IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GILEAD SCIENCES, INC., Plaintiff, v. APOTEX, INC., LUPIN LIMITED, LAURUS LABS LIMITED, SHILPA MEDICARE LIMITED, SUNSHINE LAKE PHARMA CO., LTD., NATCO PHARMA LIMITED, CIPLA LIMITED, MACLEODS PHARMACEUTICALS LTD., HETERO USA INC., HETERO LABS LIMITED UNIT-V, AND HETERO LABS LIMITED, Defendants.	C.A. No. 20-189 (MN) **JURY TRIAL DEMANDED**

PLAINTIFF GILEAD SCIENCES, INC.'S SECOND AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Gilead Sciences, Inc. ("Gilead"), by its undersigned attorneys, hereby alleges as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, against Defendants Apotex, Inc. ("Apotex"), Lupin Limited ("Lupin"), Laurus Labs Limited ("Laurus Labs"), Shilpa Medicare Limited ("Shilpa"), Sunshine Lake Pharma Co., Ltd. ("Sunshine Lake"), Natco Pharma Limited ("Natco"), Cipla Limited ("Cipla"), Macleods Pharmaceuticals Ltd. ("Macleods"), and Hetero USA Inc., Hetero Labs Limited Unit-V, and Hetero Labs Limited (collectively, "Hetero"). This action arises out of Defendants' filing of one or more Abbreviated New Drug Applications ("ANDA") with the United States Food and Drug Administration ("FDA").

2. Defendants seek approval to market generic versions of Gilead's products containing tenofovir alafenamide ("TAF"), including VEMLIDY®, DESCOVY®, and ODEFSEY®, prior to the expiration of two or more of U.S. Patent Nos. 7,390,791; 7,803,788; 8,754,065; and 9,296,769 (collectively, the "Patents-In-Suit"). Gilead attaches hereto a true and accurate copy of each of the Patents-In-Suit as Exhibits A-D.

PARTIES

Plaintiff

3. Gilead is a corporation organized and existing under the laws of the state of Delaware, having its principal place of business at 333 Lakeside Drive, Foster City, California 94404.

4. Gilead is a research-based pharmaceutical company that discovers, develops, and brings to market revolutionary pharmaceutical products in areas of unmet medical need, including treatments for human immunodeficiency virus ("HIV"), hepatitis B virus ("HBV"), hepatitis C virus ("HCV"), liver diseases, serious cardiovascular and respiratory diseases, and cancer. Gilead's portfolio of products includes treatments for HBV and HIV using the drug TAF. Gilead sells TAF-containing pharmaceuticals under the registered trademarks VEMLIDY, DESCOVY, and ODEFSEY in this District and throughout the United States.

Defendant Apotex

5. On information and belief, Apotex is a foreign corporation organized and existing under the laws of Canada, having its principal place of business at 150 Signet Drive, Toronto, Ontario, Canada M9l 1T9.

6. On information and belief, Apotex, itself and through its subsidiaries, affiliates, and agents, manufactures, distributes, and/or imports generic pharmaceutical products for sale and use throughout the United States, including in this District.

7. On information and belief, Apotex prepared and filed ANDA No. 213867 ("Apotex's VEMLIDY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's VEMLIDY product ("Apotex's VEMLIDY ANDA Product") in the United States, including in this District, if the FDA approves Apotex's VEMLIDY ANDA.

8. On information and belief, Apotex prepared and filed ANDA No. 214053 ("Apotex's DESCOVY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's DESCOVY product ("Apotex's DESCOVY ANDA Product") in the United States, including in this District, if the FDA approves Apotex's DESCOVY ANDA.

9. On information and belief, Apotex prepared and filed ANDA No. 214095 ("Apotex's ODEFSEY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's ODEFSEY product ("Apotex's ODEFSEY ANDA Product") in the United States, including in this District, if the FDA approves Apotex's ODEFSEY ANDA.

Defendant Lupin

10. On information and belief, Lupin is a foreign corporation organized and existing under the laws of India, having its principal place of business at 3rd Floor, Kalpataru Inspire, Off. Western Expressway Highway, Santacruz (East), Mumbai, 400055, India.

11. On information and belief, Lupin, itself and through its subsidiaries, affiliates, and agents, manufactures, distributes, and/or imports generic pharmaceutical products for sale and use throughout the United States, including in this District.

12. On information and belief, Lupin prepared and filed ANDA No. 214226 ("Lupin's

VEMLIDY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's VEMLIDY product ("Lupin's VEMLIDY ANDA Product") in the United States, including in this District, if the FDA approves Lupin's VEMLIDY ANDA.

13. On information and belief, Lupin prepared and filed ANDA No. 213926 ("Lupin's DESCOVY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's DESCOVY product ("Lupin's DESCOVY ANDA Product") in the United States, including in this District, if the FDA approves Lupin's DESCOVY ANDA.

14. On information and belief, Lupin prepared and filed ANDA No. 214227 ("Lupin's ODEFSEY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's ODEFSEY product ("Lupin's ODEFSEY ANDA Product") in the United States, including in this District, if the FDA approves Lupin's ODEFSEY ANDA.

Defendant Laurus Labs

15. On information and belief, Laurus Labs is a foreign corporation organized and existing under the laws of India, having its principal place of business at Serene Chambers, Road No. 7, Banjarahills, Hyderabad, 500 034, India.

16. On information and belief, Laurus Labs itself and through its subsidiaries, affiliates, and agents, manufactures, distributes, and/or imports generic pharmaceutical products for sale and use throughout the United States, including in this District.

17. On information and belief, Laurus Labs prepared and filed ANDA No. 214030 ("Laurus Labs's VEMLIDY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's VEMLIDY product ("Laurus Labs's VEMLIDY ANDA Product") in the United States, including in this District, if the FDA approves Laurus Labs's VEMLIDY ANDA.

18. On information and belief, Laurus Labs prepared and filed ANDA No. 213989 ("Laurus Labs's DESCOVY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's DESCOVY product ("Laurus Labs's DESCOVY ANDA Product") in the United States, including in this District, if the FDA approves Laurus Labs's DESCOVY ANDA.

Defendant Shilpa

19. On information and belief, Shilpa is a foreign corporation organized and existing under the laws of India, having its principal place of business at #12-6-214/A1, Hyberabad Road, Raichur – 584 135, Karnataka, India.

20. On information and belief, Shilpa itself and through its subsidiaries, affiliates, and agents, manufactures, distributes, and/or imports generic pharmaceutical products for sale and use throughout the United States, including in this District.

21. On information and belief, Shilpa prepared and filed ANDA No. 214072 ("Shilpa's VEMLIDY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's VEMLIDY product ("Shilpa's VEMLIDY ANDA Product") in the United States, including in this District, if the FDA approves Shilpa's VEMLIDY ANDA.

Defendant Sunshine Lake

22. On information and belief, Sunshine Lake is a foreign corporation organized and existing under the laws of China, having its principal place of business at Northern Industry Road No. 1, Song Shan Lake Technology Industry Park, Dongguan 52380-8 Guangdong, China.

23. On information and belief, Sunshine Lake itself and through its subsidiaries, affiliates, and agents, manufactures, distributes, and/or imports generic pharmaceutical products for sale and use throughout the United States, including in this District.

24. On information and belief, Sunshine Lake prepared and filed ANDA No. 213845 ("Sunshine Lake's VEMLIDY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's VEMLIDY product ("Sunshine Lake's VEMLIDY ANDA Product") in the United States, including in this District, if the FDA approves Sunshine Lake's VEMLIDY ANDA.

Defendant Natco

25. On information and belief, Natco is a foreign limited liability company organized and existing under the laws of India, having its principal place of business at Natco House, Road No. 2, Banjara Hills, Hyderabad, 500-034, India.

26. On information and belief, Natco itself and through its subsidiaries, affiliates, and agents, manufactures, distributes, and/or imports generic pharmaceutical products for sale and use throughout the United States, including in this District.

27. On information and belief, Natco prepared and filed ANDA No. 214173 ("Natco's DESCOVY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's DESCOVY product ("Natco's DESCOVY ANDA Product") in the United States, including in this District, if the FDA approves Natco's DESCOVY ANDA.

Defendant Cipla

28. On information and belief, Cipla is organized and existing under the laws of India, having its principal place of business at Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400013, India.

29. On information and belief, Cipla itself and through its subsidiaries, affiliates, and agents, manufactures, distributes, and/or imports generic pharmaceutical products for sale and use throughout the United States, including in this District.

30. On information and belief, Cipla prepared and filed ANDA No. 214059 ("Cipla's DESCOVY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's DESCOVY product ("Cipla's DESCOVY ANDA Product") in the United States, including in this District, if the FDA approves Cipla's DESCOVY ANDA.

31. On information and belief, Cipla prepared and filed ANDA No. 214058 ("Cipla's ODEFSEY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's ODEFSEY product ("Cipla's ODEFSEY ANDA Product") in the United States, including in this District, if the FDA approves Cipla's ODEFSEY ANDA.

Defendant Macleods

32. On information and belief, Macleods is organized and existing under the laws of India, having its principal place of business at Atlanta Arcade, Marol Church Rd., Andheri (East), Mumbai, 400059, India.

33. On information and belief, Macleods itself and through its subsidiaries, affiliates, and agents, manufactures, distributes, and/or imports generic pharmaceutical products for sale and use throughout the United States, including in this District.

34. On information and belief, Macleods prepared and filed ANDA No. 214216 ("Macleods's DESCOVY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's DESCOVY product ("Macleods's DESCOVY ANDA Product") in the United States, including in this District, if the FDA approves Macleods's DESCOVY ANDA.

Defendant Hetero

35. On information and belief, Hetero USA Inc. is a corporation organized and existing under the laws of the State of Delaware, having a registered agent for the service of process at W/K Incorporating Services, Inc., 3500 S Dupont Hwy, Dover, Delaware 19901, and its principal

place of business at 1035 Centennial Avenue, Piscataway, New Jersey 08854. On information and belief, Hetero USA Inc. is the U.S. Regulatory Agent for Hetero Labs Limited, including Hetero Labs Limited Unit-V.

36. On information and belief, Hetero Labs Limited is a corporation organized and existing under the laws of India, having a principal place of business at 7-2-A2 Hetero Corporate, Industrial Estates, Sanath Nagar, Hyberabad 500 018, Telengana, India.

37. On information and belief, Hetero Labs Limited Unit-V is a corporation organized and existing under the laws of India, having a principal place of business at 7-2-A2, Hetero Corporate Industrial Estates, Sanath Nagar, Hyderabad, Telangana 500018, India. On information and belief, Hetero Labs Limited Unit-V is a division of Hetero Labs Limited.

38. On information and belief, Hetero prepared and filed ANDA No. 214179 ("Hetero's VEMLIDY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's VEMLIDY product ("Hetero's VEMLIDY ANDA Product") in the United States, including in this District, if the FDA approves Hetero's VEMLIDY ANDA.

39. On information and belief, Hetero prepared and filed ANDA No. 211850 ("Hetero's DESCOVY ANDA"), seeking approval to manufacture, import, market, and/or sell a generic version of Gilead's DESCOVY product ("Hetero's DESCOVY ANDA Product") in the United States, including in this District, if the FDA approves Hetero's DESCOVY ANDA.

JURISDICTION AND VENUE

40. This action arises under the patent laws of the United States of America, 35 U.S.C. §§ 100 et seq., including §§ 271(e)(2), 271(a), 271(b), 271(c), 271(g) and 28 U.S.C. §§ 2201 and 2202. This Court has jurisdiction over this action under 28 U.S.C. §§ 1331 and 1338(a).

41. The Court also has jurisdiction to adjudicate this action under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, substantial, and justiciable controversy exists between Plaintiff and Defendants of sufficient immediacy and reality to warrant the issuance of a declaratory judgment regarding the parties' adverse legal interests with respect to the Patents-In-Suit.

Jurisdiction and Venue for Defendant Apotex

42. This Court has personal jurisdiction over Apotex by virtue of, *inter alia*, its systematic and continuous contacts with this jurisdiction, as alleged herein. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Apotex regularly and continuously transacts business within Delaware, including by manufacturing, selling, offering for sale, marketing, distributing, and/or importing generic versions of pharmaceutical products in the United States, including Delaware. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Apotex currently markets and sells over 90 pharmaceutical products throughout the United States, including in Delaware. On information and belief, Apotex derives substantial revenue from the sale of those products in Delaware and has availed itself of the privilege of conducting business within Delaware.

43. On information and belief, Apotex markets and distributes its pharmaceutical products through subsidiaries, agents, and/or affiliates including Apotex Corp., a Delaware corporation that is registered to do business and has appointed an agent to accept service in Delaware. On information and belief, Apotex, through Apotex Corp., is licensed to sell generic pharmaceutical products in the State of Delaware, pursuant to 24 Del. C. § 2540.

44. This Court also has personal jurisdiction because Apotex has filed its ANDAs for VEMLIDY, DESCOVY, and ODEFSEY, seeking approval from the FDA to market and sell

Apotex's VEMLIDY ANDA Product, Apotex's DESCOVY ANDA Product, and Apotex's ODEFSEY ANDA Product (collectively, "Apotex's TAF ANDA Products") throughout the United States, including in Delaware. On information and belief, Apotex intends to commercially manufacture, use, and sell Apotex's TAF ANDA Products upon receiving FDA approval. On information and belief, if and when the FDA approves Apotex's ANDAs, Apotex's TAF ANDA Products would, among other things, be marketed, distributed and sold in Delaware, and/or prescribed by physicians practicing and dispensed by pharmacies located within Delaware, all of which would have a substantial effect on Delaware. By filing its ANDAs, Apotex has made clear that it intends to use its distribution channels to direct sales of Apotex's TAF ANDA Products into Delaware.

45. Further, this Court has personal jurisdiction over Apotex because Apotex has previously been sued in this district and has not challenged personal jurisdiction, and Apotex has affirmatively availed itself of this Court's jurisdiction by filing counterclaims in this district. *See, e.g.*, *Forest Labs. Inc. et al. v. Apotex Corp. et al.*, Civil Action No. 1:14-cv-00200, D.I. 32 (D. Del. May 6, 2014); *Senju Pharm. Co. Ltd. et al. v. Apotex Inc. et al.*, Civil Action No. 1:07-cv-00779, D.I. 13 (D. Del. Jan. 22, 2008). Upon information and belief, Apotex has also availed itself of the legal protections of the State of Delaware by having filed suit in this jurisdiction. *See, e.g.*, *Apotex, Inc. v. et al. v. Lupin Ltd. et al.*, Civil Action No. 1:15-cv-00357, D.I. 1 (D. Del. May 4, 2015); *Apotex Inc. et al. v. Senju Pharm. Co., Ltd. et al.*, Civil Action No. 1:12-cv-00196, D.I. 1 (D. Del. Feb. 16, 2012).

46. Alternatively, this Court may exercise personal jurisdiction over Apotex pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) Gilead's claims arise under federal law; (b) Apotex is a foreign company not subject to personal jurisdiction in the courts of any state; and

(c) Apotex has sufficient contacts with the United States as a whole, including but not limited to marketing and/or selling generic pharmaceutical products that are distributed and sold throughout the United States, such that this Court's exercise of jurisdiction over Apotex satisfies due process.

47. Venue is proper in this Court under 28 U.S.C. §§ 1391(c)(3) because Apotex is a foreign corporation and may be sued in any judicial district in the United States in which it is subject to the court's personal jurisdiction, including in this District.

Jurisdiction and Venue for Defendant Lupin

48. This Court has personal jurisdiction over Lupin by virtue of, *inter alia*, its systematic and continuous contacts with this jurisdiction, as alleged herein. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Lupin regularly and continuously transacts business within Delaware, including by manufacturing, selling, offering for sale, marketing, distributing, and/or importing generic versions of pharmaceutical products in the United States, including Delaware. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Lupin received more than 75 FDA approvals to market and sell pharmaceutical products throughout the United States, including in Delaware. On information and belief, Lupin derives substantial revenue from the sale of those products in Delaware and has availed itself of the privilege of conducting business within Delaware.

49. On information and belief, Lupin markets and distributes its pharmaceutical products through subsidiaries, agents, and/or affiliates including Lupin Pharmaceuticals, Inc., a Delaware corporation that is registered to do business and has appointed an agent to accept service in Delaware. On information and belief, Lupin, through Lupin Pharmaceuticals, Inc., is licensed to sell generic pharmaceutical products in the State of Delaware, pursuant to 24 Del. C. § 2540.

50. This Court also has personal jurisdiction because Lupin has filed its ANDAs for

VEMLIDY, DESCOVY, and ODEFSEY, seeking approval from the FDA to market and sell Lupin's VEMLIDY ANDA Product, DESCOVY ANDA Product, and ODEFSEY ANDA Product (collectively, "Lupin's TAF ANDA Products") throughout the United States, including in Delaware. On information and belief, Lupin intends to commercially manufacture, use, and sell Lupin's TAF ANDA Products upon receiving FDA approval. On information and belief, if and when the FDA approves Lupin's ANDAs, Lupin's TAF ANDA Products would, among other things, be marketed, distributed and sold in Delaware, and/or prescribed by physicians practicing and dispensed by pharmacies located within Delaware, all of which would have a substantial effect on Delaware. By filing its ANDAs, Lupin has made clear that it intends to use its distribution channels to direct sales of Lupin's TAF ANDA Products into Delaware.

