

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

ONYX THERAPEUTICS, INC., )  
 )  
 Plaintiff, )  
 )  
 v. ) C.A. No. \_\_\_\_\_  
 )  
 APOTEX INC. and APOTEX CORP., )  
 )  
 Defendants. )

**COMPLAINT FOR PATENT INFRINGEMENT**

Plaintiff Onyx Therapeutics, Inc. (“Plaintiff” or “Onyx”) brings this action for patent infringement against Apotex Inc. and Apotex Corp. (collectively, “Defendants” or “Apotex”).

**THE PARTIES**

1. Plaintiff Onyx is a corporation organized under the laws of the State of Delaware, having a principal place of business at One Amgen Center Drive, Thousand Oaks, California 91320-1799. Onyx is a wholly owned subsidiary of Onyx Pharmaceuticals, Inc. Onyx Pharmaceuticals, Inc. is a wholly owned subsidiary of Amgen Inc.

2. On information and belief, Defendant Apotex Inc. is a Canadian corporation, having a principal place of business at 150 Signet Drive, Toronto, Ontario M9L 1T9, Canada.

3. On information and belief, Defendant Apotex Corp. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326.

4. On information and belief, Apotex has made or has caused to be made the proposed generic carfilzomib 30 mg lyophilized powder for reconstitution and for intravenous administration (the “Proposed ANDA Product”) that is the subject of ANDA No. 211185 and, through the filing of that ANDA with the U.S. Food and Drug Administration (“FDA”) pursuant

to 21 U.S.C. § 355(j) (Section 505(j) of the Federal Food, Drug and Cosmetic Act), seeks regulatory approval to market and sell the Proposed ANDA Product throughout the United States, including within this District.

5. On information and belief, Apotex Corp. is a wholly owned subsidiary of Apotex Inc., and is controlled by Apotex Inc.

6. On information and belief, Apotex Corp. acts as the U.S. agent of Apotex Inc. with respect to ANDA No. 211185, and it will work, either directly or indirectly, to manufacture, import, market, and sell the Proposed ANDA Product.

7. On information and belief, Apotex Corp. and Apotex Inc. are in the business of, among other things, developing, preparing, manufacturing, selling, marketing, and distributing generic pharmaceutical products throughout the United States, including in the State of Delaware.

#### **NATURE OF THE ACTION**

8. This is a civil action for patent infringement under the patent laws of the United States, Title 35, United States Code, arising out of Apotex's ANDA No. 211185, filed with the FDA seeking approval to engage in the commercial manufacture, use and sale of the Proposed ANDA Product prior to the expiration of U.S. Patent Nos. 7,417,042; 7,232,818; 7,491,704; 7,737,112; 8,129,346; 8,207,125; 8,207,126; 8,207,127; and 8,207,297 ("the Patents-in-Suit"), which are owned by Onyx.

9. The Proposed ANDA Product is a generic version of Onyx's KYPROLIS<sup>®</sup> (carfilzomib) for injection.

**JURISDICTION AND VENUE**

10. This Court has jurisdiction over the subject matter of this action, which arises under the patent laws of the United States, pursuant to 28 U.S.C. §§ 1331 and 1338(a), and 35 U.S.C. § 1 et seq.

11. This Court has personal jurisdiction over Defendants because, on information and belief, Defendants directly or indirectly, manufacture, import, market, and sell generic drugs throughout the United States and in this judicial district.

12. On information and belief, Apotex Corp. and Apotex Inc. are working in concert for the purposes of developing, formulating, manufacturing, marketing, and selling drug products throughout the United States, including Delaware, and Delaware will be a destination of the Proposed ANDA Product.

13. This Court also has jurisdiction over Defendants because, *inter alia*, this action arises from actions of Defendants directed toward Delaware, and because Defendants have purposefully availed themselves of the rights and benefits of Delaware law by engaging in systematic and continuous contacts with Delaware. Upon information and belief, Defendants regularly and continuously transact business within Delaware, including by selling pharmaceutical products in Delaware, either on their own or through their affiliates. Upon information and belief, Defendants derive substantial revenue from the sale of those products in Delaware and have availed themselves of the privilege of conducting business within Delaware.

14. This Court has jurisdiction over Defendants because, *inter alia*, upon information and belief, Defendants have previously been sued in this judicial district without objecting on the basis of lack of personal jurisdiction and have availed themselves of Delaware courts through the assertions of counterclaims in suits brought in Delaware. *See, e.g., Senju Pharm. Co. Ltd. et al.*

*v. Apotex Inc. et al.*, Civil Action No. 07-0779 (D. Del.); *Forest Labs. Inc. et al. v. Apotex Corp. et al.*, Civil Action No. 14-0200 (D. Del.); *Onyx Therapeutics, Inc. v. Apotex Inc. et al.*, Civil Action No. 16-1039 (D. Del.); *Onyx Therapeutics, Inc. v. Apotex Inc. et al.*, Civil Action No. 17-1202 (D. Del.). Upon information and belief, Defendants have previously submitted to the jurisdiction of this Court and have availed themselves of the legal protections of the State of Delaware by having filed suit in this jurisdiction. *See, e.g., Apotex Inc. et al. v. Senju Pharm. Co., Ltd. et al.*, Civil Action No. 12-196 (D. Del.); *Apotex Inc. et al. v. Pfizer Inc. et al.*, Civil Action No. 03-0900 (D. Del.).

15. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391(b), (c) and 1400(b).

**THE PATENTS-IN-SUIT**

16. United States Patent No. 7,417,042 (the “’042 Patent”), entitled “Compounds For Enzyme Inhibition,” was duly and legally issued on August 26, 2008 and will expire on July 20, 2026. Onyx is the owner of the ’042 Patent. A copy of the ’042 Patent is attached as Exhibit A.

17. United States Patent No. 7,232,818 (the “’818 Patent”), entitled “Compounds For Enzyme Inhibition,” was duly and legally issued on June 19, 2007 and will expire on April 14, 2025. Onyx is the owner of the ’818 Patent. A copy of the ’818 Patent is attached as Exhibit B.

18. United States Patent No. 7,491,704 (the “’704 Patent”), entitled “Compounds For Enzyme Inhibition,” was duly and legally issued on February 17, 2009 and will expire on April 14, 2025. Onyx is the owner of the ’704 Patent. A copy of the ’704 Patent is attached as Exhibit C.

19. United States Patent No. 7,737,112 (the “’112 Patent”), entitled “Composition For Enzyme Inhibition,” was duly and legally issued on June 15, 2010 and will expire on December

7, 2027. Onyx is the owner of the '112 Patent. A copy of the '112 Patent is attached as Exhibit D.

20. United States Patent No. 8,129,346 (the "'346 Patent"), entitled "Compounds For Enzyme Inhibition," was duly and legally issued on March 6, 2012 and will expire on April 14, 2025. Onyx is the owner of the '346 Patent. A copy of the '346 Patent is attached as Exhibit E.

21. United States Patent No. 8,207,125 (the "'125 Patent"), entitled "Compounds For Enzyme Inhibition," was duly and legally issued on June 26, 2012 and will expire on April 14, 2025. Onyx is the owner of the '125 Patent. A copy of the '125 Patent is attached as Exhibit F.

22. United States Patent No. 8,207,126 (the "'126 Patent"), entitled "Compounds For Enzyme Inhibition," was duly and legally issued on June 26, 2012 and will expire on April 14, 2025. Onyx is the owner of the '126 Patent. A copy of the '126 Patent is attached as Exhibit G.

23. United States Patent No. 8,207,127 (the "'127 Patent"), entitled "Compounds For Enzyme Inhibition," was duly and legally issued on June 26, 2012 and will expire on April 14, 2025. Onyx is the owner of the '127 Patent. A copy of the '127 Patent is attached as Exhibit H.

24. United States Patent No. 8,207,297 (the "'297 Patent"), entitled "Compounds For Enzyme Inhibition," was duly and legally issued on June 26, 2012 and will expire on April 14, 2025. Onyx is the owner of the '297 Patent. A copy of the '297 Patent is attached as Exhibit I.

### **FACTUAL BACKGROUND**

#### **KYPROLIS<sup>®</sup> (CARFILZOMIB) FOR INJECTION**

25. On July 20, 2012, the FDA granted accelerated approval to Onyx to market KYPROLIS<sup>®</sup> (carfilzomib) for injection to treat relapsed or refractory multiple myeloma, a type of cancer, and more specifically a type of hematopoietic cancer. Per the FDA, the accelerated approval program is designed to provide patients with earlier access to promising new drugs.

Previously, in January 2011, the FDA had granted KYPROLIS<sup>®</sup> (carfilzomib) for injection “Fast Track” designation, which is a unique FDA process designed to facilitate the development and expedite the review of drugs based on the FDA’s determination that it has the potential to treat serious conditions and fill an unmet medical need.

26. As described in the FDA approved label for KYPROLIS<sup>®</sup> (carfilzomib) for injection, several clinical studies have established the drug’s effectiveness for treating relapsed or refractory multiple myeloma. One such clinical study is the pivotal Phase 3 head-to-head ENDEAVOR study comparing KYPROLIS<sup>®</sup> (carfilzomib) for injection plus dexamethasone to VELCADE<sup>®</sup> (bortezomib) plus dexamethasone, which is a current standard of care in relapsed multiple myeloma. The data showed that patients treated with KYPROLIS<sup>®</sup> (carfilzomib) for injection plus dexamethasone achieved progression-free survival of 18.7 months compared to 9.4 months in those receiving VELCADE<sup>®</sup> (bortezomib) plus dexamethasone. Put differently, the ENDEAVOR study demonstrates that patients treated with KYPROLIS<sup>®</sup> (carfilzomib) for injection lived almost twice as long without disease worsening as those treated with VELCADE<sup>®</sup> (bortezomib).

