IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ONYX THERAPEUTICS, INC.,	)	
Plaintiff,	)	
v.	)	C.A. No. 18-598-LPS
CIPLA LIMITED and CIPLA USA, INC.,	)	
Defendants.	)	

DEFENDANTS' ANSWER AND
CIPLA USA, INC.'S COUNTERCLAIMS

Defendants CIPLA Limited and CIPLA USA, Inc., for their answer to the complaint by their undersigned attorneys allege as follows:

1. On information and belief, admit the allegations of paragraph 1 of the complaint.

2. Admit that CIPLA USA, Inc. is incorporated in Delaware and except as expressly admitted, deny the allegations of paragraph 2 of the complaint.

3. Admit the allegations of paragraph 3 of the complaint.

4. Admit that CIPLA Limited caused ANDA 209479 to be filed and except as so expressly admitted denies the allegations of paragraph 4 of the complaint.

5. Admit that CIPLA USA, Inc. ("CIPLA USA") is a 100% owned subsidiary of Invagen Pharmaceuticals, Inc. Invagen Pharmaceuticals, Inc. is a 100% owned subsidiary of CIPLA (EU Limited), which is a 100% owned subsidiary of CIPLA Limited, and except as so expressly admitted, deny the allegations of paragraph 5 of the complaint.

6. Admit that CIPLA USA was agent for the filing of ANDA 209479, and except as so expressly admitted, deny the allegations of paragraph 6 of the complaint.

7. Admit that this action alleges patent infringement of the listed patents arising out of ANDA 209479 filed with the FDA and seeking approval to market the ANDA product that is the subject of ANDA 209479 ("the proposed ANDA product") prior to the expiration of the listed patents, and except as so expressly admitted, deny the allegations of paragraph 7 of the complaint.

8. Admit the allegations of paragraph 8 of the complaint.

9. Admit the allegations of paragraph 9 of the complaint.

10. Admit for purpose of this action only that this Court has personal jurisdiction over CIPLA USA and except as so expressly admitted, deny the allegations of paragraph 10 of the complaint.

11. Deny the allegations of paragraph 11 of the complaint.

12. Deny the allegations of paragraph 12 of the complaint.

13. Admit that CIPLA Limited has previously sued in this district, admit that CIPLA Limited has previously consented to jurisdiction in specific cases, and except as so expressly admitted, deny the allegations of paragraph 13 of the complaint.

14. Admit for purposes of this litigation only that CIPLA Limited and CIPLA USA do not contest venue, and except as so expressly admitted, deny the allegations of paragraph 14 of the complaint.

15. Admit that U.S. Patent No. 7,417,042 ("the '042 patent") was issued on August 26, 2008 and will expire on July 20, 2026, and deny knowledge and information

sufficient to form a belief as to the owner of the ‘042 patent, admit that a copy of the ‘042 patent is attached to the complaint as Exhibit A, and except as so expressly admitted, deny the allegations of paragraph 15 of the complaint.

16. Admit that U.S. Patent No. 7,737,112 (“the ‘112 patent”) was issued on June 15, 2010 and will expire on December 7, 2027, deny knowledge and information sufficient to form a belief as to the owner of the ’112 patent, admit that a copy of the ‘112 patent is attached to the complaint as Exhibit B, and except as so expressly admitted, deny the allegations of paragraph 16 of the complaint.

17. Admit that U.S. Patent No. 8,207,125 (“the ‘125 patent”) was issued on June 26, 2012 and will expire on April 14, 2025, deny knowledge and information sufficient to form a belief as to the owner of the ‘125 patent, admit that a copy of the ‘125 patent is attached to the complaint as Exhibit C, and except as so expressly admitted, deny the allegations of paragraph 17 of the complaint.

18. Admit that U.S. Patent No. 8,207,126 (“the ‘126 patent) was issued on June 26, 2012 and will expire on April 14, 2025, deny knowledge and information sufficient to form a belief as to the owner of the ‘126 patent, admit that a copy of the ‘126 patent is attached to the complaint as Exhibit D, and except as so expressly admitted, deny the allegations of paragraph 18 of the complaint.

19. Admit that U.S. Patent No. 8,207,127 (“the ‘127 patent”) was issued on June 26, 2012 and will expire on April 14, 2025, deny knowledge and information sufficient to form a belief as to the owner of the ’127 patent, admit that a copy of the ’127 patent is attached to the complaint as Exhibit E, and except as so expressly admitted, deny the allegations of paragraph 19 of the complaint.