51. Further, this Court has personal jurisdiction over Lupin because Lupin has previously been sued in this district and has not challenged personal jurisdiction, and Lupin has affirmatively availed itself of this Court's jurisdiction by filing counterclaims in this district. *See, e.g.*, *Forest Labs, LLC, et al. v. Lupin Limited, et al.*, Civil Action No. 1:14-cv-01058, D.I. 15 (D. Del. Sept. 8, 2014); *ViiV Healthcare UK Ltd., et al. v. Lupin Ltd, et al.*, Civil Action No. 1:14-cv-00369, D.I. 10 (D. Del. June 12, 2014); *Teijin Limited, et al. v. Lupin Limited, et al.*, Civil Action No. 1:14-cv-00184, D.I. 20 (D. Del. April 1, 2014).

52. Alternatively, this Court may exercise personal jurisdiction over Lupin pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) Gilead's claims arise under federal law; (b) Lupin is a foreign company not subject to personal jurisdiction in the courts of any state; and (c) Lupin has sufficient contacts with the United States as a whole, including but not limited to marketing and/or selling generic pharmaceutical products that are distributed and sold throughout the United States, such that this Court's exercise of jurisdiction over Lupin satisfies due process.

53. Venue is proper in this Court under 28 U.S.C. §§ 1391(c)(3) because Lupin is a foreign corporation and may be sued in any judicial district in the United States in which it is subject to the court's personal jurisdiction, including in this District.

Jurisdiction and Venue for Defendant Laurus Labs

54. This Court has personal jurisdiction over Laurus Labs by virtue of, *inter alia*, its systematic and continuous contacts with this jurisdiction, as alleged herein. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Laurus Labs regularly and continuously transacts business within Delaware, including by manufacturing, selling, offering for sale, marketing, distributing, and/or importing generic versions of pharmaceutical products in the United States, including Delaware. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Laurus Labs currently markets and sells at least two pharmaceutical products throughout the United States, including in Delaware. On information and belief, Laurus Labs derives substantial revenue from the sale of those products in Delaware and has availed itself of the privilege of conducting business within Delaware.

55. On information and belief, Laurus Labs markets and distributes its pharmaceutical products through subsidiaries, agents, and/or affiliates including Laurus Generics Inc., a Delaware corporation that is registered to do business and has appointed an agent to accept service in Delaware.

56. This Court also has personal jurisdiction because Laurus Labs has filed its ANDAs for VEMLIDY and DESCOVY, seeking approval from the FDA to market and sell Laurus Labs's VEMLIDY ANDA Product and Laurus Labs's DESCOVY ANDA Product (collectively, "Laurus Labs's TAF ANDA Products") throughout the United States, including in Delaware. On information and belief, Laurus Labs intends to commercially manufacture, use, and sell Laurus

Labs's TAF ANDA Products upon receiving FDA approval. On information and belief, if and when the FDA approves Laurus Labs's ANDAs, Laurus Labs's TAF ANDA Products would, among other things, be marketed, distributed and sold in Delaware, and/or prescribed by physicians practicing and dispensed by pharmacies located within Delaware, all of which would have a substantial effect on Delaware. By filing its ANDAs, Laurus Labs has made clear that it intends to use its distribution channels to direct sales of Laurus Labs's TAF ANDA Products into Delaware.

57. Further, this Court has personal jurisdiction over Laurus Labs because Laurus Labs has previously been sued in this district and has not challenged personal jurisdiction, and Laurus Labs has affirmatively availed itself of this Court's jurisdiction by filing counterclaims in this district. *See, e.g.*, *Genentech, Inc. et al. v. Laurus Labs Ltd. et al.*, Civil Action No. 1:19-cv-00104, D.I. 12 (D. Del. Mar. 7, 2019); *Boehringer Ingelheim Pharma. Inc. et al. v. Laurus Labs Ltd. et al.*, Civil Action No. 1:18-cv-01758, D.I. 13 (D. Del. Jan. 11, 2019).

58. Alternatively, this Court may exercise personal jurisdiction over Laurus Labs pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) Gilead's claims arise under federal law; (b) Laurus Labs is a foreign company not subject to personal jurisdiction in the courts of any state; and (c) Laurus Labs has sufficient contacts with the United States as a whole, including but not limited to marketing and/or selling generic pharmaceutical products that are distributed and sold throughout the United States, such that this Court's exercise of jurisdiction over Laurus Labs satisfies due process.

59. Venue is proper in this Court under 28 U.S.C. §§ 1391(c)(3) because Laurus Labs is a foreign corporation and may be sued in any judicial district in the United States in which it is subject to the court's personal jurisdiction, including in this District.

Jurisdiction and Venue for Defendant Shilpa

60. This Court has personal jurisdiction over Shilpa by virtue of, *inter alia*, its systematic and continuous contacts with this jurisdiction, as alleged herein. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Shilpa regularly and continuously transacts business within Delaware, including by manufacturing, selling, offering for sale, marketing, distributing, and/or importing generic versions of pharmaceutical products in the United States, including Delaware. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Shilpa currently markets and sells at least eight pharmaceutical products throughout the United States, including in Delaware. On information and belief, Shilpa derives substantial revenue from the sale of those products in Delaware and has availed itself of the privilege of conducting business within Delaware.

61. On information and belief, Shilpa markets and distributes its pharmaceutical products through subsidiaries, agents, and/or affiliates including Shilpa, Inc., a Delaware corporation that is registered to do business and has appointed an agent to accept service in Delaware.

62. This Court also has personal jurisdiction because Shilpa has filed its ANDA for VEMLIDY, seeking approval from the FDA to market and sell Shilpa's VEMLIDY ANDA Product throughout the United States, including in Delaware. On information and belief, Shilpa intends to commercially manufacture, use, and sell Shilpa's VEMLIDY ANDA Product upon receiving FDA approval. On information and belief, if and when the FDA approves Shilpa's VEMLIDY ANDA, Shilpa's VEMLIDY ANDA Product would, among other things, be marketed, distributed and sold in Delaware, and/or prescribed by physicians practicing and dispensed by pharmacies located within Delaware, all of which would have a substantial effect on Delaware.

By filing its VEMLIDY ANDA, Shilpa has made clear that it intends to use its distribution channels to direct sales of Shilpa's VEMLIDY ANDA Product into Delaware.

63. Further, this Court has personal jurisdiction over Shilpa because Shilpa has previously been sued in this district and has not challenged personal jurisdiction, and Shilpa has affirmatively availed itself of this Court's jurisdiction by filing counterclaims in this district. *See, e.g.*, *Pharmacyclics LLC et al. v. Shilpa Medicare Ltd. et al.*, Civil Action No. 1:18-cv-00237, D.I. 24 (D. Del. May 4, 2018); *Biogen MA Inc. v. Shilpa Medicare Ltd.*, Civil Action No. 1:17-cv-00847, D.I. 8 (D. Del. Oct. 16, 2017).

64. Alternatively, this Court may exercise personal jurisdiction over Shilpa pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) Gilead's claims arise under federal law; (b) Shilpa is a foreign company not subject to personal jurisdiction in the courts of any state; and (c) Shilpa has sufficient contacts with the United States as a whole, including but not limited to marketing and/or selling generic pharmaceutical products that are distributed and sold throughout the United States, such that this Court's exercise of jurisdiction over Shilpa satisfies due process.

65. Venue is proper in this Court under 28 U.S.C. §§ 1391(c)(3) because Shilpa is a foreign corporation and may be sued in any judicial district in the United States in which it is subject to the court's personal jurisdiction, including in this District.

Jurisdiction and Venue for Defendant Sunshine Lake

66. This Court has personal jurisdiction over Sunshine Lake by virtue of, *inter alia*, its systematic and continuous contacts with this jurisdiction, as alleged herein. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Sunshine Lake regularly and continuously transacts business within Delaware, including by manufacturing, selling, offering for sale, marketing, distributing, and/or importing generic versions of pharmaceutical

products in the United States, including Delaware. On information and belief, Sunshine Lake derives substantial revenue from the sale of those products in Delaware and has availed itself of the privilege of conducting business within Delaware.

67. On information and belief, Sunshine Lake markets and distributes its pharmaceutical products through subsidiaries, agents, and/or affiliates including Sunshine Lake LLC, a Delaware limited liability company that is registered to do business and has appointed an agent to accept service in Delaware.

68. This Court also has personal jurisdiction because Sunshine Lake has filed its ANDAs for VEMLIDY, seeking approval from the FDA to market and sell Sunshine Lake's VEMLIDY ANDA Product throughout the United States, including in Delaware. On information and belief, Sunshine Lake intends to commercially manufacture, use, and sell Sunshine Lake's VEMLIDY ANDA Product upon receiving FDA approval. On information and belief, if and when the FDA approves Sunshine Lake's VEMLIDY ANDA, Sunshine Lake's VEMLIDY ANDA Product would, among other things, be marketed, distributed and sold in Delaware, and/or prescribed by physicians practicing and dispensed by pharmacies located within Delaware, all of which would have a substantial effect on Delaware. By filing its VEMLIDY ANDA, Sunshine Lake has made clear that it intends to use its distribution channels to direct sales of Sunshine Lake's VEMLIDY ANDA Product into Delaware.

69. Further, this Court has personal jurisdiction over Sunshine Lake because Sunshine Lake has previously been sued in this district and has not challenged personal jurisdiction, and Sunshine Lake has affirmatively availed itself of this Court's jurisdiction by filing counterclaims in this district. *See, e.g.*, *Bristol-Myers Squibb Co. et al. v. Sunshine Lake Pharma Co., Ltd., et al.*, Civil Action No. 1:17-cv-00380, D.I. 9 (D. Del. June 26, 2017).

70. Alternatively, this Court may exercise personal jurisdiction over Sunshine Lake pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) Gilead's claims arise under federal law; (b) Sunshine Lake is a foreign company not subject to personal jurisdiction in the courts of any state; and (c) Sunshine Lake has sufficient contacts with the United States as a whole, including but not limited to marketing and/or selling generic pharmaceutical products that are distributed and sold throughout the United States, such that this Court's exercise of jurisdiction over Sunshine Lake satisfies due process.

71. Venue is proper in this Court under 28 U.S.C. §§ 1391(c)(3) because Sunshine Lake is a foreign corporation and may be sued in any judicial district in the United States in which it is subject to the court's personal jurisdiction, including in this District.

Jurisdiction and Venue for Defendant Natco

72. This Court has personal jurisdiction over Natco by virtue of, *inter alia*, its systematic and continuous contacts with this jurisdiction, as alleged herein. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Natco regularly and continuously transacts business within Delaware, including by manufacturing, selling, offering for sale, marketing, distributing, and/or importing generic versions of pharmaceutical products in the United States, including Delaware. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Natco currently markets and sells over 20 pharmaceutical products throughout the United States, including in Delaware. On information and belief, Natco derives substantial revenue from the sale of those products in Delaware and has availed itself of the privilege of conducting business within Delaware.

73. On information and belief, Natco markets and distributes its pharmaceutical products through subsidiaries, agents, and/or affiliates including Natco Pharma, Inc., a Delaware

corporation that is registered to do business and has appointed an agent to accept service in Delaware.

74. This Court also has personal jurisdiction because Natco has filed its ANDA for DESCOVY, seeking approval from the FDA to market and sell Natco's DESCOVY ANDA Product throughout the United States, including in Delaware. On information and belief, Natco intends to commercially manufacture, use, and sell Natco's DESCOVY ANDA Product upon receiving FDA approval. On information and belief, if and when the FDA approves Natco's DESCOVY ANDA, Natco's DESCOVY ANDA Product would, among other things, be marketed, distributed and sold in Delaware, and/or prescribed by physicians practicing and dispensed by pharmacies located within Delaware, all of which would have a substantial effect on Delaware. By filing its DESCOVY ANDA, Natco has made clear that it intends to use its distribution channels to direct sales of Natco's DESCOVY ANDA Product into Delaware.

75. Further, this Court has personal jurisdiction over Natco because Natco has previously been sued in this district and has not challenged personal jurisdiction, and Natco has affirmatively availed itself of this Court's jurisdiction by filing counterclaims in this district. *See, e.g.*, *Novartis Pharmaceuticals Corporation et al. v. Natco Pharma Ltd.*, Civil Action No. 1:15-cv-00987, D.I. 12 (D. Del. Jan. 19, 2016); *Shire Canada Inc. et al. v. Natco Pharma Ltd.*, Civil Action No. 1:09-cv-03165, D.I. 36 (D. Del. Jan. 13, 2010).

76. Alternatively, this Court may exercise personal jurisdiction over Natco pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) Gilead's claims arise under federal law; (b) Natco is a foreign company not subject to personal jurisdiction in the courts of any state; and (c) Natco has sufficient contacts with the United States as a whole, including but not limited to

marketing and/or selling generic pharmaceutical products that are distributed and sold throughout the United States, such that this Court's exercise of jurisdiction over Natco satisfies due process.

77. Venue is proper in this Court under 28 U.S.C. §§ 1391(c)(3) because Natco is a foreign corporation and may be sued in any judicial district in the United States in which it is subject to the court's personal jurisdiction, including in this District.

Jurisdiction and Venue for Defendant Cipla

78. This Court has personal jurisdiction over Cipla by virtue of, *inter alia*, its systematic and continuous contacts with this jurisdiction, as alleged herein. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Cipla regularly and continuously transacts business within Delaware, including by manufacturing, selling, offering for sale, marketing, distributing, and/or importing generic versions of pharmaceutical products in the United States, including Delaware. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Cipla has submitted more than 170 ANDAs to the FDA in order to market and sell pharmaceutical products throughout the United States, including in Delaware. On information and belief, Cipla derives substantial revenue from the sale of those products in Delaware and has availed itself of the privilege of conducting business within Delaware.

79. On information and belief, Cipla markets and distributes its pharmaceutical products through subsidiaries, agents, and/or affiliates including Cipla USA Inc., a Delaware corporation that is registered to do business and has appointed an agent to accept service in Delaware.

80. This Court also has personal jurisdiction because Cipla has filed its ANDAs for DESCOVY, and ODEFSEY, seeking approval from the FDA to market and sell Cipla's

DESCOVY ANDA Product and Cipla's ODEFSEY ANDA Product (collectively, "Cipla's TAF ANDA Products") throughout the United States, including in Delaware. On information and belief, Cipla intends to commercially manufacture, use, and sell Cipla's TAF ANDA Products upon receiving FDA approval. On information and belief, if and when the FDA approves Cipla's ANDAs, Cipla's TAF ANDA Products would, among other things, be marketed, distributed and sold in Delaware, and/or prescribed by physicians practicing and dispensed by pharmacies located within Delaware, all of which would have a substantial effect on Delaware. By filing its ANDAs, Cipla has made clear that it intends to use its distribution channels to direct sales of Cipla's TAF ANDA Products into Delaware.

81. Further, this Court has personal jurisdiction over Cipla because Cipla has previously been sued in this district and has not challenged personal jurisdiction, and Cipla has affirmatively availed itself of this Court's jurisdiction by filing counterclaims in this district. *See, e.g.*, *Biogen Int'l GmbH et al. v. Cipla Ltd. et al.*, Civil Action No. 1:17-cv-00851, D.I. 10 (D. Del. Oct. 16, 2017); *Onyx Therapeutics, Inc. v. Cipla Ltd.*, Civil Action No. 1:16-cv-00988, D.I. 12 (D. Del. Jan. 13, 2017). Upon information and belief, Cipla has also availed itself of the legal protections of the State of Delaware by having filed suit in this jurisdiction. *See, e.g.*, *Cipla Ltd. et al. v. Amgen Inc.*, Civil Action No. 1:19-cv-00044, D.I. 1 (D. Del. Jan. 8, 2019); *Cipla Ltd. v. Sunovion Pharma. Inc.*, Civil Action No. 1:15-cv-00424, D.I. 1 (D. Del. May 26, 2015).

82. Alternatively, this Court may exercise personal jurisdiction over Cipla pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) Gilead's claims arise under federal law; (b) Cipla is a foreign company not subject to personal jurisdiction in the courts of any state; and (c) Cipla has sufficient contacts with the United States as a whole, including but not limited to

marketing and/or selling generic pharmaceutical products that are distributed and sold throughout the United States, such that this Court's exercise of jurisdiction over Cipla satisfies due process.

83. Venue is proper in this Court under 28 U.S.C. §§ 1391(c)(3) because Cipla is a foreign corporation and may be sued in any judicial district in the United States in which it is subject to the court's personal jurisdiction, including in this District.

Jurisdiction and Venue for Defendant Macleods

84. This Court has personal jurisdiction over Macleods by virtue of, *inter alia*, its systematic and continuous contacts with this jurisdiction, as alleged herein. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Macleods regularly and continuously transacts business within Delaware, including by manufacturing, selling, offering for sale, marketing, distributing, and/or importing generic versions of pharmaceutical products in the United States, including Delaware. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Macleods currently markets and sells over 62 FDA-approved pharmaceutical products throughout the United States, including in Delaware. On information and belief, Macleods derives substantial revenue from the sale of those products in Delaware and has availed itself of the privilege of conducting business within Delaware.

85. On information and belief, Macleods markets and distributes its pharmaceutical products through subsidiaries, agents, and/or affiliates including Macleods Pharma USA, Inc., a Delaware corporation that is registered to do business and has appointed an agent to accept service in Delaware.

86. This Court also has personal jurisdiction because Macleods has filed its ANDA for DESCOVY, seeking approval from the FDA to market and sell Macleods's DESCOVY ANDA Product throughout the United States, including in Delaware. On information and belief, Macleods

intends to commercially manufacture, use, and sell Macleods's DESCOVY ANDA Product upon receiving FDA approval. On information and belief, if and when the FDA approves Macleods's DESCOVY ANDA, Macleods's DESCOVY ANDA Product would, among other things, be marketed, distributed and sold in Delaware, and/or prescribed by physicians practicing and dispensed by pharmacies located within Delaware, all of which would have a substantial effect on Delaware. By filing its DESCOVY ANDA, Macleods has made clear that it intends to use its distribution channels to direct sales of Macleods's DESCOVY ANDA Product into Delaware.