27. KYPROLIS<sup>®</sup> (carfilzomib) for injection is approved by the FDA in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy; and as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

28. KYPROLIS<sup>®</sup> (carfilzomib) for injection is FDA approved for intravenous use. It is FDA approved as a lyophilized powder in a single-dose 30 mg or 60 mg vial. Each 30 mg vial contains 30 mg of carfilzomib, 1500 mg sulfobutylether beta-cyclodextrin, and 28.9 mg

anhydrous citric acid and sodium hydroxide for pH adjustment (target pH 3.5). Each 60 mg vial contains 60 mg of carfilzomib, 3000 mg sulfobutylether beta-cyclodextrin, 57.7 mg citric acid, and sodium hydroxide for pH adjustment (target pH 3.5). The FDA approved label for KYPROLIS<sup>®</sup> (carfilzomib) for injection, provides detailed instructions for reconstituting the lyophilized KYPROLIS<sup>®</sup> (carfilzomib) powder before injection, including reconstituting each vial by slowly injecting Sterile Water for Injection, USP through the stopper and directing the solution into the inside wall of the vial, then gently swirling and/or inverting the vial slowly for about one minute, or until complete dissolution.

29. Carfilzomib, the active ingredient in KYPROLIS<sup>®</sup> (carfilzomib) for injection, is a proteasome inhibitor. The proteasome is the cell's "garbage disposal"; it breaks down unneeded or damaged proteins for reuse in the cell. Carfilzomib, a tetrapeptide epoxyketone, inhibits proteasome function by irreversibly binding to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. This causes the accumulation of protein in multiple myeloma cells, which triggers the body's mechanisms to kill the multiple myeloma cell through a process called apoptosis. According to the FDA approved label for KYPROLIS<sup>®</sup> (carfilzomib) for injection, carfilzomib has antiproliferative and proapoptotic activities *in vitro* in solid and hematologic tumor cells. In animals, carfilzomib inhibits proteasome activity in blood and tissue and delays tumor growth in models of multiple myeloma, hematologic, and solid tumors.

30. Onyx is the holder of approved New Drug Application ("NDA") No. 20-2714 for KYPROLIS<sup>®</sup> (carfilzomib) for injection. Onyx is the authorized agent for matters related to NDA No. 20-2714 in the United States.

31. KYPROLIS<sup>®</sup> (carfilzomib) for injection, its active pharmaceutical ingredient carfilzomib, its method of manufacture, and use are covered by one or more claims of the

Patents-in-Suit, and the Patents-in-Suit have been listed for NDA No. 20-2714 in the FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is referred to as the "Orange Book."

32. Pursuant to NDA No. 20-2714, Onyx markets and distributes KYPROLIS<sup>®</sup> (carfilzomib) for injection in the United States.

**DEFENDANTS' ANDA**

33. On December 14, 2017, Onyx received a letter, dated December 11, 2017, from Apotex Inc. notifying Onyx that Apotex seeks through ANDA No. 211185 approval to engage in the commercial manufacture, use, sale, and offer for sale of the Proposed ANDA Product prior to the expiration of the Patents-in-Suit. Included within ANDA No. 211185 is a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certification") that the Patents-in-Suit are invalid, unenforceable, and/or will not be infringed by the manufacture, use, importation, sale or offer for sale of the Proposed ANDA Product.

34. Onyx commenced this action within 45 days of receipt of the Notice Letter.

35. Defendants were aware of the Patents-in-Suit when ANDA No. 211185 was filed with a Paragraph IV Certification.

36. On information and belief, carfilzomib is the active ingredient in the Proposed ANDA Product and is a proteasome inhibitor approved by the FDA in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy, and as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy. 21 U.S.C. § 355(j)(2); 21 C.F.R. § 314.94(a)(5).

37. On information and belief, ANDA No. 211185 refers to and relies upon the NDA for KYPROLIS<sup>®</sup> (carfilzomib) for injection and contains data that, according to Defendants,



demonstrate the bioequivalence of the Proposed ANDA Product and KYPROLIS<sup>®</sup> (carfilzomib) for injection. 21 U.S.C. § 355(j)(2); 21 C.F.R. § 314.94(a)(7).

38. On information and belief, the Proposed ANDA Product will have instructions for use that substantially copy the instructions accompanying KYPROLIS<sup>®</sup> (carfilzomib) for injection, including instructions for administering the Proposed ANDA Product by intravenous injection to treat multiple myeloma in humans, as well as instructions for reconstituting the Proposed ANDA Product before injection by slowly injecting Sterile Water for Injection, USP into each vial through the stopper and directing the solution into the inside wall of the vial, then gently swirling and/or inverting the vial slowly for about one minute, or until complete dissolution. 21 U.S.C. § 355(j)(2); 21 C.F.R. § 314.94(a)(4) and (8). The instructions accompanying the Proposed ANDA Product will induce healthcare providers to use the Proposed ANDA Product in a manner set forth in those instructions.

