ming Chang**, Tustin, CA (US); **Gary J. Beck**, Fullerton, CA (US); **Cynthia C. Pratt**, Mission Viejo, CA (US); **Amy L. Batoosingh**, Mission Viejo, CA (US)

(73) Assignee: **Allergan, Inc.**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 494 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/946,828**

(22) Filed: **Nov. 28, 2007**

(65) **Prior Publication Data**

US 2008/0132512 A1 Jun. 5, 2008

Related U.S. Application Data

(63) Continuation of application No. 10/685,941, filed on Oct. 14, 2003, now Pat. No. 7,320,976, which is a continuation of application No. 10/126,790, filed on Apr. 19, 2002, now Pat. No. 7,030,149.

(51) **Int. Cl.**
A61K 31/517 (2006.01)
A61K 31/535 (2006.01)

(52) **U.S. Cl.** **514/249**; 514/236.2

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are pharmaceutical compositions comprising brimondine and timolol for topical ophthalmic delivery and a method of treatment comprising administering said composition when indicated for glaucoma and associated conditions such as elevated intraocular pressure in the eyes of humans.

15 Claims, No Drawings

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COMBINATION OF BRIMONIDINE AND TIMOLOL FOR TOPICAL OPHTHALMIC USE

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is continuing application of patent application Ser. No. 10/685,941, filed Oct. 14, 2003, now U.S. Pat. No. 7,320,976 which is a continuing application of patent application Ser. No. 10/126,790, filed on Apr. 19, 2002 now U.S. Pat. No. 7,030,149.

BACKGROUND

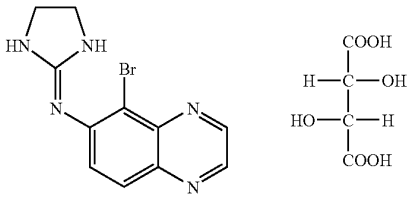
This invention relates to the topical ophthalmic use of brimonidine in combination with timolol when indicated for treatment of glaucoma or ocular hypertension. Such combinations or formulations are available for separate use in the ophthalmic art and have been combined in serial application during the course of treatment of glaucoma. However, there are concerns and expressed reservations in the ophthalmic community about patient compliance when the patient is required to administer separate medications to treat a single disease or condition such as glaucoma. There is, moreover, a long felt need for an effective and safe topical ophthalmic pharmaceutical composition including brimonidine and timolol which has increased stability and requires a lower effective concentration of preservative as compared to the individual agents taken alone. Finally, there is a need to increase the efficacy of many topical ophthalmic agents, without increasing the systemic concentration of such topical agents, since it is well known that many of such topically-applied ophthalmic agents cause systemic side effects, e.g. drowsiness, heart effects, etc. Unexpectedly it has been discovered that brimonidine in combination with timolol meets these criteria.

Brimonidine is disclosed in U.S. Pat. No. 3,890,319. The use of brimonidine for providing neuroprotection to the eye is disclosed in U.S. Pat. Nos. 5,856,329; 6,194,415 and 6,248,741.

Timolol, as an ophthalmic drug, is disclosed in U.S. Pat. Nos. 4,195,085 and 4,861,760.

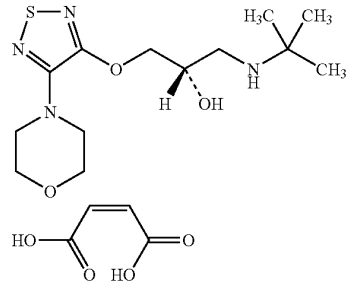
DESCRIPTION OF THE INVENTION

Brimonidine is an alpha adrenergic agonist represented by the following formula:



The chemical name for brimonidine is 5-Bromo-6-(2-imidazolidinylideneamino)quinoxaline L-tartrate.

Timolol is a beta adrenergic agent represented by the following formula:



Brimonidine is available from Allergan, Inc., Irvine, Calif. as an ophthalmic pharmaceutical product having the name Alphagan®. Timolol is available from various sources, including Merck Co., Rahway, N.J.