87. Further, this Court has personal jurisdiction over Macleods because Macleods has previously been sued in this district and has not challenged personal jurisdiction, and Macleods has affirmatively availed itself of this Court's jurisdiction by filing counterclaims in this district. *See, e.g.*, *Merck Sharp & Dohme Corp. v. Macleods Pharma. Ltd. et al.*, Civil Action No. 1:19-cv-00316, D.I. 11 (D. Del. Apr. 8, 2019); *Biogen Int'l GmbH et al. v. Macleods Pharma., Ltd. et al.*, Civil Action No. 1:17-cv-00857, D.I. 7 (D. Del. July 17, 2017).

88. Alternatively, this Court may exercise personal jurisdiction over Macleods pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) Gilead's claims arise under federal law; (b) Macleods is a foreign company not subject to personal jurisdiction in the courts of any state; and (c) Macleods has sufficient contacts with the United States as a whole, including but not limited to marketing and/or selling generic pharmaceutical products that are distributed and sold throughout the United States, such that this Court's exercise of jurisdiction over Macleods satisfies due process.

89. Venue is proper in this Court under 28 U.S.C. §§ 1391(c)(3) because Macleods is a foreign corporation and may be sued in any judicial district in the United States in which it is subject to the court's personal jurisdiction, including in this District.

Jurisdiction and Venue for Hetero Defendants

90. This Court has personal jurisdiction over Hetero USA Inc. because, on information and belief, Hetero USA Inc. is incorporated in Delaware.

91. This Court has personal jurisdiction over Hetero Labs Limited and Hetero Labs Limited Unit-V by virtue of, *inter alia*, their systematic and continuous contacts with this jurisdiction, as alleged herein. On information and belief, either directly or through their subsidiaries, agents, and/or affiliates, Hetero Labs Limited and Hetero Labs Limited Unit-V regularly and continuously transact business within Delaware, including by manufacturing, selling, offering for sale, marketing, distributing, and/or importing generic versions of pharmaceutical products in the United States, including Delaware. On information and belief, either directly or through its subsidiaries, agents, and/or affiliates, Hetero Labs Limited and Hetero Labs Limited Unit-V currently markets or sells over 200 pharmaceutical products throughout the United States, including in Delaware. On information and belief, Hetero Labs Limited Unit-V and Hetero Labs Limited derive substantial revenue from the sale of those products in Delaware and have availed themselves of the privilege of conducting business within Delaware.

92. On information and belief, Hetero Labs Limited and Hetero Labs Limited Unit-V markets and distributes their pharmaceutical products through subsidiaries, agents, and/or affiliates including Hetero USA, Inc., a Delaware corporation that is registered to do business and has appointed an agent to accept service in Delaware. On information and belief, Hetero USA, Inc. is licensed to sell generic pharmaceutical products in the State of Delaware, pursuant to 24 Del. C. § 2540.

93. This Court also has personal jurisdiction over Hetero USA Inc., Hetero Labs Limited, and Hetero Labs Limited Unit-V because they, collectively and/or in concert with each

other, filed the Hetero ANDAs for VEMLIDY and DESCOVY, seeking approval from the FDA to market and sell Hetero's VEMLIDY ANDA Product and Hetero's DESCOVY ANDA Product (collectively, "Hetero's TAF ANDA Products") throughout the United States, including in Delaware. On information and belief, Hetero USA Inc., Hetero Labs Limited, and Hetero Labs Limited Unit-V, collectively and/or in concert with each other, intend to commercially manufacture, use, and sell Hetero's TAF ANDA Products upon receiving FDA approval. On information and belief, if and when the FDA approves Hetero's ANDAs, Hetero's TAF ANDA Products would, among other things, be marketed, distributed and sold in Delaware, and/or prescribed by physicians practicing and dispensed by pharmacies located within Delaware, all of which would have a substantial effect on Delaware. By filing its ANDAs, Hetero USA Inc., Hetero Labs Limited, and Hetero Labs Limited Unit-V have made clear that it intends to use its distribution channels to direct sales of Hetero's TAF ANDA Products into Delaware.

94. Further, this Court has personal jurisdiction over Hetero Labs Limited because it has previously been sued in this district and has not challenged personal jurisdiction, and Hetero Labs Limited has affirmatively availed itself of this Court's jurisdiction by filing counterclaims in this district. *See, e.g.*, *Biogen Int'l GmbH et al. v. Hetero USA Inc. et al.*, Civil Action No. 1:17-cv-00825, D.I. 13 (D. Del. Oct. 16, 2017); *Bristol-Myers Squibb Co. et al. v. Hetero USA Inc. et al.*, Civil Action No. 1:17-cv-00376, D.I. 9 (D. Del. June 16, 2017).

95. Alternatively, this Court may exercise personal jurisdiction over Hetero Labs Limited and Hetero Labs Limited Unit-V pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) Gilead's claims arise under federal law; (b) Hetero Labs Limited and Hetero Labs Limited Unit-V are a foreign companies not subject to personal jurisdiction in the courts of any state; and (c) Hetero Labs Limited and Hetero Labs Limited Unit-V have sufficient contacts with

the United States as a whole, including but not limited to marketing and/or selling generic pharmaceutical products that are distributed and sold throughout the United States, such that this Court's exercise of jurisdiction over Hetero Labs Limited and Hetero Labs Limited Unit-V satisfies due process.

96. Venue is proper in this Court under 28 U.S.C. §§ 1391(c)(3) because Hetero Labs Limited and Hetero Labs Limited Unit-V are both foreign corporations and may be sued in any judicial district in the United States in which they are subject to the court's personal jurisdiction, including in this District.

97. Venue is also proper in this District under 28 U.S.C. § 1400(b) because Hetero USA Inc. is a Delaware corporation.

PATENTS-IN-SUIT

98. On June 24, 2008, the U.S. Patent and Trademark Office duly and legally issued U.S. Patent No. 7,390,791 (the "'791 patent"), titled, "Prodrugs of Phosphonate Nucleotide Analogues." A true and correct copy of the '791 patent is attached hereto as Exhibit A. The claims of the '791 patent are valid, enforceable, and not expired. Gilead is the assignee of the '791 patent.

99. On September 28, 2010, the U.S. Patent and Trademark Office duly and legally issued U.S. Patent No. 7,803,788 (the "'788 patent"), titled, "Prodrugs of Phosphonate Nucoleotide [sic] Analogues." A true and correct copy of the '788 patent is attached hereto as Exhibit B. The claims of the '788 patent are valid, enforceable, and not expired. Gilead is the assignee of the '788 patent.

100. On June 17, 2014, the U.S. Patent and Trademark Office duly and legally issued U.S. Patent No. 8,754,065 (the "'065 patent"), titled, "Tenofovir Alafenamide Hemifumarate." A

true and correct copy of the '065 patent is attached hereto as Exhibit C. The claims of the '065 patent are valid, enforceable, and not expired. Gilead is the assignee of the '065 patent.

101. On March 29, 2016, the U.S. Patent and Trademark Office duly and legally issued U.S. Patent No. 9,296,769 (the "'769 patent"), titled, "Tenofovir Alafenamide Hemifumarate." A true and correct copy of the '769 patent is attached hereto as Exhibit D. The claims of the '769 patent are valid, enforceable, and not expired. Gilead is the assignee of the '769 patent.

ACTS GIVING RISE TO THIS ACTION

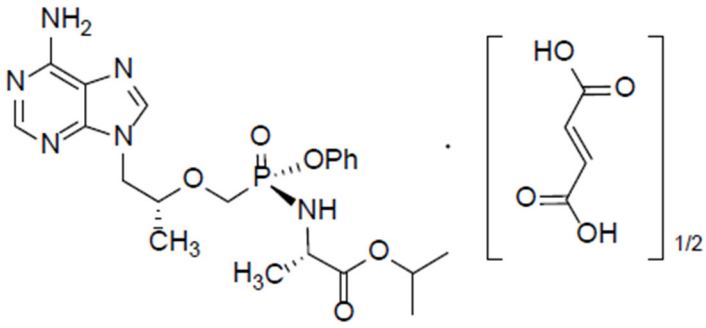
VEMLIDY

102. Gilead holds approved New Drug Application ("NDA") No. 208464 for 25 mg tablets containing tenofovir alafenamide for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease, as further described in the VEMLIDY label.

103. Gilead markets the tablets approved under NDA No. 208464 in the United States under the registered trademark VEMLIDY. FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book") identifies the following patents for VEMLIDY: U.S. Patent Nos. 7,390,791; 7,803,788; 8,754,065; and 9,296,769.

104. Gilead describes its VEMLIDY tablets as containing a tenofovir alafenamide fumarate active ingredient with the following empirical and structural formulas:

It has an empirical formula of $C_{21}H_{29}O_5N_6P \cdot ½(C_4H_4O_4)$ and a formula weight of 534.50. It has the following structural formula:



105. Gilead's VEMLIDY tablets contain less than 5% by weight tenofovir alafenamide monofumarate.

106. At least one claim of each of the Patents-In-Suit (all of which are listed in the Orange Book) covers VEMLIDY, or approved methods of using VEMLIDY.

107. Defendants Apotex, Lupin, Laurus Labs, Shilpa, Sunshine Lake, and Hetero filed ANDAs listing VEMLIDY as the reference listed drug ("RLD").

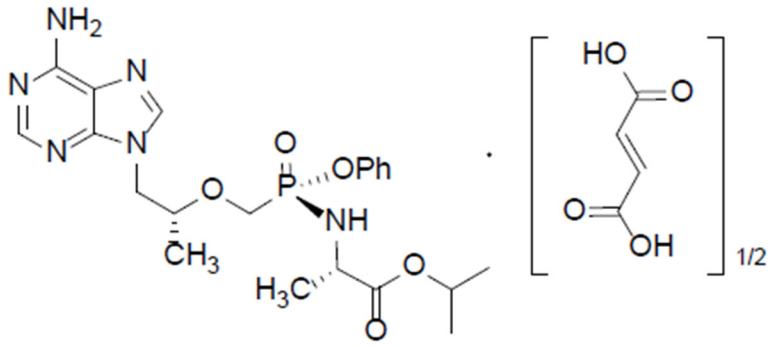
DESCOVY

108. Gilead holds approved NDA No. 208215 for tablets containing 200 mg of emtricitabine and 25 mg of tenofovir alafenamide, in combination with other antiretroviral agents, for treatment of HIV-1 infection in adults and pediatric patients, and for at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection, as further described on the DESCOVY label.

109. Gilead markets the tablets approved under NDA No. 208215 in the United States under the registered trademark DESCOVY. The Orange Book identifies the following patents for DESCOVY: U.S. Patent Nos. 6,642,245; 6,703,396; 7,390,791; 7,803,788; 8,754,065; and 9,296,769.

110. Gilead describes its DESCOVY tablets as containing a tenofovir alafenamide fumarate active ingredient, among others, with the following empirical and structural formulas:

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P \cdot \frac{1}{2}(C_4H_4O_4)$ and a formula weight of 534.50 and has the following structural formula:



111. Gilead's DESCOVY tablets contain less than 5% by weight tenofovir alafenamide monofumarate.

112. At least one claim of each of the Patents-In-Suit (all of which are listed in the Orange Book) covers DESCOVY, or approved methods of using DESCOVY.

113. Defendants Apotex, Lupin, Laurus Labs, Natco, Cipla, Macleods, and Hetero filed ANDAs listing DESCOVY as the RLD.

ODEFSEY

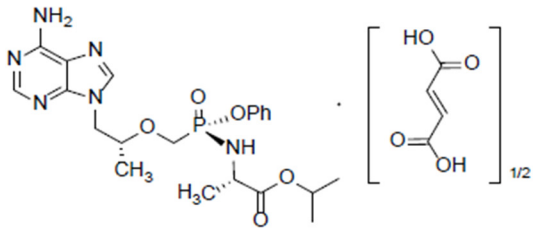
114. Gilead holds approved NDA No. 208351 for tablets containing 200 mg emtricitabine, 25 mg of rilpivirine, and 25 mg of tenofovir alafenamide for the treatment of HIV-1 infection in adults and pediatric patients either as an initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL or to replace a stable antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months with no history of treatment failure and no known substitutions

associated with resistance to the individual components of the tablets, as further described on the ODEFSEY label.

115. Gilead markets the tablets approved under NDA No. 208351 in the United States under the registered trademark ODEFSEY. The Orange Book identifies the following patents for ODEFSEY: U.S. Patent Nos. 6,642,245; 6,703,396; 6,838,464; 7,125,879; 7,390,791; 7,803,788; 8,080,551; 8,101,629; 8,754,065; and 9,296,769.

116. Gilead describes its ODEFSEY tablets as containing a tenofovir alafenamide fumarate active ingredient, among others, with the following empirical and structural formulas:

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P \cdot ½(C_4H_4O_4)$ and a formula weight of 534.50 and has the following structural formula:



117. Gilead's ODEFSEY tablets contain less than 5% by weight tenofovir alafenamide monofumarate.

118. At least one claim of each of the Patents-In-Suit (all of which are listed in the Orange Book) covers ODEFSEY, or approved methods of using ODEFSEY.

119. Defendants Apotex, Lupin, and Cipla filed ANDAs listing ODEFSEY as the RLD.

Apotex's Acts Regarding VEMLIDY

120. On information and belief, Apotex submitted to the FDA its VEMLIDY ANDA under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) (the "FFDCA"), seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Apotex's VEMLIDY ANDA Product before the

expiration of the '065 and '769 patents. On information and belief, the FDA assigned Apotex the ANDA number 213867.

121. On information and belief, Apotex sent a letter dated December 30, 2019 to Gilead ("Apotex's VEMLIDY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Apotex's VEMLIDY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769 patents.

122. Gilead received Apotex's VEMLIDY Notice Letter on or about December 31, 2019.

123. This action is being commenced before the expiration of 45 days from the date Gilead received Apotex's VEMLIDY Notice Letter, which triggers a stay of FDA approval of Apotex's VEMLIDY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

124. By filing its VEMLIDY ANDA, Apotex has necessarily represented to FDA that its VEMLIDY ANDA Product has the same active ingredient as VEMLIDY; has the same dosage form and strength as VEMLIDY; and is bioequivalent to VEMLIDY.

125. On information and belief, Apotex is seeking approval to market its VEMLIDY ANDA Product for the same approved indication as VEMLIDY.

126. On information and belief, Apotex's proposed label for its VEMLIDY ANDA Product ("Apotex's Proposed VEMLIDY Label") will refer to the product as, *inter alia*, a hepatitis B virus nucleoside analog reverse transcriptase inhibitor for the treatment of chronic hepatitis B infection in adults with compensated liver disease, and will describe the tablet strength of Apotex's VEMLIDY ANDA Product as 25 mg.

127. On information and belief, Apotex's Proposed VEMLIDY Label will instruct physicians and healthcare providers to administer Apotex's VEMLIDY ANDA Product for, *inter*

alia, the treatment of chronic hepatitis B infection in adults with compensated liver disease.

128. On information and belief, Apotex's Proposed VEMLIDY Label will contain data relating to the treatment of patients with hepatitis B infection, obtained from clinical studies involving, *inter alia*, VEMLIDY.

Apotex's Acts Regarding DESCOVY

129. On information and belief, Apotex submitted to the FDA its DESCOVY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Apotex's DESCOVY ANDA Product before the expiration of the '065 and '769 patents. On information and belief, the FDA assigned Apotex the ANDA number 214053.

130. On information and belief, Apotex sent a letter dated December 30, 2019 to Gilead ("Apotex's DESCOVY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Apotex's DESCOVY Notice Letter includes certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769 patents.

131. Gilead received Apotex's DESCOVY Notice Letter on or about December 31, 2019.

132. This action is being commenced before the expiration of 45 days from the date Gilead received Apotex's DESCOVY Notice Letter, which triggers a stay of FDA approval of Apotex's DESCOVY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

133. By filing its DESCOVY ANDA, Apotex has necessarily represented to FDA that its DESCOVY ANDA product has the same active ingredients as DESCOVY; has the same dosage forms and strengths as DESCOVY; and is bioequivalent to DESCOVY.

134. On information and belief, Apotex is seeking approval to market its DESCOVY ANDA Product for the same approved indications as DESCOVY.

135. On information and belief, Apotex's proposed label for its DESCOVY ANDA Product ("Apotex's Proposed DESCOVY Label") will refer to the product as, *inter alia*, a two-drug combination of emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors, used in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients, and for at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection, and will describe the fixed-dose combination tablets as containing 200 mg of emtricitabine and 25 mg of tenofovir alafenamide.

136. On information and belief, Apotex's Proposed DESCOVY Label will instruct physicians and healthcare providers to administer Apotex's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in adults and pediatric patients, and at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection.

137. On information and belief, Apotex's Proposed DESCOVY Label will contain data relating to the treatment of patients with HIV-1 infection, obtained from clinical studies involving, *inter alia*, DESCOVY.

Apotex's Acts Regarding ODEFSEY

138. On information and belief, Apotex submitted to the FDA its ODEFSEY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Apotex's ODEFSEY ANDA Product before the expiration of the '065 and '769 patents. On information and belief, the FDA assigned Apotex the ANDA number 214095.

139. On information and belief, Apotex sent a letter dated December 30, 2019 to Gilead ("Apotex's ODEFSEY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Apotex's ODEFSEY Notice Letter includes certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769 patents.