39. On information and belief, Apotex intends to have healthcare providers use its Proposed ANDA Product, if approved, as set forth in its Proposed ANDA Product label. On information and belief, Apotex's Proposed ANDA Product label instructs healthcare providers to administer its Proposed ANDA Product by intravenous injection to treat multiple myeloma in humans after reconstituting the Proposed ANDA Product by slowly injecting Sterile Water for Injection, USP into each vial through the stopper and directing the solution into the inside wall of the vial, then gently swirling and/or inverting the vial slowly for about one minute, or until complete dissolution. Thus, Apotex knowingly intends to encourage healthcare providers to administer its ANDA Product by intravenous injection to treat multiple myeloma in humans in a manner that infringes the Patent-in-Suit.

40. On information and belief, the active ingredient in the Proposed ANDA Product—carfilzomib—will irreversibly bind to the N-terminal threonine-containing active sites of the 20S proteasome and inhibit proteasome activity in blood and tissue and delay tumor growth when administered by healthcare providers as directed by Apotex’s Proposed ANDA Product label. Thus, Apotex knows and intends for the carfilzomib in its ANDA Product to irreversibly bind to the N-terminal threonine-containing active sites of the 20S proteasome and inhibit proteasome activity in blood and tissue and delay tumor growth in humans in a manner that infringes one or more of the Patents-in-Suit.

41. On information and belief, the Proposed ANDA Product will have no substantial non-infringing use.

**COUNT I: INFRINGEMENT OF U.S. PATENT NO. 7,417,042**

42. Plaintiff hereby realleges and incorporates the allegations of paragraphs 1 – 41 of this Complaint.

43. On information and belief, the Proposed ANDA Product is covered by at least Claims 1-6, 15-24, and 37 of the ’042 Patent, because it contains carfilzomib as its active ingredient.

44. Defendants’ submission of ANDA No. 211185 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product before the expiration of the ’042 Patent constitutes infringement of the ’042 Patent under 35 U.S.C. § 271(e)(2).

45. On information and belief, Defendants plan to, intend to, and will engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA

Product immediately upon approval of ANDA No. 211185 and will instruct healthcare providers to use the Proposed ANDA Product in accordance with the proposed product labeling.

46. On information and belief, Defendants know that the Proposed ANDA Product, when commercially manufactured, offered for sale, sold, and/or imported, and when used will directly infringe at least Claims 1-6, 15-24, and 37 of the '042 Patent under 35 U.S.C. § 271(a).

47. Upon FDA approval of ANDA No. 211185, Defendants will infringe at least Claims 1-6, 15-24, and 37 of the '042 Patent by making, using, offering to sell, selling, and/or importing the Proposed ANDA Product in the United States, and by actively inducing and/or contributing to infringement by others under 35 U.S.C. § 271(b) and/or (c).

48. On information and belief, Defendants had knowledge of the '042 Patent when Defendants submitted ANDA No. 211185 to the FDA and Defendants know or should know that they will induce or contribute to another's direct infringement of at least Claims 1-6, 15-24, and 37 of the '042 Patent.

49. Absent from the Notice Letter are any allegations that Claims 1-6, 15-24, or 37 of the '042 Patent are not infringed by the Proposed ANDA Product.

50. Defendants have knowledge of the '042 Patent and are knowingly and intentionally infringing the '042 Patent.

51. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

52. On information and belief, Defendants lacked a good faith basis for alleging invalidity of the '042 Patent when Defendants filed their Paragraph IV Certification. Accordingly, this case is exceptional under 35 U.S.C. § 285.

**COUNT II: INFRINGEMENT OF U.S. PATENT NO. 7,232,818**

53. Plaintiff hereby realleges and incorporates the allegations of paragraphs 1 – 52 of this Complaint.

54. On information and belief, the Proposed ANDA Product is covered by at least Claims 1-4, 23-25, 38, and 49-50 of the '818 Patent, because it contains carfilzomib as its active ingredient.

55. Defendants' submission of ANDA No. 211185 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product before the expiration of the '818 Patent constitutes infringement of the '818 Patent under 35 U.S.C. § 271(e)(2).

56. On information and belief, Defendants plan to, intend to, and will engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product immediately upon approval of ANDA No. 211185 and will instruct healthcare providers to use the Proposed ANDA Product in accordance with the proposed product labeling.

57. On information and belief, Defendants know that the Proposed ANDA Product, when commercially manufactured, offered for sale, sold, and/or imported, and when used will directly infringe at least Claims 1-4, 23-25, 38, and 49-50 of the '818 Patent under 35 U.S.C. § 271(a).

58. Upon FDA approval of ANDA No. 211185, Defendants will infringe at least Claims 1-4, 23-25, 38, and 49-50 of the '818 Patent by making, using, offering to sell, selling, and/or importing the Proposed ANDA Product in the United States, and by actively inducing and/or contributing to infringement by others under 35 U.S.C. § 271(b) and/or (c).