20. Deny knowledge or information sufficient to form a belief as to the allegations of paragraph 20 of the complaint.

21. Deny knowledge or information sufficient to form a belief as to the allegations of paragraph 21 of the complaint.

22. Admit that Kyprolis® for injection is FDA approved for intravenous use, refer to the product label for the contents thereof, and except as so expressly admitted, deny knowledge and information sufficient to form a belief as to the allegations of paragraph 22 of the complaint.

23. Admit that Kyprolis® for injection is FDA approved for intravenous use, refer to the product label for the contents thereof, and deny knowledge or information sufficient to form a belief as to the allegations of paragraph 23 of the complaint.

24. Admit that carfilzomib is the active ingredient in Kyprolis®, refer to the Kyprolis® label for the contents thereof, and deny knowledge and information sufficient to form a belief as to the allegations of paragraph 24 of the complaint.

25. Admit on information and belief the allegations of paragraph 25 of the complaint.

26. Admit that the patents in suit have been listed in the Orange book for the product Kyprolis®, and except as so expressly admitted, deny the allegations of paragraph 26 of the complaint.

27. Deny knowledge and information sufficient to form a belief as to the allegations of paragraph 27 of the complaint.

28. Admit the allegations of paragraph 28 of the complaint.

29. Admit the allegations of paragraph 29 of the complaint.

30. Deny the allegations of paragraph 30 for the complaint.

31. Admit the allegations of paragraph 31 of the complaint.

32. Admit that carfilzomib is the active ingredient in the proposed ANDA product, refer to the proposed ANDA product label of the reference product for the contents thereof and FDA approvals, and except as so expressly admitted, deny the allegations of paragraph 32 of the complaint.

33. Admit that the proposed ANDA product is bioequivalent to Kyprolis®, and except as so expressly admitted, deny the allegations of paragraph 33 of the complaint.

34. Deny the allegations of paragraph 34 of the complaint.

35. Deny the allegations of paragraph 35 of the complaint.

36. Deny knowledge and information sufficient to form a belief as to the allegations of paragraph 36 of the complaint.

37. Deny the allegations of paragraph 37 of the complaint.

38. Defendants incorporate the answers to paragraphs 1--37 of the complaint herein as if fully set forth.

39. Admit that the proposed ANDA product contains carfilzomib as its active ingredient, and except as so expressly admitted, deny the allegations of paragraph 39 of the complaint.

40. Admit that the submission of the ANDA 209479 constitutes a technical act of infringement for the purpose only of giving the court jurisdiction to litigate patent

infringement, validity and enforceability issues, and except as so admitted, deny the allegations of paragraph 40 of the complaint.

41. Admit that the defendants plan to commercially manufacture and sell the proposed ANDA product, at some time after approval by the FDA, and except as so expressly admitted, deny the allegations of paragraph 41 of the complaint.

42. Deny the allegations of paragraph 42 of the complaint.

43. Deny the allegations of paragraph 43 of the complaint.

44. Admit that the defendants had knowledge of the '042 patent when ANDA 209479 was filed, and except as so expressly admitted, deny the allegations of paragraph 44 of the complaint.

45. Refer to the contents of the letter dated March 19, 2018 for the contents thereof and except as so expressly admitted, deny the allegations of paragraph 45 of the complaint.

46. Deny the allegations of paragraph 46 of the complaint.

47. Deny the allegations of paragraph 47 of the complaint.

48. Deny the allegations of paragraph 48 of the complaint.

49. Defendants reallege the answers to paragraphs 1--48 of the complaint herein as if fully set forth.

50. Admit that the proposed ANDA product contains carfilzomib, SBECD, and citric acid, and except as so expressly admitted, deny the allegations of paragraph 50 of the complaint.

51. Admit that the submission of the ANDA 209479 constitutes a technical act of infringement for the purpose only of giving the court jurisdiction to litigate the issues of patent infringement, validity, and enforceability, and except as so expressly admitted, deny the allegations of paragraph 51 of the complaint.

52. Admit that the defendants plan to commercially manufacture and sell the proposed ANDA product, at some time after approval by the FDA, and except as so expressly admitted, deny the allegations of paragraph 52 of the complaint.

53. Deny the allegations of paragraph 53 of the complaint.

54. Deny the allegations of paragraph 54 of the complaint.

55. Admit that the defendants had knowledge of the ’112 patent when ANDA 209479 was filed with the FDA, and except as so expressly admitted, deny the allegations of paragraph 55 of the complaint.

56. Refer to the contents of the March 19, 2018 notice letter for the contents thereof, and except as expressly admitted, deny the allegations of paragraph 56 of the complaint.