140. Gilead received the Apotex ODEFSEY Notice Letter on or about December 31, 2019.

141. This action is being commenced before the expiration of 45 days from the date Gilead received Apotex's ODEFSEY Notice Letter, which triggers a stay of FDA approval of Apotex's ODEFSEY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

142. By filing its ODEFSEY ANDA, Apotex has necessarily represented to FDA that its ODEFSEY ANDA Product has the same active ingredients as ODEFSEY; has the same dosage forms and strengths as ODEFSEY; and is bioequivalent to ODEFSEY.

143. On information and belief, Apotex is seeking approval to market its ODEFSEY ANDA Product for the same approved indication as ODEFSEY.

144. On information and belief, Apotex's proposed label for its ODEFSEY ANDA Product ("Apotex's Proposed ODEFSEY Label") will refer to the product as, *inter alia*, a three-drug combination of emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors, and rilpivirine, a non-nucleoside reverse transcriptase inhibitor, as a complete regimen for the treatment of HIV-1 infection in patients, and will describe the fixed-dose combination tablets as containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 25 mg of tenofovir alafenamide.

145. On information and belief, Apotex's Proposed ODEFSEY Label will instruct physicians and healthcare providers to administer Apotex's ODEFSEY ANDA Product for, *inter*

alia, the treatment of HIV-1 infection in patients.

146. On information and belief, Apotex's Proposed ODEFSEY Label will contain data relating to the treatment of patients with HIV-1 infection, obtained from clinical studies involving, *inter alia*, ODEFSEY.

Lupin's Acts Regarding VEMLIDY

147. On information and belief, Lupin submitted to the FDA its VEMLIDY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Lupin's VEMLIDY ANDA Product before the expiration of all four Patents-In-Suit. On information and belief, the FDA assigned Lupin the ANDA number 214226.

148. On information and belief, Lupin sent a letter dated January 2, 2020 to Gilead ("Lupin's VEMLIDY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Lupin's VEMLIDY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to all four Patents-In-Suit.

149. Gilead received Lupin's VEMLIDY Notice Letter on or about January 3, 2020.

150. This action is being commenced before the expiration of 45 days from the date Gilead received VEMLIDY Notice Letter, which triggers a stay of FDA approval of Lupin's VEMLIDY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

151. By filing its VEMLIDY ANDA, Lupin has necessarily represented to FDA that its VEMLIDY ANDA product has the same active ingredient as VEMLIDY; has the same dosage form and strength as VEMLIDY; and is bioequivalent to VEMLIDY.

152. On information and belief, Lupin is seeking approval to market its VEMLIDY ANDA Product for the same approved indication as VEMLIDY.

153. On information and belief, Lupin's proposed label for its VEMLIDY ANDA Product ("Lupin's Proposed VEMLIDY Label") will refer to the product as, *inter alia*, a hepatitis B virus nucleoside analog reverse transcriptase inhibitor for the treatment of chronic hepatitis B infection in adults with compensated liver disease, and will describe the tablet strength of Lupin's VEMLIDY ANDA Product as 25 mg.

154. On information and belief, Lupin's Proposed VEMLIDY Label will instruct physicians and healthcare providers to administer Lupin's VEMLIDY ANDA Product for, *inter alia*, the treatment of chronic hepatitis B infection in adults with compensated liver disease.

155. On information and belief, Lupin's Proposed VEMLIDY Label will contain data relating to the treatment of patients with hepatitis B infection, obtained from clinical studies involving, *inter alia*, VEMLIDY.

Lupin's Acts Regarding DESCOVY

156. On information and belief, Lupin submitted to the FDA its DESCOVY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Lupin's DESCOVY ANDA Product before the expiration of all four Patents-In-Suit. On information and belief, the FDA assigned Lupin ANDA number 213926.

157. On information and belief, Lupin sent a letter dated January 2, 2020 to Gilead ("Lupin's DESCOVY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Lupin's DESCOVY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to all four Patents-In-Suit.

158. Gilead received Lupin's DESCOVY Notice Letter on or about January 3, 2020.

159. This action is being commenced before the expiration of 45 days from the date

Gilead received Lupin's DESCOVY Notice Letter, which triggers a stay of FDA approval of Lupin's DESCOVY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

160. By filing its DESCOVY ANDA, Lupin has necessarily represented to FDA that its DESCOVY ANDA product has the same active ingredients as DESCOVY; has the same dosage forms and strengths as DESCOVY; and is bioequivalent to DESCOVY.

161. On information and belief, Lupin is seeking approval to market its DESCOVY ANDA Product for the same approved indications as DESCOVY.

162. On information and belief, Lupin's proposed label for its DESCOVY ANDA Product ("Lupin's Proposed DESCOVY Label") will refer to the product as, *inter alia*, a two-drug combination of emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors, used in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients, and for at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection, and will describe the fixed-dose combination tablets as containing 200 mg of emtricitabine and 25 mg of tenofovir alafenamide.

163. On information and belief, Lupin's Proposed DESCOVY Label will instruct physicians and healthcare providers to administer Lupin's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in adults and pediatric patients, and at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection.

164. On information and belief, Lupin's Proposed DESCOVY Label will contain data relating to the treatment of patients with HIV-1 infection, obtained from clinical studies involving, *inter alia*, DESCOVY.

Lupin's Acts Regarding ODEFSEY

165. On information and belief, Lupin submitted to the FDA its ODEFSEY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Lupin's ODEFSEY ANDA Product before the expiration of all four Patents-In-Suit. On information and belief, the FDA assigned Lupin ANDA number 214227.

166. On information and belief, Lupin sent a letter dated January 2, 2020 to Gilead ("Lupin's ODEFSEY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Lupin's ODEFSEY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to all four Patents-In-Suit.

167. Gilead received the Lupin ODEFSEY Notice Letter on or about January 3, 2020.

168. This action is being commenced before the expiration of 45 days from the date Gilead received Lupin's ODEFSEY Notice Letter, which triggers a stay of FDA approval of Lupin's ODEFSEY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

169. By filing its ODEFSEY ANDA, Lupin has necessarily represented to FDA that its ODEFSEY ANDA Product has the same active ingredients as ODEFSEY; has the same dosage forms and strengths as ODEFSEY; and is bioequivalent to ODEFSEY.

170. On information and belief, Lupin is seeking approval to market its ODEFSEY ANDA Product for the same approved indication as ODEFSEY.

171. On information and belief, Lupin's proposed label for its ODEFSEY ANDA Product ("Lupin's Proposed ODEFSEY Label") will refer to the product as, *inter alia*, a three-drug combination of emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors, and rilpivirine, a non-nucleoside reverse transcriptase inhibitor, as a

complete regimen for the treatment of HIV-1 infection in patients, and will describe the fixed-dose combination tablets as containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 25 mg of tenofovir alafenamide.

172. On information and belief, Lupin's Proposed ODEFSEY Label will instruct physicians and healthcare providers to administer Lupin's ODEFSEY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in patients.

173. On information and belief, Lupin's Proposed ODEFSEY Label will contain data relating to the treatment of patients with HIV-1 infection, obtained from clinical studies involving, *inter alia*, ODEFSEY.

Laurus Labs's Acts Regarding VEMLIDY

174. On information and belief, Laurus Labs submitted to the FDA its VEMLIDY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Laurus Labs's VEMLIDY ANDA Product before the expiration of the '791, '065, and '769 patents. On information and belief, the FDA assigned Laurus Labs ANDA number 214030.

175. On information and belief, Laurus Labs sent a letter dated January 6, 2020 to Gilead ("Laurus Labs's First VEMLIDY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Laurus Labs's First VEMLIDY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769 patents.

176. On information and belief, Laurus Labs sent a second letter dated October 7, 2020 to Gilead ("Laurus Labs's Second VEMLIDY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Laurus Labs's Second VEMLIDY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '791 patent.

177. Gilead received Laurus Labs's First VEMLIDY Notice Letter on or about January 7, 2020, and Laurus Labs's Second VEMLIDY Notice Letter on or about October 8, 2020.

178. Gilead filed its initial complaint in this matter before the expiration of 45 days from the date Gilead received Laurus Labs's First VEMLIDY Notice Letter, which triggered a stay of FDA approval of Laurus Labs's VEMLIDY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

179. Gilead filed its first amended complaint before the expiration of 45 days from the date Gilead received Laurus Labs's Second VEMLIDY Notice Letter, in accordance with 21 U.S.C. § 355(j)(5)(B)(iii).

180. By filing its VEMLIDY ANDA, Laurus Labs has necessarily represented to FDA that its VEMLIDY ANDA product has the same active ingredient as VEMLIDY; has the same dosage form and strength as VEMLIDY; and is bioequivalent to VEMLIDY.

181. On information and belief, Laurus Labs is seeking approval to market its VEMLIDY ANDA Product for the same approved indication as VEMLIDY.

182. On information and belief, Laurus Labs's proposed label for its VEMLIDY ANDA Product ("Laurus Labs's Proposed VEMLIDY Label") will refer to the product as, *inter alia*, a hepatitis B virus nucleoside analog reverse transcriptase inhibitor for the treatment of chronic hepatitis B infection in adults with compensated liver disease, and will describe the tablet strength of Laurus Labs's VEMLIDY ANDA Product as 25 mg.

183. On information and belief, Laurus Labs's Proposed VEMLIDY Label will instruct physicians and healthcare providers to administer Laurus Labs's VEMLIDY ANDA Product for, *inter alia*, the treatment of chronic hepatitis B infection in adults with compensated liver disease.

184. On information and belief, Laurus Labs's Proposed VEMLIDY Label will contain data relating to the treatment of patients with hepatitis B infection, obtained from clinical studies involving, *inter alia*, VEMLIDY.

Laurus Labs's Acts Regarding DESCOVY

185. On information and belief, Laurus Labs has submitted to the FDA its DESCOVY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Laurus Labs's DESCOVY ANDA Product before the expiration of the '791, '065, and '769 patents. On information and belief, the FDA assigned Laurus Labs the ANDA number 213989.

186. On information and belief, Laurus Labs sent a letter dated January 7, 2020 to Gilead ("Laurus Labs's First DESCOVY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Laurus Labs's DESCOVY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769.

187. On information and belief, Laurus Labs sent a second letter dated October 7, 2020 to Gilead ("Laurus Labs's Second DESCOVY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Laurus Labs's Second DESCOVY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '791 patent.

188. Gilead received Laurus Labs's First DESCOVY Notice Letter on or about January 8, 2020, and Laurus Labs's Second DESCOVY Notice Letter on or about October 8, 2020.

189. Gilead filed its initial complain in this matter before the expiration of 45 days from the date Gilead received Laurus Labs's First DESCOVY Notice Letter, which triggered a stay of FDA approval of Laurus Labs's DESCOVY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

190. Gilead filed its first amended complaint before the expiration of 45 days from the

date Gilead received Laurus Labs's Second DESCOVY Notice Letter in accordance with 21 U.S.C. § 355(j)(5)(B)(iii).

191. By filing its DESCOVY ANDA, Laurus Labs has necessarily represented to FDA that its DESCOVY ANDA product has the same active ingredients as DESCOVY; has the same dosage forms and strengths as DESCOVY; and is bioequivalent to DESCOVY.

192. On information and belief, Laurus Labs is seeking approval to market its DESCOVY ANDA Product for the same approved indications as DESCOVY.

193. On information and belief, Laurus Labs's proposed label for its DESCOVY ANDA Product (Laurus Labs's "Proposed DESCOVY Label") will refer to the product as, *inter alia*, a two-drug combination of emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors, used in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients, and for at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection, and will describe the fixed-dose combination tablets as containing 200 mg of emtricitabine and 25 mg of tenofovir alafenamide.

194. On information and belief, Laurus Labs's Proposed DESCOVY Label will instruct physicians and healthcare providers to administer Laurus Labs's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in adults and pediatric patients, and at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection.

195. On information and belief, Laurus Labs's Proposed DESCOVY Label will contain data relating to the treatment of patients with HIV-1 infection, obtained from clinical studies involving, *inter alia*, DESCOVY.

Shilpa's Acts Regarding VEMLIDY

196. On information and belief, Shilpa submitted to the FDA its VEMLIDY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Shilpa's VEMLIDY ANDA Product before the expiration of the '065 and '769 patents. On information and belief, the FDA assigned Shilpa ANDA number 214072.

197. On information and belief, Shilpa sent a letter dated January 2, 2020 to Gilead ("Shilpa's VEMLIDY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Shilpa's VEMLIDY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769 patents.

198. Gilead received Shilpa's VEMLIDY Notice Letter on or about January 3, 2020.

199. This action is being commenced before the expiration of 45 days from the date Gilead received Shilpa's VEMLIDY Notice Letter, which triggers a stay of FDA approval of Shilpa's VEMLIDY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

200. By filing its VEMLIDY ANDA, Shilpa has necessarily represented to FDA that its VEMLIDY ANDA product has the same active ingredient as VEMLIDY; has the same dosage form and strength as VEMLIDY; and is bioequivalent to VEMLIDY.

201. On information and belief, Shilpa is seeking approval to market its VEMLIDY ANDA Product for the same approved indication as VEMLIDY.

202. On information and belief, Shilpa's proposed label for its VEMLIDY ANDA Product ("Shilpa's Proposed VEMLIDY Label") will refer to the product as, *inter alia*, a hepatitis B virus nucleoside analog reverse transcriptase inhibitor for the treatment of chronic hepatitis B infection in adults with compensated liver disease, and will describe the tablet strength of Shilpa's

VEMLIDY ANDA Product as 25 mg.

203. On information and belief, Shilpa's Proposed VEMLIDY Label will instruct physicians and healthcare providers to administer Shilpa's VEMLIDY ANDA Product for, *inter alia*, the treatment of chronic hepatitis B infection in adults with compensated liver disease.

204. On information and belief, Shilpa's Proposed VEMLIDY Label will contain data relating to the treatment of patients with hepatitis B infection, obtained from clinical studies involving, *inter alia*, VEMLIDY.

Sunshine Lake's Acts Regarding VEMLIDY

205. On information and belief, Sunshine Lake submitted to the FDA its VEMLIDY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Sunshine Lake's VEMLIDY ANDA Product before the expiration of the '065 and '769 patents. On information and belief, the FDA assigned Sunshine Lake ANDA number 213845.

206. On information and belief, Sunshine Lake sent a letter dated January 2, 2020 to Gilead ("Sunshine Lake's VEMLIDY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Sunshine Lake's VEMLIDY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769 patents.

207. Gilead received Sunshine Lake's VEMLIDY Notice Letter on or about January 3, 2020.

208. This action is being commenced before the expiration of 45 days from the date Gilead received Sunshine Lake's VEMLIDY Notice Letter, which triggers a stay of FDA approval of Sunshine Lake's VEMLIDY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

209. By filing its VEMLIDY ANDA, Sunshine Lake has necessarily represented to FDA that its VEMLIDY ANDA product has the same active ingredient as VEMLIDY; has the same dosage form and strength as VEMLIDY; and is bioequivalent to VEMLIDY.

210. On information and belief, Sunshine Lake is seeking approval to market its VEMLIDY ANDA Product for the same approved indication as VEMLIDY.

211. On information and belief, Sunshine Lake's proposed label for its VEMLIDY ANDA Product ("Sunshine Lake's Proposed VEMLIDY Label") will refer to the product as, *inter alia*, a hepatitis B virus nucleoside analog reverse transcriptase inhibitor for the treatment of chronic hepatitis B infection in adults with compensated liver disease, and will describe the tablet strength of Sunshine Lake's VEMLIDY ANDA Product as 25 mg.

212. On information and belief, Sunshine Lake's Proposed VEMLIDY Label will instruct physicians and healthcare providers to administer Sunshine Lake's VEMLIDY ANDA Product for, *inter alia*, the treatment of chronic hepatitis B infection in adults with compensated liver disease.

213. On information and belief, Sunshine Lake's Proposed VEMLIDY Label will contain data relating to the treatment of patients with hepatitis B infection, obtained from clinical studies involving, *inter alia*, VEMLIDY.

Natco's Acts Regarding DESCOVY

214. On information and belief, Natco has submitted to the FDA its DESCOVY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Natco's DESCOVY ANDA Product before the expiration of the '791, '065, and '769 patents. On information and belief, the FDA assigned Natco ANDA number 214173.

215. On information and belief, Natco sent a letter dated January 7, 2020 to Gilead ("Natco's First DESCOVY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Natco's First DESCOVY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769 patents.

216. On information and belief, Natco sent a second letter dated January 21, 2020 to Gilead ("Natco's Second DESCOVY Notice Letter"), purporting to be a notice of recertification pursuant to 21 U.S.C. § 355(j)(2)(B) and 21 C.F.R. § 314.96(d)(1)(i). Natco's Recertification DESCOVY Notice Letter purports to incorporate Natco's First DESCOVY Notice Letter. Natco's Recertification DESCOVY Notice Letter also purports to have been made with regard to certain use codes associated with the '065 and '769 patents.

217. On information and belief, Natco sent a third letter dated October 15, 2020 to Gilead ("Natco's Third DESCOVY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Natco's Third DESCOVY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '791 patent.

218. Gilead received Natco's First DESCOVY Notice Letter on or about January 8, 2020, Natco's Second DESCOVY Notice Letter on or about January 22, 2020, and Natco's Third DESCOVY Notice Letter on or about October 16, 2020..

219. Gilead filed its initial complaint in this matter before the expiration of 45 days from the date Gilead received Natco's First DESCOVY Notice Letter, which triggered a stay of FDA approval of Natco's DESCOVY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

220. Gilead filed its first amended complaint before the expiration of 45 days from the date Gilead received Natco's Third DESCOVY Notice Letter, in accordance with 21 U.S.C. § 355(j)(5)(B)(iii).