The compositions of the present invention are administered topically. The dosage is 0.001 to 1.0, e.g. mg/per eye BID; wherein the cited mass figures represent the sum of the two components, brimonidine and timolol. The compositions of the present invention can be administered as solutions in a suitable ophthalmic vehicle.

In forming compositions for topical administration, the mixtures are preferably formulated as 0.01 to 0.5 percent by weight brimonidine and 0.1 to 1.0 percent by weight timolol solution in water at a pH of 4.5 to 8.0, e.g. about 6.9. While the precise regimen is left to the discretion of the clinician, it is recommended that the solution be topically applied by placing one drop in each eye two times a day. Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents and viscosity building agents.

Antimicrobial Preservative:

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. In the prior art ophthalmic products, typically such preservatives are employed at a level of from 0.004% to 0.02%. In the compositions of the present application the preservative, preferably benzalkonium chloride, may be employed at a level of from 0.001% to less than 0.01%, e.g. from 0.001% to 0.008%, preferably about 0.005% by weight. It has been found that a concentration of benzalkonium chloride of 0.005% is sufficient to preserve the compositions of the present invention from microbial attack. This concentration may be advantageously compared to the requirement of 0.01% benzalkonium chloride to preserve timolol in the individual, commercially-available ophthalmic products. Moreover, it has been found that adequate lowering of intraocular pressure has been obtained when administering the compositions of this invention twice a day as compared to the FDA-approved regimen wherein brimonidine ophthalmic solution, i.e. Alphagan® ophthalmic solution is administered three times a day and timolol ophthalmic solution, i.e. Timoptic® ophthalmic solution is administered twice a day. This results in the exposure of the patient to 67% and 50% of benzalkonium chloride, with the compositions of this invention, as compared to the administration of Alphagan® and Timoptic®, respectively. In FDA-approved adjunctive

therapy, wherein Alphagan® and Timoptic® are serially administered, the patient is exposed to almost three times the concentration of benzalkonium chloride as compared to the administration of the compositions of this invention twice a day. (It is noted that it is known that benzalkonium chloride at high concentrations is cytotoxic. Therefore, minimizing the patient's exposure to benzalkonium chloride, while providing the preservative effects afforded by benzalkonium chloride, is clearly desirable.)

Co-Solvents:

The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such cosolvents include polysorbate 20, 60, and 80, Pluronic F68, F-84 and P-103, cyclodextrin, or other agents known to those skilled in the art. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

Viscosity Agents:

Viscosity increased above that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulation, to decrease physical separation of components of a suspension or emulsion of the formulation and/or to otherwise improve the ophthalmic formulation. Such viscosity building agents include as examples polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

The present invention further comprises an article of manufacture comprising packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for lowering intraocular pressure and wherein the packaging material comprises a label which indicates the pharmaceutical agent can be used for lowering intraocular pressure and wherein said pharmaceutical agent comprises an effective amount of brimonidine and an effective amount of timolol.

The following example is a representative pharmaceutical composition of the invention for topical use when indicated for treating glaucoma.

EXAMPLE I

The combination of active pharmaceutical ingredients is as follows: Brimonidine Tartrate 0.20% (w/v) and Timolol Maleate 0.68% (w/v) (Equivalent to 0.50% (w/v) timolol)

The Brimonidine-Timolol combination formulation presented in the Table, below, is a sterile, preserved, aqueous solution. The formulation vehicle is based upon a timolol ophthalmic solution which contains an isotonic phosphate buffer system at pH 6.9. The formulation preservative is benzalalkonium chloride (BAK) at a concentration of 0.005% (w/v) (50 ppm). The formulation passes regulatory required preservative efficacy testing (PET) criteria for USP (United States Pharmacopoeia) and EP (European Pharmacopoeia-A and -B over 24 months.