57. Deny the allegations of paragraph 57 of the complaint.

58. Deny the allegations of paragraph 58 of the complaint.

59. Deny the allegations of paragraph 59 of the complaint.

60. Defendants reallege the answers to paragraphs 1--59 of the complaint as if fully set forth herein.

61. Admit that the proposed ANDA product contains carfilzomib, and except as so expressly admitted, deny the allegations of paragraph 61 of the complaint.

62. Admit that the submission of ANDA 209479 constitutes a technical act of infringement for the purpose only of giving the court jurisdiction to litigate the issues of patent infringement, validity, and enforceability, and except as so expressly admitted, deny the allegations of paragraph 62 of the complaint.

63. Admit that the defendants plan to commercially manufacture and sell the proposed ANDA product at some time after approval by the FDA, and except as so expressly admitted, deny the allegations of paragraph 63 of the complaint.

64. Deny the allegations of paragraph 64 of the complaint.

65. Deny the allegations of paragraph 65 of the complaint.

66. Admit that the defendants had knowledge of the '125 patent when ANDA 209479 was filed, and except as so expressly admitted, deny the allegations of paragraph 66 of the complaint.

67. Deny the allegations of paragraph 67 of the complaint.

68. Deny the allegations of paragraph 68 of the complaint.

69. Deny the allegations of paragraph 69 of the complaint.

70. Deny the allegations of paragraph 70 of the complaint.

71. Defendants reallege the answers to paragraphs 1--70 of the complaint as if fully set forth herein.

72. Admit that the proposed ANDA product contains carfilzomib, and except as so expressly admitted, deny the allegations of paragraph 72 of the complaint.

73. Admit that the submission of ANDA 209479 constitutes a technical act of

infringement for the purpose only of giving the court jurisdiction to litigate the issues of patent infringement, validity, and enforceability, and except as so expressly admitted, deny the allegations of paragraph 73 of the complaint.

74. Admit that the defendants plan to commercially manufacture and sell the proposed ANDA product at some time after approval by the FDA, and except as so expressly admitted, deny the allegations of paragraph 74 of the complaint.

75. Deny the allegations of paragraph 75 of the complaint.

76. Deny the allegations of paragraph 76 of the complaint.

77. Admit that defendants had knowledge of the '126 patent when ANDA 209479 was filed with the FDA, and except is so expressly admitted, deny the allegations of paragraph 77 of the complaint.

78. Refer to the March 19, 2018 notice letter for the contents thereof, and except as so expressly admitted, deny the allegations of paragraph 78 of the complaint.

79. Deny the allegations of paragraph 79 of the complaint.

80. Deny the allegations of paragraph 80 of the complaint.

81. Deny the allegations of paragraph 81 of the complaint.

82. Defendants reallege the answers to paragraphs 1--82 of the complaint as if fully set forth herein.

83. Admit that the proposed ANDA product contains carfilzomib, and except as so expressly admitted, deny the allegations of paragraph 83 of the complaint.

84. Admit that the submission of ANDA 209479 constitutes a technical act of

infringement for the purpose only of giving the court jurisdiction to litigate the issues of patent infringement, validity, and enforceability, and except as so expressly admitted, deny the allegations of paragraph 84 of the complaint.

85. Admit that the defendants plan to commercially manufacture and sell the proposed ANDA product at some time after approval by the FDA, and except as so expressly admitted, deny the allegations of paragraph 85 of the complaint.

86. Deny the allegations of paragraph 86 of the complaint.

87. Deny the allegations of paragraph 87 of the complaint.

88. Admit that defendants had knowledge of the '127 patent when ANDA 209479 was filed with the FDA, and except as so expressly admitted, deny the allegations of paragraph 88 of the complaint.

89. Deny the allegations of paragraph 89 of the complaint.

90. Deny the allegations of paragraph 90 of the complaint.

91. Deny the allegations of paragraph 91 of the complaint.

FIRST DEFENSE

92. The Court lacks personal jurisdiction over CIPLA Limited.

SECOND DEFENSE

93. The claims of the patents in suit are invalid for failure to comply with one or more requirements of 35 U.S.C. §§ 101, 102, 103 and 112.

THIRD DEFENSE

94. The claims of the '112 patent are invalid for obviousness type double patenting.

FOURTH DEFENSE

95. Plaintiffs are not entitled to any of the relief sought in the complaint.

FIFTH DEFENSE

96. Defendants reserve the right to assert any additional defenses that are made known to it in the course of discovery.

CIPLA USA'S COUNTERCALIMS

CIPLA USA alleges for its Counterclaims against Onyx Therapeutics, Inc. as follows:

97. CIPLA USA is a corporation organized under the law of the state of Delaware with its principle place of business at Cipla USA, Inc. 1560 Sawgrass Corporate Parkway, Suite 130 Sunrise, FL 33323 USA.