221. By filing its DESCOVY ANDA, Natco has necessarily represented to FDA that its DESCOVY ANDA product has the same active ingredient as DESCOVY; has the same dosage forms and strengths as DESCOVY; and is bioequivalent to DESCOVY.

222. On information and belief, Natco is seeking approval to market its DESCOVY ANDA Product for the same approved indications as DESCOVY.

223. On information and belief, Natco's proposed label for its DESCOVY ANDA Product ("Natco's Proposed DESCOVY Label") will refer to the product as, *inter alia*, a two-drug combination of emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors, used in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients, and for at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection, and will describe the fixed-dose combination tablets as containing 200 mg of emtricitabine and 25 mg of tenofovir alafenamide.

224. On information and belief, Natco's Proposed DESCOVY Label will instruct physicians and healthcare providers to administer Natco's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in adults and pediatric patients, and at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection.

225. On information and belief, Natco's Proposed DESCOVY Label will contain data relating to the treatment of patients with HIV-1 infection, obtained from clinical studies involving, *inter alia*, DESCOVY.

Cipla's Acts Regarding DESCOVY

226. On information and belief, Cipla submitted to the FDA its DESCOVY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial

manufacture, use, importation, offer for sale, and/or sale of Cipla's DESCOVY ANDA Product before the expiration of all four Patents-In-Suit. On information and belief, the FDA assigned Cipla ANDA number 214059.

227. On information and belief, Cipla sent a letter dated January 10, 2020 to Gilead ("Cipla's First DESCOVY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Cipla's First DESCOVY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '064 and '769 patents.

228. On information and belief, Cipla sent a second letter dated January 10, 2020 to Gilead ("Cipla's Second DESCOVY Notice Letter"), also purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Cipla's Second DESCOVY Notice Letter purports to incorporate Cipla's First DESCOVY Notice Letter. Cipla's Second DESCOVY Notice Letter also includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '791 and '788 patents.

229. Gilead received Cipla's First DESCOVY Notice Letter on or about January 13, 2020, and Cipla's Second DESCOVY Notice Letter on or about January 13, 2020.

230. This action is being commenced before the expiration of 45 days from the date Gilead received Cipla's DESCOVY Notice Letter, which triggers a stay of FDA approval of Cipla's DESCOVY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

231. By filing its DESCOVY ANDA, Cipla has necessarily represented to FDA that its DESCOVY ANDA product has the same active ingredients as DESCOVY; has the same dosage forms and strengths as DESCOVY; and is bioequivalent to DESCOVY.

232. On information and belief, Cipla is seeking approval to market its DESCOVY ANDA Product for the same approved indications as DESCOVY.

233. On information and belief, Cipla's proposed label for its DESCOVY ANDA Product ("Cipla's Proposed DESCOVY Label") will refer to the product as, *inter alia*, a two-drug combination of emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors, used in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients, and for at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection, and will describe the fixed-dose combination tablets as containing 200 mg of emtricitabine and 25 mg of tenofovir alafenamide.

234. On information and belief, Cipla's Proposed DESCOVY Label will instruct physicians and healthcare providers to administer Cipla's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in adults and pediatric patients, and at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection.

235. On information and belief, Cipla's Proposed DESCOVY Label will contain data relating to the treatment of patients with HIV-1 infection, obtained from clinical studies involving, *inter alia*, DESCOVY.

Cipla's Acts Regarding ODEFSEY

236. On information and belief, Cipla submitted to the FDA its ODEFSEY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Cipla's ODEFSEY ANDA Product before the expiration of all four Patents-In-Suit. On information and belief, the FDA assigned Cipla ANDA number 214058.

237. On information and belief, Cipla sent a letter dated January 9, 2020 to Gilead ("Cipla's First ODEFSEY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C.

§ 355(j)(2)(B). Cipla's First ODEFSEY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '064 and '769 patents.

238. On information and belief, Cipla sent a second letter dated January 10, 2020 to Gilead ("Cipla's Second ODEFSEY Notice Letter"), also purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Cipla's Second ODEFSEY Notice Letter purports to incorporate Cipla's First ODEFSEY Notice Letter. Cipla's Second ODEFSEY Notice Letter also includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '791 and '788 patents

239. Gilead received Cipla's First ODEFSEY Notice Letter on or about January 10, 2020, and Cipla's Second ODEFSEY Notice Letter on or about January 13, 2020.

240. This action is being commenced before the expiration of 45 days from the date Gilead received either of Cipla's ODEFSEY Notice Letters, which triggers a stay of FDA approval of Cipla's ODEFSEY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

241. By filing its ODEFSEY ANDA, Cipla has necessarily represented to FDA that its ODEFSEY ANDA Product has the same active ingredients as ODEFSEY; has the same dosage forms and strengths as ODEFSEY; and is bioequivalent to ODEFSEY.

242. On information and belief, Cipla is seeking approval to market its ODEFSEY ANDA Product for the same approved indications as ODEFSEY.

243. On information and belief, Cipla's proposed label for its ODEFSEY ANDA Product ("Cipla's Proposed ODEFSEY Label") will refer to the product as, *inter alia*, a three-drug combination of emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors, and rilpivirine, a non-nucleoside reverse transcriptase inhibitor, as a complete regimen for the treatment of HIV-1 infection in patients, and will describe the fixed-dose combination tablets as containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 25 mg of

tenofovir alafenamide.

244. On information and belief, Cipla's Proposed ODEFSEY Label will instruct physicians and healthcare providers to administer Cipla's ODEFSEY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in patients.

245. On information and belief, Cipla's Proposed ODEFSEY Label will contain data relating to the treatment of patients with HIV-1 infection, obtained from clinical studies involving, *inter alia*, ODEFSEY.

Macleods's Acts Regarding DESCOVY

246. On information and belief, Macleods submitted to the FDA its DESCOVY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Macleods's DESCOVY ANDA Product before the expiration of the '065 and '769 patents. On information and belief, the FDA assigned Macleods ANDA number 214216.

247. On information and belief, Macleods sent a letter dated January 14, 2020 to Gilead ("Macleods's DESCOVY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Macleods's DESCOVY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769 patents.

248. Gilead received Macleods's DESCOVY Notice Letter on or about January 16, 2020.

249. This action is being commenced before the expiration of 45 days from the date Gilead received Macleods's DESCOVY Notice Letter, which triggers a stay of FDA approval of Macleods's DESCOVY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

250. By filing its DESCOVY ANDA, Macleods has necessarily represented to FDA that its DESCOVY ANDA product has the same active ingredients as DESCOVY; has the same dosage forms and strengths as DESCOVY; and is bioequivalent to DESCOVY.

251. On information and belief, Macleods is seeking approval to market its DESCOVY ANDA Product for the same approved indications as DESCOVY.

252. On information and belief, Macleods's proposed label for its DESCOVY ANDA Product ("Macleods's Proposed DESCOVY Label") will refer to the product as, *inter alia*, a two-drug combination of emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors, used in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients, and for at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection, and will describe the fixed-dose combination tablets as containing 200 mg of emtricitabine and 25 mg of tenofovir alafenamide.

253. On information and belief, Macleods's Proposed DESCOVY Label will instruct physicians and healthcare providers to administer Macleods's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in adults and pediatric patients, and at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection.

254. On information and belief, Macleods's Proposed DESCOVY Label will contain data relating to the treatment of patients with HIV-1 infection, obtained from clinical studies involving, *inter alia*, DESCOVY.

Hetero's Acts Regarding VEMLIDY

255. On information and belief, Hetero has submitted to the FDA its VEMLIDY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial

manufacture, use, importation, offer for sale, and/or sale of Hetero's VEMLIDY ANDA Product before the expiration of the '791, '065 and '769 patents. On information and belief, the FDA assigned Hetero ANDA number 214179.

256. On information and belief, Hetero sent a letter dated January 15, 2020 to Gilead ("Hetero's First VEMLIDY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Hetero's First VEMLIDY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769 patents.

257. On information and belief, Hetero sent a second letter dated September 29, 2021 to Gilead ("Hetero's Second VEMLIDY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Hetero's Second VEMLIDY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '791 patent

258. Gilead received Hetero's First VEMLIDY Notice Letter on or about January 16, 2020 and Hetero's Second VEMLIDY Notice Letter on or about September 30, 2021.

259. Gilead filed its initial complaint in this matter before the expiration of 45 days from the date Gilead received Hetero's First VEMLIDY Notice Letter, which triggered a stay of FDA approval of Hetero's VEMLIDY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

260. Gilead is filing this second amended complaint before the expiration of 45 days from the date Gilead received Hetero's Second VEMLIDY Notice Letter, in accordance with 21 U.S.C. § 355(j)(5)(B)(iii).

261. By filing its VEMLIDY ANDA, Hetero has necessarily represented to FDA that its VEMLIDY ANDA product has the same active ingredient as VEMLIDY; has the same dosage form and strength as VEMLIDY; and is bioequivalent to VEMLIDY.

262. On information and belief, Hetero is seeking approval to market its VEMLIDY ANDA Product for the same approved indication as VEMLIDY.

263. On information and belief, Hetero's proposed label for its VEMLIDY ANDA Product ("Hetero's Proposed VEMLIDY Label") will refer to the product as, *inter alia*, a hepatitis B virus nucleoside analog reverse transcriptase inhibitor for the treatment of chronic hepatitis B infection in adults with compensated liver disease, and will describe the tablet strength of Hetero's VEMLIDY ANDA Product as 25 mg.

264. On information and belief, Hetero's Proposed VEMLIDY Label will instruct physicians and healthcare providers to administer Hetero's VEMLIDY ANDA Product for, *inter alia*, the treatment of chronic hepatitis B infection in adults with compensated liver disease.

265. On information and belief, Hetero's Proposed VEMLIDY Label will contain data relating to the treatment of patients with hepatitis B infection, obtained from clinical studies involving, *inter alia*, VEMLIDY.

Hetero's Acts Regarding DESCOVY

266. On information and belief, Hetero has submitted to the FDA its DESCOVY ANDA under Section 505(j) of the FFDCA, seeking the FDA's approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Hetero's DESCOVY ANDA Product before the expiration of the '791, '065 and '769 patents. On information and belief, the FDA assigned Hetero ANDA number 211850.

267. On information and belief, Hetero sent a letter dated January 15, 2020 to Gilead (Hetero's First "DESCOVY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Hetero's First DESCOVY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '065 and '769 patents.

268. On information and belief, Hetero sent a letter dated September 23, 2021 to Gilead (Hetero's Second "DESCOVY Notice Letter"), purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B). Hetero's Second DESCOVY Notice Letter includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '791 patent.

269. Gilead received Hetero's First DESCOVY Notice Letter on or about January 16, 2020 and Hetero's Second DESCOVY Notice Letter on or about September 24, 2021.

270. Gilead filed its initial complaint in this matter before the expiration of 45 days from the date Gilead received Hetero's First DESCOVY Notice Letter, which triggered a stay of FDA approval of Hetero's DESCOVY ANDA pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

271. Gilead is filing this second amended complaint before the expiration of 45 days from the date Gilead received Hetero's Second DESCOVY Notice Letter, in accordance with 21 U.S.C. § 355(j)(5)(B)(iii).

272. By filing its DESCOVY ANDA, Hetero has necessarily represented to FDA that its DESCOVY ANDA product has the same active ingredients as DESCOVY; has the same dosage forms and strengths as DESCOVY; and is bioequivalent to DESCOVY.

273. On information and belief, Hetero is seeking approval to market its DESCOVY ANDA Product for the same approved indications as DESCOVY.

274. On information and belief, Hetero's proposed label for its DESCOVY ANDA Product ("Hetero's Proposed DESCOVY Label") will refer to the product as, *inter alia*, a two-drug combination of emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors, used in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients, and for at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection, and will describe the fixed-

dose combination tablets as containing 200 mg of emtricitabine and 25 mg of tenofovir alafenamide.

275. On information and belief, Hetero's Proposed DESCOVY Label will instruct physicians and healthcare providers to administer Hetero's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in adults and pediatric patients, and at-risk adults and adolescents for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection.

276. On information and belief, Hetero's Proposed DESCOVY Label will contain data relating to the treatment of patients with HIV-1 infection, obtained from clinical studies involving, *inter alia*, DESCOVY.

Gilead's Attempts to Gain Access to Defendants' ANDAs

277. Defendants' Notice Letters each included an Offer for Confidential Access ("OCA") to their respective ANDAs on terms and conditions set forth in each Notice Letter. The OCAs requested that Gilead accept the terms of each OCA before receiving access to that Defendants' ANDAs. Under 35 U.S.C. 355(j)(5)(C)(i)(III), an OCA "shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information." Defendants' OCAs each contained unreasonable restrictions, above and beyond those that would apply under a protective order.

278. Since receiving Defendants' Notice Letters, Gilead and each of the Defendants have been negotiating in good faith to reach a mutually-acceptable agreement under which Defendants would provide their ANDAs to Gilead. To date, each Defendant has refused to offer Gilead access to its ANDA under terms consistent with a protective order entered for the purpose

of protecting trade secrets and other confidential business information. As a result, Gilead has been unable to access Defendants' ANDAs.

279. Under the Hatch-Waxman Act, an owner of a patented drug must file an action in federal court within 45 days of receiving a Paragraph IV letter in order to receive certain benefits under the Act, including a stay of approval of the generic drug for up to 30 months during the pendency of litigation, as appropriate, pursuant to 21 U.S.C. § 355(c)(3)(C).

280. Gilead is not aware of any other means of obtaining information regarding Defendants' TAF ANDA Products within the 45-day statutory period. In the absence of such information, Gilead resorts to the judicial process and the aid of discovery to obtain under appropriate judicial safeguards such information as is required to confirm its belief, and to present to the Court evidence, that Defendants have and will infringe certain claims of the Patents-In-Suit.

COUNTS I-XII AGAINST APOTEX

VEMLIDY Counts

Count I: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Apotex's VEMLIDY ANDA Product

281. Gilead realleges the foregoing paragraphs as if fully set forth herein.

282. Pursuant to 35 U.S.C. § 271(e)(2)(A), Apotex has committed an act of infringement of the '065 patent by submitting Apotex's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's VEMLIDY ANDA Product in the United States prior to the expiration of the '065 patent.

283. Apotex's commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's VEMLIDY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one

of the claims of the '065 patent, including but not limited to claim 1.[1]

284. On information and belief, for example, Apotex's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

285. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

286. Unless and until Apotex is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count II: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Apotex's VEMLIDY ANDA Product

287. Gilead realleges the foregoing paragraphs as if fully set forth herein.

288. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

289. There is an actual case or controversy such that the Court may entertain Gilead'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.

290. Apotex has submitted an ANDA for a generic version of Gilead's VEMLIDY product. According to Apotex's VEMLIDY Notice Letter, Apotex intends to manufacture, use, offer for sale, sell, and/or import Apotex's VEMLIDY ANDA Product in the United States.

291. While the FDA has not yet approved Apotex's VEMLIDY ANDA, Apotex has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Apotex's VEMLIDY ANDA Product.

[1] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

292. Apotex's actions indicate that it does not intend to change its course of conduct.

293. On information and belief, upon FDA approval of Apotex's VEMLIDY ANDA, Apotex will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[2] by making, using, offering to sell, and/or selling Apotex's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

294. On information and belief, for example, Apotex's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

295. Apotex has actual knowledge of the '065 patent.

296. On information and belief, Apotex became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

297. On information and belief, Apotex's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent.

298. On information and belief, Apotex's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Apotex in the United States by it or on its behalf.

[2] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

299. On information and belief, Apotex's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Apotex's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent.

300. On information and belief, physicians and healthcare providers will administer Apotex's VEMLIDY ANDA Product in the United States according to the directions and instructions in the Apotex's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

301. On information and belief, at least through its Proposed VEMLIDY Label, Apotex will encourage physicians and healthcare providers to administer Apotex's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent, and Apotex will know or should know that such conduct will occur.

302. On information and belief, Apotex will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

303. Through at least the foregoing actions, Apotex will actively induce the infringement of at least one claim of the '065 patent.

304. On information and belief, Apotex knows or should know that Apotex's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the '065 patent and that Apotex's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

305. The commercial manufacture, use, sale, offer for sale, and/or importation of Apotex's VEMLIDY ANDA Product will contribute to the actual infringement of the '065 patent.

306. On information and belief, Apotex knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the '065 patent.

307. Through at least the foregoing actions, Apotex will contribute to the infringement of at least one claim of the '065 patent.

308. On information and belief, if Apotex's VEMLIDY ANDA is approved by the FDA, Apotex will make its VEMLIDY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

309. On information and belief, Apotex's VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Apotex's VEMLIDY ANDA Product become a trivial and nonessential component of another product.

310. Through at least the foregoing actions, Apotex will infringe at least one claim of the '065 patent under 35 U.S.C. § 271(g).

311. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Apotex's VEMLIDY ANDA Product by Apotex prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

312. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

313. Unless and until Apotex is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count III: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Apotex's VEMLIDY ANDA Product

314. Gilead realleges the foregoing paragraphs as if fully set forth herein.

315. Pursuant to 35 U.S.C. § 271(e)(2)(A), Apotex has committed an act of infringement of the'769 patent by submitting Apotex's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's VEMLIDY ANDA Product in the United States prior to the expiration of the '769 patent.

316. Apotex's commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's VEMLIDY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[3]

317. On information and belief, for example, Apotex's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

318. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

319. Unless and until Apotex is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count IV: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Apotex's VEMLIDY ANDA Product

[3] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

320. Gilead realleges the foregoing paragraphs as if fully set forth herein.

321. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

322. There is an actual case or controversy such that the Court may entertain Gilead'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.