TABLE

Ingredient	Function	Concentration, %(w/v)
Brimonidine Tartrate	Active	0.2
Timolol Maleate, EP	Active	0.68[1]
Benzalkonium Chloride, NF, EP	Preservative	0.005
Sodium Phosphate, monobasic monohydrate, USP	Buffer	0.43
Sodium Phosphate, dibasic heptahydrate, USP	Buffer	2.15
Sodium Hydroxide, NF	pH adjust	Adjust pH to 6.9
Hydrochloric Acid, NF	pH adjust	Adjust pH to 6.9
Purified Water, USP, EP	Solvent	q.s. ad

[1]Equivalent to 0.5%(w/v) Timolol, free base

The pharmaceutical composition of Example I is used in the clinical study reported below.

EXAMPLE II

Objectives

To compare the safety and efficacy of twice-daily dosed brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution combination (henceforth referred to as Combination) with that of twice-daily dosed timolol ophthalmic solution 0.5% (henceforth referred to as Timolol) and three-times-daily dosed ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% (henceforth referred to as Brimonidine) administered for three months (plus 9-month masked extension) in patients with glaucoma or ocular hypertension.

Methodology:

Structure: multicenter, double-masked, randomized, parallel-group, active control

Randomization: patients were randomized to one of the 3 masked treatment groups (Combination, Brimonidine or Timolol) based on an even allocation at each site

Visit Schedule: prestudy, baseline (day 0), week 2, week 6, month 3, month 6, month 9, and month 12

Number of Patients (Planned and Analyzed):

560 planned to enroll; 586 enrolled (Combination=193, Brimonidine=196, Timolol=197); 502 completed. Mean (range) age: 62.4 (23 to 87) years; 46.1% (270/586) males, 53.9% (316/586) females.

Diagnosis and Main Criteria for Inclusion:

Diagnosis: ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma or pigmentary glaucoma and requiring bilateral treatment.

Key Inclusion Criteria: ≧18 years, day 0 (post-washout) intraocular pressure (IOP) ≧22 mm Hg and ≦34 mm Hg in each eye and asymmetry of IOP ≦5 mm Hg, best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity equivalent to a Snellen score of 20/100 or better in each eye.

Key Exclusion Criteria: uncontrolled systemic disease, abnormally low or high blood pressure or pulse rate for age or contraindication to beta-adrenoceptor antagonist therapy, anticipated alteration of existing chronic therapy with agents which could have a substantial effect on IOP, contraindication to brimonidine therapy, allergy or sensitivity to any of the study medication ingredients, anticipated wearing of contact lenses during the study, laser surgery, intraocular filtering surgery or any other ocular surgery within the past 3 months, or required chronic use of other ocular medications during the study (intermittent use of artificial tear product was allowed).

Test Product, Dose and Mode of Administration, Batch Number:

Brimonidine tartrate 0.2%/timolol 0.5% combination ophthalmic solution one drop (~35 μL) instilled in each eye BID in the morning and evening; and vehicle of the Combination

ophthalmic solution, one drop (~35 μL) instilled in each eye once daily (QD) in the afternoon (for masking purposes).

Duration of Treatment: 3 months (with a 9-month masked extension)

Reference Therapy, Dose and Mode of Administration, Batch Number:

Active control ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%, one drop (~35 μL) instilled in each eye TID in the morning, afternoon, and evening. Active control timolol ophthalmic solution 0.5%, one drop (~35 μL) instilled in each eye BID in the morning and evening; and vehicle of the Combination ophthalmic solution, one drop (~35 μL) instilled in each eye once daily (QD) in the afternoon (for masking purposes).

Criteria for Evaluation:

Efficacy:

IOP (hours 0, 2, 7, and 9), patient satisfaction questionnaire, patient comfort of study medication questionnaire, pharmacoeconomic evaluation by investigator

Safety:

Adverse events (AE), biomicroscopy, visual acuity (VA), visual field, opthalmoscopy, cup/disc ratio, heart rate, blood pressure, hematology, serum chemistry, urinalysis and pregnancy test.

Other:

Quantitation of plasma brimonidine and timolol concentrations (at selected sites), resource utilization (to be reported upon completion of the 1 year study).