59. On information and belief, Defendants had knowledge of the '818 Patent when Defendants submitted ANDA No. 211185 to the FDA and Defendants know or should know that they will induce or contribute to another's direct infringement of at least Claims 1-4, 23-25, 38, and 49-50 of the '818 Patent.

60. Absent from the Notice Letter are any allegations that Claims 1-4, 23-25, 38, or 49-50 of the '818 Patent are not infringed by the Proposed ANDA Product.

61. Defendants have knowledge of the '818 Patent and are knowingly and intentionally infringing the '818 Patent.

62. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

63. On information and belief, Defendants lacked a good faith basis for alleging invalidity of the '818 Patent when Defendants filed their Paragraph IV Certification. Accordingly, this case is exceptional under 35 U.S.C. § 285.

**COUNT III: INFRINGEMENT OF U.S. PATENT NO. 7,491,704**

64. Plaintiff hereby realleges and incorporates the allegations of paragraphs 1 – 63 of this Complaint.

65. On information and belief, the use of the Proposed ANDA Product is covered by at least Claims 1-3, 22-24, 37, and 48 of the '704 Patent, because the Proposed ANDA Product contains carfilzomib as its active ingredient and Defendants' Proposed Product label will have instructions for administering the Proposed ANDA Product to treat cancer, specifically multiple myeloma. 21 U.S.C. § 355(j)(2); 21 C.F.R. § 314.94(a)(4) and (8).

66. Defendants' submission of ANDA No. 211185 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product before the expiration of the '704 Patent constitutes infringement of the '704 Patent under 35 U.S.C. § 271(e)(2).

67. On information and belief, Defendants plan to, intend to, and will engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product immediately upon approval of ANDA No. 211185 and will instruct healthcare providers to use the Proposed ANDA Product in accordance with the proposed product labeling.

68. On information and belief, Defendants know that the Proposed ANDA Product, when commercially manufactured, offered for sale, sold, and/or imported, and when used as directed in their proposed product labelling, will be used in a manner that would directly infringe at least Claims 1-3, 22-24, 37, and 48 of the '704 Patent under 35 U.S.C. § 271(a).

69. Upon FDA approval of ANDA No. 211185, Defendants will infringe at least Claims 1-3, 22-24, 37, and 48 of the '704 Patent by actively inducing and/or contributing to infringement by others under 35 U.S.C. § 271(b) and/or (c).

70. On information and belief, Defendants had knowledge of the '704 Patent when Defendants submitted ANDA No. 211185 to the FDA and Defendants know or should know that they will induce and contribute to another's direct infringement of at least Claims 1-3, 22-24, 37, and 48 of the '704 Patent.

71. Absent from the Notice Letter are any allegations that Claims 1-3, 22-24, 37, or 48 of the '704 Patent are not infringed by the Proposed ANDA Product.

72. Defendants have knowledge of the '704 Patent and are knowingly and intentionally infringing the '704 Patent.

73. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

74. On information and belief, Defendants lacked a good faith basis for alleging invalidity of the '704 Patent when Defendants filed their Paragraph IV Certification. Accordingly, this case is exceptional under 35 U.S.C. § 285.

**COUNT IV: INFRINGEMENT OF U.S. PATENT No. 7,737,112**

75. Plaintiff hereby realleges and incorporates the allegations of paragraphs 1 – 74 of this Complaint.

76. On information and belief, the Proposed ANDA Product is covered by at least Claims 1-9, 14, 18-24, and 29-32 of the '112 Patent, because it contains carfilzomib, sulfobutyl ether beta-cyclodextrin (SBECD), and citric acid. 21 C.F.R. § 314.127(a)(8)(ii)(B); 21 C.F.R. § 314.94(a)(9)(iii).

77. Defendants' submission of ANDA No. 211185 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product before the expiration of the '112 Patent constitutes infringement of the '112 Patent under 35 U.S.C. § 271(e)(2).

78. On information and belief, Defendants plan to, intend to, and will engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product immediately upon approval of ANDA No. 211185 and will instruct healthcare providers to use the Proposed ANDA Product in accordance with the proposed product labeling.

79. On information and belief, Defendants know that the Proposed ANDA Product, when commercially manufactured, offered for sale, sold, and/or imported, and when used, will

directly infringe at least Claims 1-9, 14, 18-24, and 29-32 of the '112 Patent under 35 U.S.C. § 271(a).

80. Upon FDA approval of ANDA No. 211185, Defendants will infringe at least Claims 1-9, 14, 18-24, and 29-32 of the '112 Patent by making, using, offering to sell, selling, and/or importing the Proposed ANDA Product in the United States, and by actively inducing and/or contributing to infringement by others under 35 U.S.C. § 271(b) and/or (c).