323. Apotex has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Apotex's VEMLIDY Notice Letter, Apotex intends to manufacture, use, offer for sale, sell, and/or import Apotex's VEMLIDY ANDA Product within the United States.

324. While the FDA has not yet approved Apotex's VEMLIDY ANDA, Apotex has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Apotex's VEMLIDY ANDA Product.

325. Apotex's actions indicate that it does not intend to change its course of conduct.

326. On information and belief, upon FDA approval of Apotex's VEMLIDY ANDA, Apotex will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[4] by making, using, offering to sell, and/or selling Apotex's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

327. On information and belief, for example, Apotex's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition

[4] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

328. Apotex has actual knowledge of the '769 patent.

329. On information and belief, Apotex became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

330. On information and belief, Apotex's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent.

331. On information and belief, Apotex's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Apotex in the United States by it or on its behalf.

332. On information and belief, Apotex's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Apotex's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent.

333. On information and belief, physicians and healthcare providers will administer Apotex's VEMLIDY ANDA Product in the United States according to the directions and instructions in Apotex's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

334. On information and belief, at least through its Proposed VEMLIDY Label, Apotex

will encourage physicians and healthcare providers to administer Apotex's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent, and Apotex will know or should know that such conduct will occur.

335. On information and belief, Apotex will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

336. Through at least the foregoing actions, Apotex will actively induce the infringement of at least one claim of the '769 patent.

337. On information and belief, Apotex knows or should know that Apotex's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Apotex's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

338. The commercial manufacture, use, sale, offer for sale, and/or importation of Apotex's VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

339. On information and belief, Apotex knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

340. Through at least the foregoing actions, Apotex will contribute to the infringement of at least one claim of the '769 patent.

341. On information and belief, if Apotex's VEMLIDY ANDA is approved by the FDA, Apotex will make its VEMLIDY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

342. On information and belief, Apotex's VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Apotex's VEMLIDY ANDA Product become a trivial and nonessential component of another product.

343. Through at least the foregoing actions, Apotex will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

344. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Apotex's VEMLIDY ANDA Product by Apotex prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

345. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

346. Unless and until Apotex is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

DESCOVY Counts

Count V: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Apotex's DESCOVY ANDA Product

347. Gilead realleges the foregoing paragraphs as if fully set forth herein.

348. Pursuant to 35 U.S.C. § 271(e)(2)(A), Apotex has committed an act of infringement of the '065 patent by submitting Apotex's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's DESCOVY ANDA Product in the United States prior to the expiration of the '065 patent.

349. Apotex's commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's DESCOVY ANDA Product prior to the expiration of the '065 patent, and its

inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[5]

350. On information and belief, for example, Apotex's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

351. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

352. Unless and until Apotex is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count VI: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Apotex's DESCOVY ANDA Product

353. Gilead realleges the foregoing paragraphs as if fully set forth herein.

354. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

355. There is an actual case or controversy such that the Court may entertain Gilead'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.

356. Apotex has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Apotex's DESCOVY Notice Letter, Apotex intends to manufacture, use, offer for sale, sell, and/or import Apotex's DESCOVY ANDA Product within the United States.

[5] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

357. While the FDA has not yet approved Apotex's DESCOVY ANDA, Apotex has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Apotex's DESCOVY ANDA Product.

358. Apotex's actions indicate that it does not intend to change its course of conduct.

359. On information and belief, upon FDA approval of Apotex's DESCOVY ANDA, Apotex will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[6] by making, using, offering to sell, and/or selling Apotex's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

360. On information and belief, for example, Apotex's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

361. Apotex has actual knowledge of the '065 patent.

362. On information and belief, Apotex became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book as covering DESCOVY.

363. On information and belief, Apotex's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent.

[6] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

364. On information and belief, Apotex's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Apotex in the United States by it or on its behalf.

365. On information and belief, Apotex's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Apotex's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '065 patent.

366. On information and belief, physicians and healthcare providers will administer Apotex's DESCOVY ANDA Product in the United States according to the directions and instructions in Apotex's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

367. On information and belief, at least through its Proposed DESCOVY Label, Apotex will encourage physicians and healthcare providers to administer Apotex's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '065 patent, and Apotex will know or should know that such conduct will occur.

368. On information and belief, Apotex will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

369. Through at least the foregoing actions, Apotex will actively induce the infringement of at least one claim of the '065 patent.

370. On information and belief, Apotex knows or should know that Apotex's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '065 patent and that Apotex's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

371. The commercial manufacture, use, sale, offer for sale, and/or importation of Apotex's DESCOVY ANDA Product will contribute to the actual infringement of the '065 patent.

372. On information and belief, Apotex knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '065 patent.

373. Through at least the foregoing actions, Apotex will contribute to the infringement of at least one claim of the '065 patent.

374. On information and belief, if Apotex's DESCOVY ANDA is approved by the FDA, Apotex will make its DESCOVY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

375. On information and belief, Apotex's DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Apotex's DESCOVY ANDA Product become a trivial and nonessential component of another product.

376. Through at least the foregoing actions, Apotex will infringe of at least one claim of the '065 patent under 35 U.S.C. § 271(g).

377. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Apotex's DESCOVY ANDA Product by Apotex prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

378. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

379. Unless and until Apotex is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count VII: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Apotex's DESCOVY ANDA Product

380. Gilead realleges the foregoing paragraphs as if fully set forth herein.

381. Pursuant to 35 U.S.C. § 271(e)(2)(A), Apotex has committed an act of infringement of the '769 patent by submitting Apotex's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's DESCOVY ANDA Product in the United States prior to the expiration of the '769 patent.

382. Apotex's commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's DESCOVY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[7]

383. On information and belief, for example, Apotex's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

384. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's

[7] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

385. Unless and until Apotex is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count VIII: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Apotex's DESCOVY ANDA Product

386. Gilead realleges the foregoing paragraphs as if fully set forth herein.

387. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

388. There is an actual case or controversy such that the Court may entertain Gilead'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.

389. Apotex has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Apotex's DESCOVY Notice Letter, Apotex intends to manufacture, use, offer for sale, sell, and/or import Apotex's DESCOVY ANDA Product within the United States.

390. While the FDA has not yet approved Apotex's DESCOVY ANDA, Apotex has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Apotex's DESCOVY ANDA Product.

391. Apotex's actions indicate that it does not intend to change its course of conduct.

392. On information and belief, upon FDA approval of Apotex's DESCOVY ANDA, Apotex will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[8] by making, using, offering to sell, and/or selling

[8] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

Apotex's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

393. On information and belief, for example, Apotex's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

394. Apotex has actual knowledge of the '769 patent.

395. On information and belief, Apotex became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

396. On information and belief, Apotex's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent.

397. On information and belief, Apotex's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Apotex in the United States by it or on its behalf.

398. On information and belief, Apotex's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Apotex's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent.

399. On information and belief, physicians and healthcare providers will administer Apotex's DESCOVY ANDA Product in the United States according to the directions and instructions in Apotex's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

400. On information and belief, at least through its Proposed DESCOVY Label, Apotex will encourage physicians and healthcare providers to administer Apotex's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent, and Apotex will know or should know that such conduct will occur.

401. On information and belief, Apotex will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

402. Through at least the foregoing actions, Apotex will actively induce the infringement of at least one claims of the '769 patent.

403. On information and belief, Apotex knows or should know that Apotex's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Apotex's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

404. The commercial manufacture, use, sale, offer for sale, and/or importation of Apotex's DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

405. On information and belief, Apotex knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

406. Through at least the foregoing actions, Apotex will contribute to the infringement

of at least one claim of the '769 patent.

407. On information and belief, if Apotex's DESCOVY ANDA is approved by the FDA, Apotex will make its DESCOVY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

408. On information and belief, Apotex's DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Apotex's DESCOVY ANDA Product become a trivial and nonessential component of another product.

409. Through at least the foregoing actions, Apotex will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

410. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Apotex's DESCOVY ANDA Product by Apotex prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

411. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

412. Unless and until Apotex is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

ODEFSEY Counts

Count IX: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Apotex's ODEFSEY ANDA Product

413. Gilead realleges the foregoing paragraphs as if fully set forth herein.

414. Pursuant to 35 U.S.C. § 271(e)(2)(A), Apotex has committed an act of infringement of the '065 patent by submitting Apotex's ODEFSEY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's ODEFSEY ANDA Product in the United States prior to the expiration of the '065 patent.

415. Apotex's commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's ODEFSEY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[9]

416. On information and belief, for example, Apotex's ODEFSEY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

417. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

418. Unless and until Apotex is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count X: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Apotex's ODEFSEY ANDA Product

419. Gilead realleges the foregoing paragraphs as if fully set forth herein.

420. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

[9] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

421. There is an actual case or controversy such that the Court may entertain Gilead'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.

422. Apotex has submitted an ANDA for a generic version of Gilead's ODEFSEY pharmaceutical product. According to Apotex's ODEFSEY Notice Letter, Apotex intends to manufacture, use, offer for sale, sell, and/or import Apotex's ODEFSEY ANDA Product within the United States.

423. While the FDA has not yet approved Apotex's ODEFSEY ANDA, Apotex has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Apotex's ODEFSEY ANDA Product.

424. Apotex's actions indicate that it does not intend to change its course of conduct.

425. On information and belief, upon FDA approval of Apotex's ODEFSEY ANDA, Apotex will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[10] by making, using, offering to sell, and/or selling Apotex's ODEFSEY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

426. On information and belief, for example, Apotex's ODEFSEY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

427. Apotex has actual knowledge of the '065 patent.

[10] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

428. On information and belief, Apotex became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book as covering ODEFSEY.

429. On information and belief, Apotex's efforts to make, use, sell, offer for sell, and/or import its ODEFSEY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent.

430. On information and belief, Apotex's ODEFSEY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Apotex in the United States by it or on its behalf.

431. On information and belief, Apotex's Proposed ODEFSEY Label will include directions and instructions that instruct physicians and healthcare providers to administer Apotex's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '065 patent.

432. On information and belief, physicians and healthcare providers will administer Apotex's ODEFSEY ANDA Product in the United States according to the directions and instructions in Apotex's Proposed ODEFSEY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

433. On information and belief, at least through its Proposed ODEFSEY Label, Apotex will encourage physicians and healthcare providers to administer Apotex's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '065 patent, and Apotex will know or should know that such conduct will occur.

434. On information and belief, Apotex will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the ’065 patent.

435. Through at least the foregoing actions, Apotex will actively induce the infringement of at least one claim of the ’065 patent.

436. On information and belief, Apotex knows or should know that Apotex’s ODEFSEY ANDA Product will be especially made or adapted for use in infringing the ’065 patent and that Apotex’s ODEFSEY ANDA Product is not suitable for substantial non-infringing use.

437. The commercial manufacture, use, sale, offer for sale, and/or importation of Apotex’s ODEFSEY ANDA Product will contribute to the actual infringement of the ’065 patent.

438. On information and belief, Apotex knows or should know that its offer for sale, sale and/or importation of its ODEFSEY ANDA Product will contribute to the actual infringement of the ’065 patent.

439. Through at least the foregoing actions, Apotex will contribute to the infringement of at least one claim of the ’065 patent.

440. On information and belief, if Apotex’s ODEFSEY ANDA is approved by the FDA, Apotex will make its ODEFSEY ANDA Product using a process covered by one or more claims of the ’065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

441. On information and belief, Apotex’s ODEFSEY ANDA Product will not be materially changed by a subsequent process nor will Apotex’s ODEFSEY ANDA Product become a trivial and nonessential component of another product.

442. Through at least the foregoing actions, Apotex will infringe at least one claim of

the ’065 patent under 35 U.S.C. § 271(g).

443. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Apotex’s ODEFSEY ANDA Product by Apotex prior to the expiration of the ’065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the ’065 patent.

444. The commercial manufacture, importation, use, sale, or offer for sale of Apotex’s ODEFSEY ANDA Product in violation of Gilead’s patent rights will cause harm to Gilead for which damages are inadequate.

445. Unless and until Apotex is enjoined from infringing the ’065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XI: Infringement of the ’769 Patent under 35 U.S.C. § 271(e)(2) by Apotex’s ODEFSEY ANDA Product

446. Gilead realleges the foregoing paragraphs as if fully set forth herein.

447. Pursuant to 35 U.S.C. § 271(e)(2)(A), Apotex has committed an act of infringement of the ’769 patent by submitting Apotex’s ODEFSEY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex’s ODEFSEY ANDA Product in the United States prior to the expiration of the ’769 patent.

448. Apotex’s commercial manufacture, use, offer for sale, sale, and/or importation of Apotex’s ODEFSEY ANDA Product prior to the expiration of the ’769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the ’769 patent, including but not limited to claim 1.[11]

[11] Gilead will identify all asserted claims of the ’769 patent in accordance with this Court’s Local Rules and/or scheduling order.

449. On information and belief, for example, Apotex's ODEFSEY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

450. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

451. Unless and until Apotex is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XII: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Apotex's ODEFSEY ANDA Product

452. Gilead realleges the foregoing paragraphs as if fully set forth herein.

453. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

454. There is an actual case or controversy such that the Court may entertain Gilead'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.

455. Apotex has submitted an ANDA for a generic version of Gilead's ODEFSEY pharmaceutical product. According to Apotex's ODEFSEY Notice Letter, Apotex intends to manufacture, use, offer for sale, sell, and/or import Apotex's ODEFSEY ANDA Product within the United States.

456. While the FDA has not yet approved Apotex's ODEFSEY ANDA, Apotex has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Apotex's ODEFSEY ANDA Product.

457. Apotex's actions indicate that it does not intend to change its course of conduct.

458. On information and belief, upon FDA approval of Apotex's ODEFSEY ANDA, Apotex will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[12] by making, using, offering to sell, and/or selling Apotex's ODEFSEY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

459. On information and belief, for example, Apotex's ODEFSEY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

460. Apotex has actual knowledge of the '769 patent.

461. On information and belief, Apotex became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's ODEFSEY product.

462. On information and belief, Apotex's efforts to make, use, sell, offer for sell, and/or import its ODEFSEY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent.

[12] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

463. On information and belief, Apotex's ODEFSEY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Apotex in the United States by it or on its behalf.

464. On information and belief, Apotex's Proposed ODEFSEY Label will include directions and instructions that instruct physicians and healthcare providers to administer Apotex's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '769 patent.

465. On information and belief, physicians and healthcare providers will administer Apotex's ODEFSEY ANDA Product in the United States according to the directions and instructions in Apotex's Proposed ODEFSEY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

466. On information and belief, at least through its Proposed ODEFSEY Label, Apotex will encourage physicians and healthcare providers to administer Apotex's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '769 patent, and Apotex will know or should know that such conduct will occur.

467. On information and belief, Apotex will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

468. Through at least the foregoing actions, Apotex will actively induce the infringement of at least one claim of the '769 patent.

469. On information and belief, Apotex knows or should know that Apotex's ODEFSEY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that

Apotex's ODEFSEY ANDA Product is not suitable for substantial non-infringing use.

470. The commercial manufacture, use, sale, offer for sale, and/or importation of Apotex's ODEFSEY ANDA Product will contribute to the actual infringement of the '769 patent.

471. On information and belief, Apotex knows or should know that its offer for sale, sale and/or importation of its ODEFSEY ANDA Product will contribute to the actual infringement of the '769 patent.

472. Through at least the foregoing actions, Apotex will contribute to the infringement of at least one claim of the '769 patent.

473. On information and belief, if Apotex's ODEFSEY ANDA is approved by the FDA, Apotex will make its ODEFSEY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

474. On information and belief, Apotex's ODEFSEY ANDA Product will not be materially changed by a subsequent process nor will Apotex's ODEFSEY ANDA Product become a trivial and nonessential component of another product.

475. Through at least the foregoing actions, Apotex will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

476. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Apotex's ODEFSEY ANDA Product by Apotex prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

477. The commercial manufacture, importation, use, sale, or offer for sale of Apotex's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for

which damages are inadequate.

478. Unless and until Apotex is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

COUNTS XIII-XXVIII AGAINST LUPIN

VEMLIDY Counts

Count XIII: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Lupin's VEMLIDY ANDA Product

479. Gilead realleges the foregoing paragraphs as if fully set forth herein.

480. Pursuant to 35 U.S.C. § 271(e)(2)(A), Lupin has committed an act of infringement of the '065 patent by submitting Lupin's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's VEMLIDY ANDA Product in the United States prior to the expiration of the '065 patent.

481. Lupin's commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's VEMLIDY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[13]

482. On information and belief, for example, Lupin's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

483. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

[13] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

484. Unless and until Lupin is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XIV: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Lupin's VEMLIDY ANDA Product

485. Gilead realleges the foregoing paragraphs as if fully set forth herein.

486. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

487. There is an actual case or controversy such that the Court may entertain Gilead'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.

488. Lupin has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Lupin's VEMLIDY Notice Letter, Lupin intends to manufacture, use, offer for sale, sell, and/or import Lupin's VEMLIDY ANDA Product within the United States.

489. While the FDA has not yet approved Lupin's VEMLIDY ANDA, Lupin has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Lupin's VEMLIDY ANDA Product.

490. Lupin's actions indicate that it does not intend to change its course of conduct.

491. On information and belief, upon FDA approval of Lupin's VEMLIDY ANDA, Lupin will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[14] by making, using, offering to sell, and/or selling Lupin's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by

[14] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

492. On information and belief, for example, Lupin's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

493. Lupin has actual knowledge of the '065 patent.

494. On information and belief, Lupin became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

495. On information and belief, Lupin's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Lupin's VEMLIDY Notice Letter, which does not contest infringement of at least claim 1 of the '065 patent, except on the basis that the claim is allegedly invalid.