Statistical Methods:

All data were summarized with descriptive statistics, frequency tables, and/or data listings. Safety analyses included all patients who received at least 1 dose of study medication. Analyses were performed for the primary efficacy variable IOP using the intent-to-treat (ITT) population with last observation carried forward (LOCF), and the per protocol population with observed cases.

Ordinal categorical variables were analyzed by the Wilcoxon rank-sum test. Nominal categorical variables were analyzed using Fisher's exact or Pearson's chi-square tests. Within-group changes from baseline for categorical variables were analyzed using the Wilcoxon signed-rank test. Continuous variables (eg, IOP) were analyzed using analysis of variance (ANOVA). Within-group changes from baseline for continuous variables were analyzed using paired t-tests.

A 2-way ANOVA model with factors for treatment and investigator was used for the analysis of IOP. Comparisons were made between the Combination and each of the 2 monotherapies in a pairwise fashion using contrasts from the ANOVA model, with the same error term. A separate ANOVA model was employed at each hour/visit measurement of IOP. Each of the 2 null hypotheses (Combination versus Timolol and Combination versus Brimonidine) was tested at the 0.05 significance level. Point estimates of the mean treatment differences, as well as 2-sided 95% confidence intervals (CI) of the difference, were provided at each timepoint.

Summary—Conclusions:

Efficacy:

At baseline, mean values of diurnal IOP ranged from 22.2 mm Hg to 24.9 mm Hg in the Combination group, 22.5 mm Hg to 25.0 mm Hg in the Brimonidine group, and 22.3 mm Hg to 24.8 mm Hg in the Timolol group. There were no statistically significant differences between treatment groups.

Mean changes from baseline diurnal IOP at week 2, week 6 and month 3 ranged from:

−5.2 to −7.9 mm Hg in the Combination group
−3.5 to −5.7 mm Hg in the Brimonidine group
−4.5 to −6.4 mm Hg in the Timolol group

The mean decreases from baseline diurnal IOP were statistically significant within each treatment group at each follow-up timepoint ($p<0.001$).

The mean decrease from baseline diurnal IOP was statistically significantly greater with Combination than with Brimonidine at hours 0, 2, and 7 at all follow-up visits ($p<0.001$). In addition, clinically significant differences of more than 1.5 mm Hg in mean change from baseline IOP favoring Combination over Brimonidine were seen at hours 0, 2, and 7 at all follow-up visits. At hour 9, the decreases from baseline diurnal IOP were greater for the Combination group than the Brimonidine group at all follow-up visits, although the differences were not statistically significant ($p\geqq0.104$).

The mean decrease from baseline diurnal IOP was statistically significantly greater with Combination than with Timolol at hours 0, 2, 7 and 9 at all follow-up visits ($p\leqq0.041$). In addition, clinically significant differences of more than 1.5 mm Hg in mean change from baseline IOP favoring Combination over Timolol were seen at week 2 (hours 0, 2, and 7), week 6 (hours 2 and 7), and month 3 (hours 0 and 2).

Mean values of diurnal IOP at week 2, week 6 and month 3 ranged from:

15.9 to 18.1 mm Hg in the Combination group
17.4 to 21.5 mm Hg in the Brimonidine group
17.5 to 18.9 mm Hg in the Timolol group

Mean values of diurnal IOP were statistically significantly less with Combination than with Brimonidine at hours 0, 2, and 7 at all follow-up visits ($p<0.001$) and at hour 9 at week 6 and month 3 ($p\leqq0.011$). The mean values of IOP at hour 9 at week 2 were lower for the Combination group than the Brimonidine group, although the difference was not statistically significant ($p=0.205$). In addition, clinically significant differences of more than 1.5 mm Hg in mean IOP favoring Combination over Brimonidine were seen at hours 0, 2, and 7 at all follow-up visits and at hour 9 at month 3.