81. On information and belief, Defendants had knowledge of the '112 Patent when Defendants submitted ANDA No. 209526 to the FDA and Defendants know or should know that they will induce or contribute to another's direct infringement of at least Claims 1-9, 14, 18-24, and 29-32 of the '112 Patent.

82. Absent from the Notice Letter are any allegations that Claims 1-14, 18-24, and 29-32 of the '112 Patent are not infringed by the Proposed ANDA Product.

83. Defendants have knowledge of the '112 Patent and are knowingly and intentionally infringing the '112 Patent.

84. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

85. On information and belief, Defendants lacked a good faith basis for alleging invalidity of the '112 Patent when Defendants filed their Paragraph IV Certification. Accordingly, this case is exceptional under 35 U.S.C. § 285.

**COUNT V: INFRINGEMENT OF U.S. PATENT NO. 8,129,346**

86. Plaintiff hereby realleges and incorporates the allegations of paragraphs 1 – 85 of this Complaint.



87. On information and belief, the use of the Proposed ANDA Product is covered by at least Claims 1-3, 22-24, 37, 48-49, and 52-60 of the '346 Patent, because the Proposed ANDA Product contains carfilzomib as its active ingredient and Defendants' Proposed Product label will have instructions for administering the Proposed ANDA Product to inhibit an N-terminal nucleophile hydrolase. Specifically, as described in the FDA approved label for KYPROLIS<sup>®</sup> (carfilzomib) for injection that will be substantially copied by Defendants' Proposed Product Label, when administered according to the instructions, carfilzomib will irreversibly bind to the N-terminal threonine-containing active sites of the 20S proteasome and inhibit proteasome activity in blood and tissue and delay tumor growth. 21 U.S.C. § 355(j)(2); 21 C.F.R. § 314.94(a)(4) and (8).

88. Defendants' submission of ANDA No. 211185 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product before the expiration of the '346 Patent constitutes infringement of the '346 Patent under 35 U.S.C. § 271(e)(2).

89. On information and belief, Defendants plan to, intend to, and will engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product immediately upon approval of ANDA No. 211185 and will instruct healthcare providers to use the Proposed ANDA Product in accordance with the proposed product labeling.

90. On information and belief, Defendants know that the Proposed ANDA Product, when commercially manufactured, offered for sale, sold, and/or imported, and when used as directed, will be used in a manner that would directly infringe at least Claims 1-3, 22-24, 37, 48-49, and 52-60 of the '346 Patent under 35 U.S.C. § 271(a).

91. Upon FDA approval of ANDA No. 211185, Defendants will infringe at least Claims 1-3, 22-24, 37, 48-49, and 52-60 of the '346 Patent by actively inducing and/or contributing to infringement by others under 35 U.S.C. § 271(b) and/or (c).

92. On information and belief, Defendants had knowledge of the '346 Patent when Defendants submitted ANDA No. 211185 to the FDA and Defendants know or should know that they will induce or contribute to another's direct infringement of at least Claims 1-3, 22-24, 37, 48-49, and 52-60 of the '346 Patent.

93. Absent from the Notice Letter are any allegations that the Claims 1-3, 22-24, 37, 48-49, or 52-60 of the '346 Patent are not infringed by the Proposed ANDA Product.

94. Defendants have knowledge of the '346 Patent and are knowingly and intentionally infringing the '346 Patent.

95. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

96. On information and belief, Defendants lacked a good faith basis for alleging invalidity of the '346 Patent when Defendants filed their Paragraph IV Certification. Accordingly, this case is exceptional under 35 U.S.C. § 285.

**COUNT VI: INFRINGEMENT OF U.S. PATENT NO. 8,207,125**

97. Plaintiff hereby realleges and incorporates the allegations of paragraphs 1 – 96 of this Complaint.

98. On information and belief, the Proposed ANDA Product is covered by at least Claims 1, 4, 5, 7-10, 12, 13, 16, 18-25, and 27-30 of the '125 Patent, because it is a composition comprising carfilzomib.

99. Defendants' submission of ANDA No. 211185 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product before the expiration of the '125 Patent constitutes infringement of the '125 Patent under 35 U.S.C. § 271(e)(2).

100. On information and belief, Defendants plan to, intend to, and will engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product immediately upon approval of ANDA No. 211185 and will instruct healthcare providers to use the Proposed ANDA Product in accordance with the proposed product labeling.

101. On information and belief, Defendants know that the Proposed ANDA Product, when commercially manufactured, offered for sale, sold, and/or imported, and when used as directed, will directly infringe at least Claims 1, 4, 5, 7-10, 12, 13, 16, 18-25, and 27-30 of the '125 Patent under 35 U.S.C. § 271(a).

102. Upon FDA approval of ANDA No. 211185, Defendants will infringe at least Claims 1, 4, 5, 7-10, 12, 13, 16, 18-25, and 27-30 of the '125 Patent by making, using, offering to sell, selling, and/or importing the Proposed ANDA Product in the United States, and by actively inducing and/or contributing to infringement by others under 35 U.S.C. § 271(b) and/or (c).