496. On information and belief, Lupin's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Lupin in the United States by it or on its behalf.

497. On information and belief, Lupin's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Lupin's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent.

498. On information and belief, physicians and healthcare providers will administer Lupin's VEMLIDY ANDA Product in the United States according to the directions and instructions in Lupin's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

499. On information and belief, at least through its Proposed VEMLIDY Label, Lupin will encourage physicians and healthcare providers to administer Lupin's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent, and Lupin will know or should know that such conduct will occur.

500. On information and belief, Lupin will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

501. Through at least the foregoing actions, Lupin will actively induce the infringement of at least one claims of the '065 patent.

502. On information and belief, Lupin knows or should know that Lupin's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the '065 patent and that Lupin's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

503. The commercial manufacture, use, sale, offer for sale, and/or importation of Lupin's VEMLIDY ANDA Product will contribute to the actual infringement of the '065 patent.

504. On information and belief, Lupin knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the '065 patent.

505. Through at least the foregoing actions, Lupin will contribute to the infringement of at least one claim of the '065 patent.

506. On information and belief, if Lupin's VEMLIDY ANDA is approved by the FDA, Lupin will make its VEMLIDY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

507. On information and belief, Lupin's VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Lupin's VEMLIDY ANDA Product become a trivial and nonessential component of another product.

508. Through at least the foregoing actions, Lupin will infringe at least one claim of the '065 patent under 35 U.S.C. § 271(g).

509. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Lupin's VEMLIDY ANDA Product by Lupin prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

510. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

511. Unless and until Lupin is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XV: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Lupin's VEMLIDY ANDA Product

512. Gilead realleges the foregoing paragraphs as if fully set forth herein.

513. Pursuant to 35 U.S.C. § 271(e)(2)(A), Lupin has committed an act of infringement of the '769 patent by submitting Lupin's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's VEMLIDY ANDA Product in the United States prior to the expiration of the '769 patent.

514. Lupin's commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's VEMLIDY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[15]

515. On information and belief, for example, Lupin's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

516. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

517. Unless and until Lupin is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XVI: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Lupin's VEMLIDY ANDA Product

518. Gilead realleges the foregoing paragraphs as if fully set forth herein.

519. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

[15] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

520. There is an actual case or controversy such that the Court may entertain Gilead'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.

521. Lupin has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Lupin's VEMLIDY Notice Letter, Lupin intends to manufacture, use, offer for sale, sell, and/or import Lupin's VEMLIDY ANDA Product within the United States.

522. While the FDA has not yet approved Lupin's VEMLIDY ANDA, Lupin has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Lupin's VEMLIDY ANDA Product.

523. Lupin's actions indicate that it does not intend to change its course of conduct.

524. On information and belief, upon FDA approval of Lupin's VEMLIDY ANDA, Lupin will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[16] by making, using, offering to sell, and/or selling Lupin's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

525. On information and belief, for example, Lupin's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls

[16] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

526. Lupin has actual knowledge of the '769 patent.

527. On information and belief, Lupin became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

528. On information and belief, Lupin's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent. On information and belief, this knowledge is reflected through, among other things, Lupin's VEMLIDY Notice Letter, which does not contest infringement of at least claim 1 of the '769 patent, except on the basis that the claim is allegedly invalid.

529. On information and belief, Lupin's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Lupin in the United States by it or on its behalf.

530. On information and belief, Lupin's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Lupin's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent.

531. On information and belief, physicians and healthcare providers will administer Lupin's VEMLIDY ANDA Product in the United States according to the directions and instructions in Lupin's Proposed VEMLIDY Label, and such administration will constitute direct

infringement of at least one claim of the '769 patent.

532. On information and belief, at least through its Proposed VEMLIDY Label, Lupin will encourage physicians and healthcare providers to administer Lupin's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent, and Lupin will know or should know that such conduct will occur.

533. On information and belief, Lupin will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

534. Through at least the foregoing actions, Lupin will actively induce the infringement of at least one claim of the '769 patent.

535. On information and belief, Lupin knows or should know that Lupin's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Lupin's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

536. The commercial manufacture, use, sale, offer for sale, and/or importation of Lupin's VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

537. On information and belief, Lupin knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

538. Through at least the foregoing actions, Lupin will contribute to the infringement of at least one claim of the '769 patent.

539. On information and belief, if Lupin's VEMLIDY ANDA is approved by the FDA, Lupin will make its VEMLIDY ANDA Product using a process covered by one or more claims of

the ’769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

540. On information and belief, Lupin’s VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Lupin’s VEMLIDY ANDA Product become a trivial and nonessential component of another product.

541. Through at least the foregoing actions, Lupin will infringe at least one claim of the ’769 patent under 35 U.S.C. § 271(g).

542. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Lupin’s VEMLIDY ANDA Product by Lupin prior to the expiration of the ’769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the ’769 patent.

543. The commercial manufacture, importation, use, sale, or offer for sale of Lupin’s VEMLIDY ANDA Product in violation of Gilead’s patent rights will cause harm to Gilead for which damages are inadequate.

544. Unless and until Lupin is enjoined from infringing the ’769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

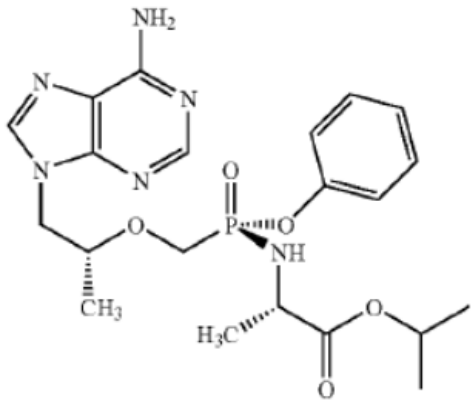
Count XVII: Infringement of the ’791 Patent under 35 U.S.C. § 271(e)(2) by Lupin’s VEMLIDY ANDA Product

545. Gilead realleges the foregoing paragraphs as if fully set forth herein.

546. Pursuant to 35 U.S.C. § 271(e)(2)(A), Lupin has committed an act of infringement of the ’791 patent by submitting Lupin’s VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Lupin’s VEMLIDY ANDA Product in the United States prior to the expiration of the ’791 patent.

547. Lupin's commercial manufacture, use, offer for sale, sale, and/or importation of the VEMLIDY ANDA Product prior to the expiration of the '791 patent would constitute infringement of at least one of the claims of the '791 patent, including but not limited to claim 7.[17]

548. On information and belief, for example, Lupin's VEMLIDY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

549. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

550. Unless and until Lupin is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XVIII: Declaratory Judgment of Infringement of the '791 Patent under 35 U.S.C. § 271(a) by Lupin's VEMLIDY ANDA Product

551. Gilead realleges the foregoing paragraphs as if fully set forth herein.

[17] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.

552. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

553. There is an actual case or controversy such that the Court may entertain Gilead'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.

554. Lupin has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Lupin's VEMLIDY Notice Letter, Lupin intends to manufacture, use, offer for sale, sell, and/or import its VEMLIDY ANDA Product within the United States.

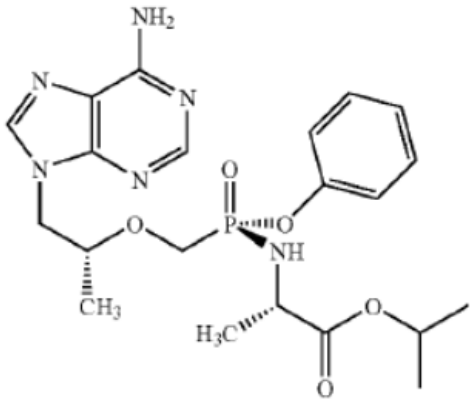
555. While the FDA has not yet approved Lupin's VEMLIDY ANDA, Lupin has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import its VEMLIDY ANDA Product.

556. Lupin's actions indicate that it does not intend to change its course of conduct.

557. On information and belief, upon FDA approval of Lupin's VEMLIDY ANDA, Lupin will infringe one or more claims of the '791 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[18] by making, using, offering to sell, and/or selling Lupin's VEMLIDY ANDA Product in the United States and/or importing said product into the United States under 35 U.S.C. § 271(a), unless enjoined by the Court.

558. On information and belief, for example, Lupin's VEMLIDY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:

[18] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

559. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Lupin's VEMLIDY ANDA Product by Lupin prior to the expiration of the '791 patent will constitute direct infringement of the '791 patent.

560. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

561. Unless and until Lupin is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

DESCOVY Counts

Count XIX: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Lupin's DESCOVY ANDA Product

562. Gilead realleges the foregoing paragraphs as if fully set forth herein.

563. Pursuant to 35 U.S.C. § 271(e)(2)(A), Lupin has committed an act of infringement of the '065 patent by submitting Lupin's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's DESCOVY ANDA Product in the United States prior to the expiration of the '065 patent.

564. Lupin's commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's DESCOVY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[19]

565. On information and belief, for example, Lupin's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

566. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

567. Unless and until Lupin is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XX: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Lupin's DESCOVY ANDA Product

568. Gilead realleges the foregoing paragraphs as if fully set forth herein.

569. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

570. There is an actual case or controversy such that the Court may entertain Gilead'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.

571. Lupin has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Lupin's DESCOVY Notice Letter, Lupin intends to

[19] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

manufacture, use, offer for sale, sell, and/or import Lupin's DESCOVY ANDA Product within the United States.

572. While the FDA has not yet approved Lupin's DESCOVY ANDA, Lupin has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Lupin's DESCOVY ANDA Product.

573. Lupin's actions indicate that it does not intend to change its course of conduct.

574. On information and belief, upon FDA approval of Lupin's DESCOVY ANDA, Lupin will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[20] by making, using, offering to sell, and/or selling Lupin's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

575. On information and belief, for example, Lupin's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

576. Lupin has actual knowledge of the '065 patent.

577. On information and belief, Lupin became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

578. On information and belief, Lupin's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of

[20] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

the ’065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the ’065 patent. On information and belief, this knowledge is reflected through, among other things, Lupin’s DESCOVY Notice Letter, which does not contest infringement of at least claim 1 of the ’065 patent, except on the basis that the claim is allegedly invalid.

579. On information and belief, Lupin’s DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Lupin in the United States by it or on its behalf.

580. On information and belief, Lupin’s Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Lupin’s DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the ’065 patent.

581. On information and belief, physicians and healthcare providers will administer Lupin’s DESCOVY ANDA Product in the United States according to the directions and instructions in Lupin’s Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the ’065 patent.

582. On information and belief, at least through its Proposed DESCOVY Label, Lupin will encourage physicians and healthcare providers to administer Lupin’s DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the ’065 patent, and Lupin will know or should know that such conduct will occur.

583. On information and belief, Lupin will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

584. Through at least the foregoing actions, Lupin will actively induce the infringement of at least one claim of the '065 patent.

585. On information and belief, Lupin knows or should know that Lupin's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '065 patent and that Lupin's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

586. The commercial manufacture, use, sale, offer for sale, and/or importation of Lupin's DESCOVY ANDA Product will contribute to the actual infringement of the '065 patent.

587. On information and belief, Lupin knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '065 patent.

588. Through at least the foregoing actions, Lupin will contribute to the infringement of at least one claim of the '065 patent.

589. On information and belief, if Lupin's DESCOVY ANDA is approved by the FDA, Lupin will make its DESCOVY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

590. On information and belief, Lupin's DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Lupin's DESCOVY ANDA Product become a trivial and nonessential component of another product.

591. Through at least the foregoing actions, Lupin will infringe at least one claim of

the ’065 patent under 35 U.S.C. § 271(g).

592. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Lupin’s DESCOVY ANDA Product by Lupin prior to the expiration of the ’065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the ’065 patent.

593. The commercial manufacture, importation, use, sale, or offer for sale of Lupin’s DESCOVY ANDA Product in violation of Gilead’s patent rights will cause harm to Gilead for which damages are inadequate.

594. Unless and until Lupin is enjoined from infringing the ’065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXI: Infringement of the ’769 Patent under 35 U.S.C. § 271(e)(2) by Lupin’s DESCOVY ANDA Product

595. Gilead realleges the foregoing paragraphs as if fully set forth herein.

596. Pursuant to 35 U.S.C. § 271(e)(2)(A), Lupin has committed an act of infringement of the ’769 patent by submitting Lupin’s DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Lupin’s DESCOVY ANDA Product in the United States prior to the expiration of the ’769 patent.

597. Lupin’s commercial manufacture, use, offer for sale, sale, and/or importation of Lupin’s DESCOVY ANDA Product prior to the expiration of the ’769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the ’769 patent, including but not limited to claim 1.[21]

[21] Gilead will identify all asserted claims of the ’769 patent in accordance with this Court’s Local Rules and/or scheduling order.

598. On information and belief, for example, Lupin's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

599. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

600. Unless and until Lupin is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXII: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Lupin's DESCOVY ANDA Product

601. Gilead realleges the foregoing paragraphs as if fully set forth herein.

602. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

603. There is an actual case or controversy such that the Court may entertain Gilead'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.

604. Lupin has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Lupin's DESCOVY Notice Letter, Lupin intends to manufacture, use, offer for sale, sell, and/or import Lupin's DESCOVY ANDA Product within the United States.

605. While the FDA has not yet approved Lupin's DESCOVY ANDA, Lupin has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Lupin's DESCOVY ANDA Product.

606. Lupin's actions indicate that it does not intend to change its course of conduct.

607. On information and belief, upon FDA approval of Lupin's DESCOVY ANDA, Lupin will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[22] by making, using, offering to sell, and/or selling Lupin's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

608. On information and belief, for example, Lupin's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

609. Lupin has actual knowledge of the '769 patent.

610. On information and belief, Lupin became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

611. On information and belief, Lupin's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent. On information and belief, this knowledge is reflected through, among other things, Lupin's DESCOVY Notice Letter, which

[22] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

does not contest infringement of at least claim 1 of the '769 patent, except on the basis that the claim is allegedly invalid.

612. On information and belief, Lupin's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Lupin in the United States by it or on its behalf.

613. On information and belief, Lupin's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Lupin's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent.

614. On information and belief, physicians and healthcare providers will administer Lupin's DESCOVY ANDA Product in the United States according to the directions and instructions in Lupin's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

615. On information and belief, at least through its Proposed DESCOVY Label, Lupin will encourage physicians and healthcare providers to administer Lupin's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent, and Lupin will know or should know that such conduct will occur.

616. On information and belief, Lupin will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

617. Through at least the foregoing actions, Lupin will actively induce the infringement of at least one claim of the '769 patent.

618. On information and belief, Lupin knows or should know that Lupin's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Lupin's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

619. The commercial manufacture, use, sale, offer for sale, and/or importation of Lupin's DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

620. On information and belief, Lupin knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

621. Through the foregoing actions, Lupin will contribute to the infringement of at least one claim of the '769 patent.

622. On information and belief, if Lupin's DESCOVY ANDA is approved by the FDA, Lupin will make its DESCOVY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

623. On information and belief, Lupin's DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Lupin's DESCOVY ANDA Product become a trivial and nonessential component of another product.

624. Through at least the foregoing actions, Lupin will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

625. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Lupin's DESCOVY ANDA Product by Lupin prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

626. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

627. Unless and until Lupin is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXIII: Infringement of the '791 Patent under 35 U.S.C. § 271(e)(2) by Lupin's DESCOVY ANDA Product

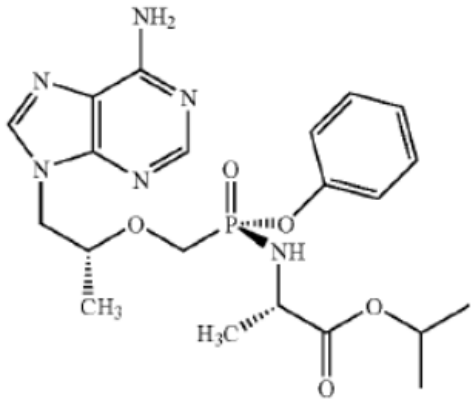
628. Gilead realleges the foregoing paragraphs as if fully set forth herein.

629. Pursuant to 35 U.S.C. § 271(e)(2)(A), Lupin has committed an act of infringement of the '791 patent by submitting Lupin's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's DESCOVY ANDA Product in the United States prior to the expiration of the '791 patent.

630. Lupin's commercial manufacture, use, offer for sale, sale, and/or importation of the DESCOVY ANDA Product prior to the expiration of the '791 patent would constitute infringement of at least one of the claims of the '791 patent, including but not limited to claim 7.[23]

631. On information and belief, for example, Lupin's DESCOVY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:

[23] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

632. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

633. Unless and until Lupin is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXIV: Declaratory Judgment of Infringement of the '791 Patent under 35 U.S.C. § 271(a) by Lupin's DESCOVY ANDA Product

634. Gilead realleges the foregoing paragraphs as if fully set forth herein.

635. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

636. There is an actual case or controversy such that the Court may entertain Gilead'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.

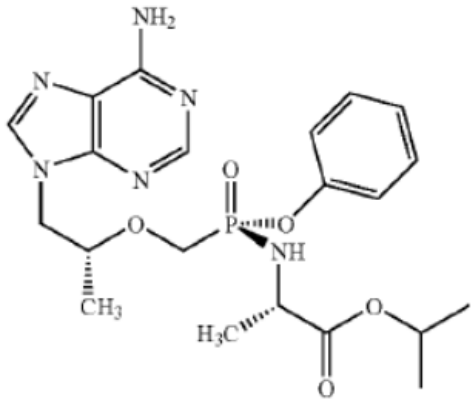
637. Lupin has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Lupin's DESCOVY Notice Letter, Lupin intends to manufacture, use, offer for sale, sell, and/or import its DESCOVY ANDA Product within the United States.