Mean values of diurnal IOP were statistically significantly less with Combination than with Timolol at hour 0 at week 2 and month 3; and at hours 2, 7 and 9 at all follow-up visits ($p\leqq0.050$). The mean values of IOP at hour 0, week 6, were lower for the Combination group than the Timolol group, although the difference was not statistically significant ($p=0.102$). In addition, clinically significant differences of more than 1.5 mm Hg in mean IOP favoring Combination over Timolol were seen at week 2 (hours 0, 2, and 7), week 6 (hours 2, 7, and 9), and month 3 (hours 2 and 9).

At the month 3 or exit visit, a statistically significantly greater "yes" response to the Investigator Pharmacoeconomic Evaluation was recorded for patients receiving Combination (91.1%, 173/190) than for patients receiving Brimonidine (73.4%, 141/192, $p<0.001$). A "yes" response was recorded for 92.7% (179/193) of patients receiving Timolol. There were no statistically significant differences in the change from baseline in treatment comfort between Combination and each of the monotherapy groups.

Treatment satisfaction was better than baseline for a statistically significantly greater percentage of patients in the Combination group (23.4%, 36/154) than in the Brimonidine group (13.2%, 20/151, $p=0.005$). A total of 19.9% (30/151) of patients in the Timolol group reported better treatment satisfaction than baseline.

Safety:

Through month 3 of the study, 53.4% (103/193) of patients in the Combination group, 61.7% (121/196) of the Brimonidine group, and 50.8% (100/197) of the Timolol group experienced one or more adverse events, regardless of causality. The incidences of oral dryness, eye pruritus, foreign body

sensation and conjunctival folliculosis were statistically significantly lower with the Combination than with Brimonidine ($p \leqq 0.034$), while burning and stinging were statistically significantly higher with the Combination than with Brimonidine ($p \leqq 0.028$). There were no statistically significant differences in adverse events between the Combination and Timolol, except for a statistically significantly higher incidence of eye discharge with the Combination (2.6%, 5/193) compared to Timolol (0%, 0/197; p=0.029). The most frequently reported adverse events (>3% in any treatment group) were as follows, tabulated by descending order in the Combination group:

Preferred Term	Combination N = 193	Brimonidine N = 196	Timolol N = 197
burning sensation in eye	23 (11.9%)	11 (5.6%)	25 (12.7%)
conjunctival hyperemia	16 (8.3%)	23 (11.7%)	11 (5.6%)
stinging sensation eye	13 (6.7%)	4 (2.0%)	11 (5.6%)
infection (body as a whole)	11 (5.7%)	6 (3.1%)	8 (4.1%)
visual disturbance	6 (3.1%)	11 (5.6%)	3 (1.5%)
epiphora	5 (2.6%)	8 (4.1%)	3 (1.5%)
oral dryness	4 (2.1%)	19 (9.7%)	1 (0.5%)
eye pruritus	3 (1.6%)	13 (6.6%)	3 (1.5%)
allergic conjunctivitis	3 (1.6%)	7 (3.6%)	0 (0.0%)
asthenia	3 (1.6%)	6 (3.1%)	1 (0.5%)
foreign body sensation	2 (1.0%)	10 (5.1%)	5 (2.5%)
conjunctival folliculosis	2 (1.0%)	9 (4.6%)	1 (0.5%)
somnolence	2 (1.0%)	7 (3.6%)	0 (0.0%)

Adverse events led to the discontinuation of 3.6% (7/193) of patients in the Combination group, similar to 3.0% (6/197) of patients in the Timolol group, and statistically significantly less than 14.3% (28/196) of patients in the Brimonidine group ($p<0.001$). Serious adverse events were reported for 1.0% (2/193) of patients in the Combination group, 2.0% (4/196) of patients in the Brimonidine group, and 2.0% (4/197) of patients in the Timolol group. Two patients receiving Timolol had 4 serious adverse events (emphysema in one patient; nausea, sweating, and tachycardia in the other patient) which were considered possibly related to the study drug. There was 1 death in the Brimonidine group, possibly due to complications from cardiac surgery, and not related to study drug.