98. On information and belief, Onyx Therapeutics, Inc. ("Onyx") is a corporation organized under the laws of Delaware with its principle place of business at One Amgen Drive, Thousand Oaks, CA 91320. Onyx alleges it is the owner of the '042 patent, the '112 patent, the '125 patent, the '126 patent, and the '127 patent and has alleged that CIPLA USA has infringed each of these patents.

99. CIPLA USA denies infringement and asserts that each of the patents asserted in this action are invalid, and an actual and present controversy exits between Onyx and

CIPLA USA.

100. This Court has jurisdiction of these counterclaims pursuant to 28 U.S.C. §§ 2201 and 1338.

101. Venue is proper in this district.

FIRST COUNTERCLAIM

102. The allegations of paragraphs 1-101 are reincorporated herein as if fully set forth.

103. The claims of the '042 patent that encompass the compound carfilzomib or compositions containing the compound carfilzomib are invalid as obvious under 35 U.S.C. § 103 because the compound is an obvious variation of compounds that are known in the art and disclosed as having the claimed utility as shown by Meng, *et al.*, "Epoxomicin, A Potent and Selective Proteasome Inhibitor Exhibits In Vivo Anti-inflammatory Activity," 96 *Proc. Nat'l Assoc. Sci.* 10403-10408 (August 1999); Meng, *et al.*, "Eponemycin Exerts Its Antitumor Effect Through the Inhibition of Proteasome Function," 59 *Cancer Research* 2798-2801 (June 15, 1999); Elofsson *et al.*, "Towards subunit-specific proteasome inhibitors: synthesis and evaluation of peptide α' β'-epoxykeytones," *Chemistry & Biology*, November 1999, pp. 811-822 ("Elofsson 1999"); WO2001/28579 A2; U.S. Patent 6,083,903; and U.S. Patent 6,265,380 B1; and U.S. patent 6,831,099.

SECOND COUNTERCLAIM

104. The allegations of paragraphs 1-103 are reincorporated herein as if fully set forth.

105. The ‘112 patent claims use of well-known excipients for their usual purposes. See, for example, Strickley, “Solubilizing Excipients in Oral and Injectable Formulations,” 21(2) *Pharmaceutical Research* 201-230 at 215 (February 2004); *Remington’s Pharmaceutical Sciences* 18th edition 1990.

106. The claims of the ‘112 patent are invalid under 35 U.S.C. § 103 as obvious.

THIRD COUNTERCLAIM

107. The allegations of paragraphs 1--106 are reincorporated herein as if fully set forth.

108. Claim 12 of the ‘112 patent requires that the buffer achieve a pH at which 10% of the inhibitor molecules are ionized, and claim 13 requires that the buffer achieve a pH where 50% of the inhibitor molecules are ionized.

109. The ‘112 patent specification provides no description of a composition with the ionization of claims 12 or 13 and no instruction on how to make such a composition.

110. Claims 12 and 13 are invalid under 35 U.S.C. § 112 for lack of a written description.

FOURTH COUNTERCLAIM

111. The allegations of paragraphs 1--110 are reincorporated herein as if fully set forth.

112. The limitations of claims 1-32 of the ‘112 patent concerning the use of routine pharmaceutical excipients in making the pharmaceutical compositions in common ranges

do not make those claims patentably distinct over claim 25 of the '125 patent. See *Remington's Pharmaceutical Sciences* 18th edition 1990.

113. Lyophilization of injectable formulations was a well-known technique. See, for example, Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," 21(2) *Pharmaceutical Research* 201-230 at 215 (February 2004), routinely used for injectable formulations in the prior art, and claim 32 of the '112 patent adds no patentable distinction over the '125 patent.

114. The claims of the '112 patent are invalid for obviousness type double patenting over the '125 patent.

FIFTH COUNTERCLAIM

115. The allegations of paragraphs 1--114 are reincorporated herein as if fully set forth.

116. The claims of the '125 patent are obvious because the claimed compound carfilzomib is obvious, and because it was obvious to make the claimed compositions which include routine pharmaceutical excipients and salts for their known purposes.

117. Claim 18 of the '125 patent is also obvious because the prior art taught the preparation of solid forms that are reconstituted for injection. Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," 21(2) *Pharmaceutical Research* 201-230 at 215 (February 2004).