103. On information and belief, Defendants had knowledge of the '125 Patent when Defendants submitted ANDA No. 211185 to the FDA and Defendants know or should know that they will induce or contribute to another's direct infringement of at least Claims 1, 4, 5, 7-10, 12, 13, 16, 18-25, and 27-30 of the '125 Patent.

104. Absent from the Notice Letter are any allegations that Claims 1, 4, 5, 7-11, or 18 of the '125 Patent are not infringed by the Proposed ANDA Product.

105. Defendants have knowledge of the '125 Patent and are knowingly and intentionally infringing the '125 Patent.

106. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

107. On information and belief, Defendants lacked a good faith basis for alleging non-infringement and invalidity of the '125 Patent when Defendants filed their Paragraph IV Certification. Accordingly, this case is exceptional under 35 U.S.C. § 285.

**COUNT VII: INFRINGEMENT OF U.S. PATENT NO. 8,207,126**

108. Plaintiff hereby realleges and incorporates by reference the allegations of paragraphs 1 – 107 of this Complaint.

109. On information and belief, the Proposed ANDA Product and its method of manufacture is covered by at least Claims 1-5, 7-14, and 16-21 of the '126 Patent, because it is a composition comprising carfilzomib prepared by the claimed method. Specifically, on information and belief, the Defendants' Proposed Product label will instruct healthcare providers to reconstitute the Proposed ANDA Product by slowly injecting Sterile Water for Injection, USP into each vial through the stopper and directing the solution into the inside wall of the vial, then gently swirling and/or inverting the vial slowly for about one minute, or until complete dissolution.

110. Defendants' submission of ANDA No. 211185 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product before the expiration of the '126 Patent constitutes infringement of the '126 Patent under 35 U.S.C. § 271(e)(2).

111. On information and belief, Defendants plan to, intend to, and will engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product immediately upon approval of ANDA No. 211185 and will instruct healthcare providers to use the Proposed ANDA Product in accordance with the proposed product labeling.

112. On information and belief, Defendants know that the Proposed ANDA Product, when commercially manufactured, offered for sale, sold, and/or imported, and when used as directed, will directly infringe at least Claims 1-5, 7-14, and 16-21 of the '126 Patent under 35 U.S.C. § 271(a) and/or § 271(g).

113. Upon FDA approval of ANDA No. 211185, Defendants will infringe at least Claims 1-5, 7-14, and 16-21 of the '126 Patent by making, using, offering to sell, selling, and/or importing the Proposed ANDA Product in the United States, and by actively inducing and/or contributing to infringement by others under 35 U.S.C. § 271(b) and/or (c).

114. On information and belief, Defendants had knowledge of the '126 Patent when Defendants submitted ANDA No. 211185 to the FDA and Defendants know or should know that they will induce or contribute to another's direct infringement of at least Claims 1-5, 7-14, and 16-21 of the '126 Patent.

115. Absent from the Notice Letter are any allegations that Claims 1-6, 9-15, or 18-21 of the '126 Patent are not infringed by the Proposed ANDA Product.

116. Defendants have knowledge of the '126 Patent and are knowingly and intentionally infringing the '126 Patent.

117. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

118. On information and belief, Defendants lacked a good faith basis for alleging non-infringement and invalidity of the '126 Patent when Defendants filed their Paragraph IV Certification. Accordingly, this case is exceptional under 35 U.S.C. § 285.

**COUNT VIII: INFRINGEMENT OF U.S. PATENT NO. 8,207,127**

119. Plaintiff hereby realleges and incorporates the allegations of paragraphs 1 – 118 of this Complaint.

120. On information and belief, the use of the Proposed ANDA Product is covered by at least Claims 1, 12-17, 19, 20, and 23-27 of the '127 Patent, because the Proposed ANDA Product contains carfilzomib as its active ingredient and Defendants' Proposed Product label will have instructions for administering the Proposed ANDA Product to treat multiple myeloma, which is a type of hematopoietic cancer. 21 U.S.C. § 355(j)(2); 21 C.F.R. § 314.94(a)(4) and (8).

121. Defendants' submission of ANDA No. 211185 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product before the expiration of the '127 Patent constitutes infringement of the '127 Patent under 35 U.S.C. § 271(e)(2).

122. On information and belief, Defendants plan to, intend to, and will engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product immediately upon approval of ANDA No. 211185 and will instruct healthcare providers to use the Proposed ANDA Product in accordance with the proposed product labeling.

123. On information and belief, Defendants know that the Proposed ANDA Product, when commercially manufactured, offered for sale, sold, and/or imported, and when used as directed, will be used in a manner that would directly infringe at least Claims 1, 12-17, 19, 20, and 23-27 of the '127 Patent under 35 U.S.C. § 271(a).