There were no clinically relevant differences between the Combination and either of the individual components in the mean change from baseline to month 3 for any hematology, chemistry, or urinalysis parameter. Statistically significant ($p \leqq 0.048$) within-group changes from baseline were found, but were small and not clinically relevant.

Small but statistically significant ($p \leqq 0.001$) mean reductions in heart rate ranging from −2.1 to −3.7 bpm were seen with the Combination, similar to Timolol. Small but statistically significant ($p \leqq 0.003$) mean reductions in blood pressure at hour 2 (postdose) were seen with the Combination, similar to Brimonidine. These small changes in mean heart rate and blood pressure were associated with clinical symptoms in only a few patients.

Increases from baseline in the severity of conjunctival erythema and conjunctival follicles on biomicroscopy were statistically significantly less with the Combination than with Brimonidine ($p \leqq 0.011$). The majority of patients in each treatment group showed less than a 2-line change from baseline visual acuity.

There were no significant between-group differences for changes in visual fields or cup/disc ratio.

Pharmacokinetics:

Blood samples were available for 55 patients in the Combination group, 49 patients in the Brimonidine group, and 54 patients in the Timolol group. All samples were assayed for both brimonidine (lower limit of quantitation [LLOQ] 5 pg/mL) and timolol (LLOQ 5 pg/mL). Plasma brimonidine and timolol concentrations were not quantifiable in all but 1 sample on day 0, hour 0 for both Combination and the monotherapy treatment groups.

In the Combination group, mean ±standard deviation (SD) plasma brimonidine concentrations 1 hour postdose at week 2 and month 3 were 49.7±36.1 and 52.8±46.7 pg/mL, respectively. In the Brimonidine group, mean ±SD plasma brimonidine concentrations at week 2 and month 3 were 81.0±63.8 and 78.6±48.9 pg/mL, respectively. In the Combination group, mean ±SD plasma timolol concentrations at week 2 and month 3 were 0.499±0.327 and 0.586±0.580 ng/mL, respectively. In the Timolol group, mean ±SD plasma timolol concentrations at week 2 and month 3 were 0.950±0.709 and 0.873±0.516 ng/mL, respectively.

Plasma brimonidine and timolol concentrations 1 hour postdose were steady and did not increase over the 3-month study duration. Brimonidine concentrations were 39%, 34% and 39% lower in the Combination group than in the monotherapy group at week 2 (p=0.004), month 3 (p=0.013), and month 12, respectively.

Timolol concentrations were 47% and 33% lower in the Combination group than in the monotherapy group at week 2 ($p<0.001$) and month 3 (p=0.011), respectively.

Timolol concentrations were also significantly lower in the combination treatment group than in the Timolol monotherapy treatment group (p=0.0006). Timolol concentrations were 49%, 32%, and 21% lower in the combination group than in the monotherapy group at week 2, month 3, and month 12, respectively.

The plasma brimonidine concentration in males was statistically significantly lower than in females for the Brimonidine group (37% lower at week 2 [p=0.034] and 37% lower at month 3 [p=0.017]); the difference was not statistically significant in the Combination group. The plasma timolol concentration in males was statistically significantly lower than in females for both the Combination group (not statistically significant at week 2; 52% lower at month 3 [p=0.012]) and the Timolol group (45% lower at week 2 [p=0.006] and 39% lower at month 3 [p=0.003]).

Plasma brimonidine concentration in the elderly group was not significantly different from in the young group for the combined data from both the combination and Brimonidine treatment groups (p-value=0.1323). However, plasma timolol concentration in the young group was significantly lower than in the elderly group for combined data from both the combination and the Timolol treatment groups (p-value=0.0005).

CONCLUSIONS

The Combination treatment (brimonidine tartrate 0.2%/timolol 0.5%) administered BID for 3 months was superior to Timolol (timolol 0.5%) BID and Brimonidine (brimonidine tartrate 0.2%) TID in lowering the elevated IOP of patients with glaucoma or ocular hypertension. The Combination administered BID demonstrated a favorable safety profile that was comparable to Timolol BID and better than Brimonidine TID with regard to the incidence of adverse events and discontinuations due to adverse events.