118. Claims 14 and 15 of the '125 patent, which require one or more other therapeutic agents in addition to carfilzomib in a composition is obvious because the prior art taught the use of related proteasome inhibitors in combination with other therapeutic agents,

including anti-cancer agents. See U.S. Patent No. 6,831,099.

119. The claims of the '125 patent are invalid under 35 U.S.C. § 103.

SIXTH COUNTERCLAIM

120. The allegations of paragraphs 1--119 are reincorporated herein as if fully set forth.

121. The claims 1-19 of the '126 patent are to the process of mixing the obvious compound carfilzomib with pharmaceutical carriers.

122. Claims 20 and 21 of the '126 are to compositions prepared by these methods.

123. Pharmaceutical carriers are routinely mixed with pharmaceutical compounds to make drug products, and it is obvious to combine an obvious pharmaceutical compound with pharmaceutical carriers. See *Remington's Pharmaceutical Sciences*, 18th edition 1990.

124. The claims of the '126 patent are invalid under 35 U.S.C. § 103.

SEVENTH COUNTERCLAIM

125. The allegations of paragraphs 1--124 are reincorporated herein as if fully set forth.

126. Claims 1-19 of the '126 patent are process claims and are not eligible for listing in the Orange Book.

127. The filing of ANDA 209479 is not an act of infringement of those claims.

EIGHTH COUNTERCLAIM

128. The allegations of paragraphs 1--127 are reincorporated herein as if fully set forth.

129. The prior art taught that proteasome inhibitors, such as the obvious compound carfilzomib, were useful in the treatment of cancers, including specifically the treatment of hematopoietic cancers such as leukemia and multiple myeloma. See, for example, Orlowski, *et al.*, "Phase I Trial of the Proteasome Inhibitor PS-341 in Patients with Refractory Hematologic Malignancies," 20(22) *J. Clin. Oncology* 4420-4427 (Nov. 15, 2002).

130. Claims 12-20 of the '127 patent recite the use of standard pharmaceutical excipients in the formation of pharmaceutical compositions of the compound carfilzomib or its pharmaceutically acceptable salts.

131. Claims 21 and 22 of the '127 patent require the presence of a second unspecified therapeutic agent or an unspecified chemotherapeutic agent in the composition. The prior art specifically taught the use of closely related proteasome inhibitors with a second anti-cancer agent.

132. Claims 23-27 of the '127 patent specify a formulation that is in intravenous form, or solid form reconstituted for intravenous administration and the prior art taught the use of such forms with proteasome inhibitors.

133. The claims of the '127 patent are invalid under 35 U.S.C. § 103.

NINTH COUNTERCLAIM

134. The allegations of paragraphs 1--133 are reincorporated herein as if fully set forth.

135. If the claims of the ‘127 patent are not obvious based on the prior art disclosure, they are not enabled under 35 U.S.C. §112 because the specification has no other evidence of the effectiveness of the claimed compounds in treating hematopoietic cancers.

TENTH COUNTERCLAIM

136. The allegations of paragraphs 1--135 are reincorporated herein as if fully set forth.

137. CIPLA USA is a pharmaceutical company that does not treat patients or administer pharmaceuticals.

138. CIPLA USA will not directly infringe nor induce infringement nor contribute to infringement of any of the method of treatment claims of the ‘127 patent.

ELEVENTH COUNTERCLAIM

139. The allegations of paragraphs 1--138 are reincorporated herein as if fully set forth.

140. Plaintiff had knowledge that the patents in suit were invalid and not infringed when it commenced this action.

141. This is an exceptional case.

WHEREFORE, the defendants respectfully request the Court to grant the following relief:

1. Dismiss the complaint with prejudice and deny each request for relief made by patentee therein;

2. Declare each of the claims of the patents in suit invalid;

3. Declare that no valid claim of the patents in suit are infringed by the defendants;

4. Declare that there is no direct, indirect (induced or contributory), literal infringement or under doctrine of equivalents by the defendants;

5. Award to defendants their costs and attorneys' fees; and

6. Such other and further relief as is just and proper.

Respectfully submitted,

GREENBERG TRAURIG, LLP

/s/ Benjamin J. Schladweiler

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Dated: May 16, 2018

CERTIFICATE OF SERVICE

I, Benjamin J. Schladweiler, hereby certify that on May 16, 2018, a true copy of the foregoing ***Defendants' Answer and CIPLA USA, Inc.'s Counterclaims*** was served via electronic mail upon the following counsel of record:

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