124. Upon FDA approval of ANDA No. 211185, Defendants will infringe at least Claims 1, 12-17, 19, 20, and 23-27 of the '127 Patent by actively inducing and/or contributing to infringement by others under 35 U.S.C. § 271(b) and/or (c).

125. On information and belief, Defendants had knowledge of the '127 Patent when Defendants submitted ANDA No. 211185 to the FDA and Defendants know or should know that they will induce or contribute to another's direct infringement of at least Claims 1, 12-17, 19, 20, and 23-27 of the '127 Patent.

126. Absent from the Notice Letter are any allegations that Claims 1, 12-17, 23, or 27 of the '127 Patent are not infringed by the Proposed ANDA Product.

127. Defendants have knowledge of the '127 Patent and is knowingly and intentionally infringing the '127 Patent.

128. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

129. On information and belief, Defendants lacked a good faith basis for alleging non-infringement and invalidity of the '127 Patent when Defendants filed their Paragraph IV Certification. Accordingly, this case is exceptional under 35 U.S.C. § 285.

**COUNT IX: INFRINGEMENT OF U.S. PATENT NO. 8,207,297**

130. Plaintiff hereby realleges and incorporates the allegations of paragraphs 1 – 129 of this Complaint.

131. Absent from the Notice Letter are any specifics regarding how Defendants have purportedly avoided infringing the Claims of the '297 Patent. 21 U.S.C. § 355(b)(3)(D)(ii).

132. On information and belief, the Proposed ANDA Product is covered by at least Claims 1-8, 10-17, and 19-24 of the '297 Patent, because it is a composition comprising carfilzomib prepared by the claimed methods.

133. Defendants' submission of ANDA No. 211185 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product before the expiration of the '297 Patent constitutes infringement of the '297 Patent under 35 U.S.C. § 271(e)(2).

134. On information and belief, Defendants plan to, intend to, and will engage in the commercial manufacture, use, importation, sale and/or offer for sale of the Proposed ANDA Product immediately upon approval of ANDA No. 211185 and will instruct healthcare providers on the use of the Proposed ANDA Product through product labeling.

135. On information and belief, Defendants know that the Proposed ANDA Product, when commercially manufactured, offered for sale, sold, and/or imported, and when used as directed, will directly infringe at least Claims 1-8, 10-17, and 19-24 of the '297 Patent under 35 U.S.C. § 271(a) and/or § 271(g).

136. Upon FDA approval of ANDA No. 211185, Defendants will infringe at least Claims 1-8, 10-17, and 19-24 of the '297 Patent by making, using, offering to sell, selling, and/or importing the Proposed ANDA Product in the United States, and by actively inducing and/or contributing to infringement by others under 35 U.S.C. § 271(b) and/or (c).

137. On information and belief, Defendants had knowledge of the '297 Patent when Defendants submitted ANDA No. 211185 to the FDA and Defendants know or should know that they will induce or contribute to another's direct infringement of at least Claims 1-8, 10-17, and 19-24 of the '297 Patent.



138. Defendants have knowledge of the '297 Patent and are knowingly and intentionally infringing the '297 Patent.

139. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

140. On information and belief, Defendants lacked a good faith basis for alleging non-infringement and invalidity of the '297 Patent when Defendants filed their Paragraph IV Certification. Accordingly, this case is exceptional under 35 U.S.C. § 285.

#### **PRAYER FOR RELIEF**

WHEREFORE, Plaintiff respectfully requests that this Court grant the following relief:

a) Judgment that Defendants' submission of ANDA No. 211185 to the FDA was an act of infringement of one or more Claims of the '042, '818, '704, '112, '346, '125, '126, '127, and '297 Patents under 35 U.S.C. § 271(e)(2);

b) Judgment that Defendants' making, using, offering to sell, selling, or importing into the United States of the Proposed ANDA Product prior to the expiration of the '042, '818, '704, '112 '346, '125, '126, '127, and '297 Patents, will infringe, will actively induce infringement, and/or will contribute to the infringement of one or more Claims of those Patents;

c) An Order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any FDA approval of ANDA No. 211185 shall be a date that is not earlier than the expiration of the '042, '818, '704, '112, '346, '125, '126, '127, and '297 Patents plus any other exclusivity to which Plaintiff is or becomes entitled;

d) An Order permanently enjoining Defendants, Defendants' affiliates and subsidiaries, each of their officers, agents, servants and employees, and any person acting in

concert with Defendants, from making, using, offering to sell, selling, or importing into the United States the Proposed ANDA Product until after the expiration of the '042, '818 '704, '112, '346, '125, '126, '127, and '297 Patents plus any other exclusivity to which Plaintiff is or becomes entitled;

- e) A declaration that this case is exceptional within the meaning of 35 U.S.C. § 285 and an award of reasonable attorneys' fees, expenses, and disbursements of this action;
- f) An award of Plaintiff's reasonable costs and expenses in this action; and
- g) Such further and other relief as this Court deems proper and just.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

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