The invention has been described herein by reference to certain preferred embodiments. However, as obvious varia-

tions thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto.

The invention claimed is:

1. A method of treating a patient exhibiting elevated intraocular pressure (IOP), the method comprising administering twice daily to an affected eye a composition comprising 0.2% w/v, brimonidine and 0.5% w/v, timolol in a single composition, wherein said method results in a lower incidence of one or more adverse events, as compared to brimonidine in the absence of timolol, where the adverse event is selected from the group consisting of oral dryness, eye pruritus, foreign body sensation, allergic conjunctivitis, somnolence and conjunctival folliculosis.

2. A method according to claim **1**, wherein the brimonidine is selected from the group consisting of brimonidine tartrate and brimonidine free base.

3. A method according to claim **1**, wherein the timolol is selected from the group consisting of timolol tartrate, timolol maleate and timolol free base.

4. A method according to claim **1**, wherein the brimonidine is selected from the group consisting of brimonidine tartrate and brimonidine free base and the timolol is selected from the group consisting of timolol tartrate, timolol maleate and timolol free base.

5. A method according to claim **1**, wherein the brimonidine is brimonidine tartrate.

6. A method according to claim **1**, wherein the timolol is timolol maleate.

7. A method according to claim **1**, wherein the brimonidine is brimonidine tartrate and the timolol is timolol maleate.

8. A method according to claim **1** wherein the composition further comprises benzalkonium chloride.

9. A method according to claim **8** wherein the composition further comprises from 0.001% w/v to less than 0.01% w/v benzalkonium chloride.

10. A method according to claim **9** wherein the composition further comprises about 0.005% w/v benzalkonium chloride.

11. A method according to any one of claims **1**, **4**, **8** and **9** wherein the adverse event is allergic conjunctivitis.

12. A method according to claim **1**, wherein the patient has one or more of ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma or pigmentary glaucoma.

13. A method of reducing elevated intraocular pressure associated with glaucoma or ocular hypertension comprising administering twice daily to an affected eye a single composition comprising both 0.2% w/v brimonidine tartrate and about 0.5% w/v timolol, wherein the method results in a lower incidence of oral dryness, eye pruritus, allergic conjunctivitis, foreign body sensation, somnolence, or conjunctival folliculosis as compared to using 0.2% w/v brimonidine tartrate in the absence of timolol.

14. The method of claim **13**, wherein the composition is administered twice daily for at least 3 months.

15. The method of claim **14**, wherein the composition is administered twice daily for at least 1 year.

* * * * *

JS 44 (Rev. 09/11)

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 civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS
Allergan, Inc.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Gregory P. Love, Stevens Love, P. O. Box 3427, Longview, Texas 75606-3427, 903/753-6760

DEFENDANTS
Sandoz, Inc., Alcon Research, Ltd., Alcon Laboratories, Inc., Falcon Pharmaceuticals, Ltd., Apotex Inc., Apotex Corp., and Watson Laboratories, Inc.

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF 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) (For Diversity Cases Only) and One Box for Defendant)*

	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
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- ☐ 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
- ☐ 362 Personal Injury - Med. Malpractice

PERSONAL INJURY
- ☐ 365 Personal Injury - Product Liability
- ☐ 367 Health Care/ Pharmaceutical 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
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 448 Education

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 463 Habeas Corpus - Alien Detainee (Prisoner Petition)
- ☐ 465 Other Immigration Actions

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
- ☐ 375 False Claims Act
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 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

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(e)(2), 28 U.S.C. 2201-02 and 35 U.S.C. 271(a), (b) and (c)

Brief description of cause:
Patent Infringement and Declaratory Judgment of 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 _____

DATE 04/13/2012

SIGNATURE OF ATTORNEY OF RECORD /s/ Gregory P. Love

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

JS 44 Reverse (Rev. 09/11)

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 statutes 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.