638. While the FDA has not yet approved Lupin's DESCOVY ANDA, Lupin has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import its DESCOVY ANDA Product.

639. Lupin's actions indicate that it does not intend to change its course of conduct.

640. On information and belief, upon FDA approval of Lupin's DESCOVY ANDA, Lupin will infringe one or more claims of the '791 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[24] by making, using, offering to sell, and/or selling Lupin's DESCOVY ANDA Product in the United States and/or importing said product into the United States under 35 U.S.C. § 271(a), unless enjoined by the Court.

641. On information and belief, for example, Lupin's DESCOVY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

642. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for

[24] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.

sale, sale, and/or importation of Lupin's DESCOVY ANDA Product by Lupin prior to the expiration of the '791 patent will constitute direct infringement of the '791 patent.

643. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

644. Unless and until Lupin is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

ODEFSEY Counts

Count XXV: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Lupin's ODEFSEY ANDA Product

645. Gilead realleges the foregoing paragraphs as if fully set forth herein.

646. Pursuant to 35 U.S.C. § 271(e)(2)(A), Lupin has committed an act of infringement of the '065 patent by submitting Lupin's ODEFSEY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's ODEFSEY ANDA Product in the United States prior to the expiration of the '065 patent.

647. Lupin's commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's ODEFSEY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[25]

648. On information and belief, for example, Lupin's ODEFSEY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

[25] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

649. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

650. Unless and until Lupin is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXVI: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Lupin's ODEFSEY ANDA Product

651. Gilead realleges the foregoing paragraphs as if fully set forth herein.

652. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

653. There is an actual case or controversy such that the Court may entertain Gilead'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.

654. Lupin has submitted an ANDA for a generic version of Gilead's ODEFSEY pharmaceutical product. According to Lupin's ODEFSEY Notice Letter, Lupin intends to manufacture, use, offer for sale, sell, and/or import Lupin's ODEFSEY ANDA Product within the United States.

655. While the FDA has not yet approved Lupin's ODEFSEY ANDA, Lupin has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Lupin's ODEFSEY ANDA Product.

656. Lupin's actions indicate that it does not intend to change its course of conduct.

657. On information and belief, upon FDA approval of Lupin's ODEFSEY ANDA, Lupin will infringe one or more claims of the '065 patent, either literally or under the doctrine of

equivalents, including but not limited to claim 1,[26] by making, using, offering to sell, and/or selling Lupin's ODEFSEY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

658. On information and belief, for example, Lupin's ODEFSEY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

659. Lupin has actual knowledge of the '065 patent.

660. On information and belief, Lupin became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's ODEFSEY product.

661. On information and belief, Lupin's efforts to make, use, sell, offer for sell, and/or import its ODEFSEY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Lupin's ODEFSEY Notice Letter, which does not contest infringement of at least claim 1 of the '065 patent, except on the basis that the claim is allegedly invalid.

662. On information and belief, Lupin's ODEFSEY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Lupin in the United States by it or on its behalf.

[26] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

663. On information and belief, Lupin's Proposed ODEFSEY Label will include directions and instructions that instruct physicians and healthcare providers to administer Lupin's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '065 patent.

664. On information and belief, physicians and healthcare providers will administer Lupin's ODEFSEY ANDA Product in the United States according to the directions and instructions in Lupin's Proposed ODEFSEY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

665. On information and belief, at least through its Proposed ODEFSEY Label, Lupin will encourage physicians and healthcare providers to administer Lupin's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '065 patent, and Lupin will know or should know that such conduct will occur.

666. On information and belief, Lupin will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

667. Through at least the foregoing actions, Lupin will actively induce the infringement of at least one claim of the '065 patent.

668. On information and belief, Lupin knows or should know that Lupin's ODEFSEY ANDA Product will be especially made or adapted for use in infringing the '065 patent and that Lupin's ODEFSEY ANDA Product is not suitable for substantial non-infringing use.

669. The commercial manufacture, use, sale, offer for sale, and/or importation of Lupin's ODEFSEY ANDA Product will contribute to the actual infringement of the '065 patent.

670. On information and belief, Lupin knows or should know that its offer for sale, sale and/or importation of its ODEFSEY ANDA Product will contribute to the actual infringement of the '065 patent.

671. Through at least the foregoing actions, Lupin will contribute to the infringement of at least one claim of the '065 patent.

672. On information and belief, if Lupin's ODEFSEY ANDA is approved by the FDA, Lupin will make its ODEFSEY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

673. On information and belief, Lupin's ODEFSEY ANDA Product will not be materially changed by a subsequent process nor will Lupin's ODEFSEY ANDA Product become a trivial and nonessential component of another product.

674. Through at least the foregoing actions, Lupin will infringe at least one claim of the '065 patent under 35 U.S.C. § 271(g).

675. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Lupin's ODEFSEY ANDA Product by Lupin prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

676. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

677. Unless and until Lupin is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXVII: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Lupin's ODEFSEY ANDA Product

678. Gilead realleges the foregoing paragraphs as if fully set forth herein.

679. Pursuant to 35 U.S.C. § 271(e)(2)(A), Lupin has committed an act of infringement of the '769 patent by submitting Lupin's ODEFSEY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's ODEFSEY ANDA Product in the United States prior to the expiration of the '769 patent.

680. Lupin's commercial manufacture, use, offer for sale, sale, and/or importation of Lupin's ODEFSEY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[27]

681. On information and belief, for example, Lupin's ODEFSEY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

682. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

683. Unless and until Lupin is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXVIII: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Lupin's ODEFSEY ANDA Product

[27] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

684. Gilead realleges the foregoing paragraphs as if fully set forth herein.

685. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

686. There is an actual case or controversy such that the Court may entertain Gilead'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.

687. Lupin has submitted an ANDA for a generic version of Gilead's ODEFSEY pharmaceutical product. According to Lupin's ODEFSEY Notice Letter, Lupin intends to manufacture, use, offer for sale, sell, and/or import Lupin's ODEFSEY ANDA Product within the United States.

688. While the FDA has not yet approved Lupin's ODEFSEY ANDA, Lupin has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Lupin's ODEFSEY ANDA Product.

689. Lupin's actions indicate that it does not intend to change its course of conduct.

690. On information and belief, upon FDA approval of Lupin's ODEFSEY ANDA, Lupin will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[28] by making, using, offering to sell, and/or selling Lupin's ODEFSEY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

691. On information and belief, for example, Lupin's ODEFSEY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition

[28] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

692. Lupin has actual knowledge of the '769 patent.

693. On information and belief, Lupin became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's ODEFSEY product.

694. On information and belief, Lupin's efforts to make, use, sell, offer for sell, and/or import its ODEFSEY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent. On information and belief, this knowledge is reflected through, among other things, Lupin's ODEFSEY Notice Letter, which does not contest infringement of at least claim 1 of the '769 patent, except on the basis that the claim is allegedly invalid.

695. On information and belief, Lupin's ODEFSEY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Lupin in the United States by it or on its behalf.

696. On information and belief, Lupin's Proposed ODEFSEY Label will include directions and instructions that instruct physicians and healthcare providers to administer Lupin's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '769 patent.

697. On information and belief, physicians and healthcare providers will administer Lupin's ODEFSEY ANDA Product in the United States according to the directions and

instructions in Lupin's Proposed ODEFSEY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

698. On information and belief, at least through its Proposed ODEFSEY Label, Lupin will encourage physicians and healthcare providers to administer Lupin's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '769 patent, and Lupin will know or should know that such conduct will occur.

699. On information and belief, Lupin will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

700. Through at least the foregoing actions, Lupin will actively induce the infringement of at least one claim of the '769 patent.

701. On information and belief, Lupin knows or should know that Lupin's ODEFSEY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Lupin's ODEFSEY ANDA Product is not suitable for substantial non-infringing use.

702. The commercial manufacture, use, sale, offer for sale, and/or importation of Lupin's ODEFSEY ANDA Product will contribute to the actual infringement of the '769 patent.

703. On information and belief, Lupin knows or should know that its offer for sale, sale and/or importation of its ODEFSEY ANDA Product will contribute to the actual infringement of the '769 patent.

704. Through at least the foregoing actions, Lupin will contribute to the infringement of at least one claim of the '769 patent.

705. On information and belief, if Lupin's ODEFSEY ANDA is approved by the FDA,

Lupin will make its ODEFSEY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

706. On information and belief, Lupin's ODEFSEY ANDA Product will not be materially changed by a subsequent process nor will Lupin's ODEFSEY ANDA Product become a trivial and nonessential component of another product.

707. Through at least the foregoing actions, Lupin will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

708. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Lupin's ODEFSEY ANDA Product by Lupin prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

709. The commercial manufacture, importation, use, sale, or offer for sale of Lupin's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

710. Unless and until Lupin is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

COUNTS XXIX-XL AGAINST LAURUS LABS

VEMLIDY Counts

Count XXIX: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Laurus Labs's VEMLIDY ANDA Product

711. Gilead realleges the foregoing paragraphs as if fully set forth herein.

712. Pursuant to 35 U.S.C. § 271(e)(2)(A), Laurus Labs has committed an act of infringement of the '065 patent by submitting Laurus Labs's VEMLIDY ANDA to obtain approval

to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's VEMLIDY ANDA Product in the United States prior to the expiration of the '065 patent.

713. Laurus Labs's commercial manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's VEMLIDY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[29]

714. On information and belief, for example, Laurus Labs's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

715. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

716. Unless and until Laurus Labs is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXX: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Laurus Labs's VEMLIDY ANDA Product

717. Gilead realleges the foregoing paragraphs as if fully set forth herein.

718. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

719. There is an actual case or controversy such that the Court may entertain Gilead'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.

[29] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

720. Laurus Labs has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Laurus Labs's First VEMLIDY Notice Letter, Laurus Labs intends to manufacture, use, offer for sale, sell, and/or import Laurus Labs's VEMLIDY ANDA Product within the United States.

721. While the FDA has not yet approved Laurus Labs's VEMLIDY ANDA, Laurus Labs has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Laurus Labs's VEMLIDY ANDA Product.

722. Laurus Labs's actions indicate that it does not intend to change its course of conduct.

723. On information and belief, upon FDA approval of Laurus Labs's VEMLIDY ANDA, Laurus Labs will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[30] by making, using, offering to sell, and/or selling Laurus Labs's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

724. On information and belief, for example, Laurus Labs's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

725. Laurus Labs has actual knowledge of the '065 patent.

726. On information and belief, Laurus Labs became aware of the '065 patent no later

[30] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

727. On information and belief, Laurus Labs's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Laurus Labs's First VEMLIDY Notice Letter, which does not contest infringement of at least claim 1 of the '065 patent, except on the basis that the claim is allegedly invalid.

728. On information and belief, Laurus Labs's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Laurus Labs in the United States by it or on its behalf.

729. On information and belief, Laurus Labs's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Laurus Labs's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent.

730. On information and belief, physicians and healthcare providers will administer Laurus Labs's VEMLIDY ANDA Product in the United States according to the directions and instructions in Laurus Labs's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

731. On information and belief, at least through its Proposed VEMLIDY Label, Laurus Labs will encourage physicians and healthcare providers to administer Laurus Labs's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods

described/claimed in the ’065 patent, and Laurus Labs will know or should know that such conduct will occur.

732. On information and belief, Laurus Labs will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the ’065 patent.

733. Through at least the foregoing actions, Laurus Labs will actively induce the infringement of at least one claim of the ’065 patent.

734. On information and belief, Laurus Labs knows or should know that Laurus Labs’s VEMLIDY ANDA Product will be especially made or adapted for use in infringing the ’065 patent and that Laurus Labs’s VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

735. The commercial manufacture, use, sale, offer for sale, and/or importation of Laurus Labs’s VEMLIDY ANDA Product will contribute to the actual infringement of the ’065 patent.

736. On information and belief, Laurus Labs knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the ’065 patent.

737. Through at least the foregoing actions, Laurus Labs will contribute to the infringement of at least one claim of the ’065 patent.

738. On information and belief, if Laurus Labs’s VEMLIDY ANDA is approved by the FDA, Laurus Labs will make its VEMLIDY ANDA Product using a process covered by one or more claims of the ’065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

739. On information and belief, Laurus Labs’s VEMLIDY ANDA Product will not be

materially changed by a subsequent process nor will Laurus Labs's VEMLIDY ANDA Product become a trivial and nonessential component of another product.

740. Through at least the foregoing actions, Laurus Labs will infringe at least one claim of the '065 patent under 35 U.S.C. § 271(g).

741. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's VEMLIDY ANDA Product by Laurus Labs prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

742. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

743. Unless and until Laurus Labs is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXXI: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Laurus Labs's VEMLIDY ANDA Product

744. Gilead realleges the foregoing paragraphs as if fully set forth herein.

745. Pursuant to 35 U.S.C. § 271(e)(2)(A), Laurus Labs has committed an act of infringement of the '769 patent by submitting Laurus Labs's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's VEMLIDY ANDA Product in the United States prior to the expiration of the '769 patent.

746. Laurus Labs's commercial manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's VEMLIDY ANDA Product prior to the expiration of the '769 patent, and its

inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[31]

747. On information and belief, for example, Laurus Labs's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

748. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

749. Unless and until Laurus Labs is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXXII: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Laurus Labs's VEMLIDY ANDA Product

750. Gilead realleges the foregoing paragraphs as if fully set forth herein.

751. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

752. There is an actual case or controversy such that the Court may entertain Gilead'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.

753. Laurus Labs has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Laurus Labs's First VEMLIDY Notice Letter, Laurus Labs

[31] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

intends to manufacture, use, offer for sale, sell, and/or import Laurus Labs's VEMLIDY ANDA Product within the United States.

754. While the FDA has not yet approved Laurus Labs's VEMLIDY ANDA, Laurus Labs has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Laurus Labs's VEMLIDY ANDA Product.

755. Laurus Labs's actions indicate that it does not intend to change its course of conduct.

756. On information and belief, upon FDA approval of Laurus Labs's VEMLIDY ANDA, Laurus Labs will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[32] by making, using, offering to sell, and/or selling Laurus Labs's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

757. On information and belief, for example, Laurus Labs's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

758. Laurus Labs has actual knowledge of the '769 patent.

[32] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

759. On information and belief, Laurus Labs became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

760. On information and belief, Laurus Labs's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent. On information and belief, this knowledge is reflected through, among other things, Laurus Labs's First VEMLIDY Notice Letter, which does not contest infringement of at least claim 1 of the '769 patent, except on the basis that the claim is allegedly invalid.

761. On information and belief, Laurus Labs's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Laurus Labs in the United States by it or on its behalf.

762. On information and belief, Laurus Labs's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Laurus Labs's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent.

763. On information and belief, physicians and healthcare providers will administer Laurus Labs's VEMLIDY ANDA Product in the United States according to the directions and instructions in Laurus Labs's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

764. On information and belief, at least through its Proposed VEMLIDY Label, Laurus Labs will encourage physicians and healthcare providers to administer Laurus Labs's VEMLIDY

ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent, and Laurus Labs will know or should know that such conduct will occur.

765. On information and belief, Laurus Labs will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

766. Through at least the foregoing actions, Laurus Labs will actively induce the infringement of at least one claim of the '769 patent.

767. On information and belief, Laurus Labs knows or should know that Laurus Labs's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Laurus Labs's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

768. The commercial manufacture, use, sale, offer for sale, and/or importation of Laurus Labs's VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

769. On information and belief, Laurus Labs knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

770. Through at least the foregoing actions, Laurus Labs will contribute to the infringement of at least one claim of the '769 patent.

771. On information and belief, if Laurus Labs's VEMLIDY ANDA is approved by the FDA, Laurus Labs will make its VEMLIDY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

772. On information and belief, Laurus Labs's VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Laurus Labs's VEMLIDY ANDA Product become a trivial and nonessential component of another product.

773. Through at least the foregoing actions, Laurus Labs will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

774. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's VEMLIDY ANDA Product by Laurus Labs prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

775. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

776. Unless and until Laurus Labs is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

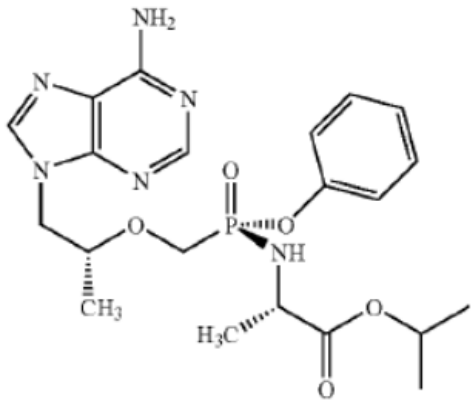
Count XXXIII: Infringement of the '791 Patent under 35 U.S.C. § 271(e)(2) by Laurus Labs's VEMLIDY ANDA Product

777. Gilead realleges the foregoing paragraphs as if fully set forth herein.

778. Pursuant to 35 U.S.C. § 271(e)(2)(A), Laurus Labs has committed an act of infringement of the '791 patent by submitting Laurus Labs's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's VEMLIDY ANDA Product in the United States prior to the expiration of the '791 patent.

779. Laurus Labs's commercial manufacture, use, offer for sale, sale, and/or importation of its VEMLIDY ANDA Product prior to the expiration of the '791 patent would constitute infringement of at least one of the claims of the '791 patent, including but not limited to claim 7.[33]

780. On information and belief, for example, Laurus Labs's VEMLIDY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

781. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

782. Unless and until Laurus Labs is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXXIV: Declaratory Judgment of Infringement of the '791 Patent under 35 U.S.C. § 271(a) by Laurus Labs's VEMLIDY ANDA Product

783. Gilead realleges the foregoing paragraphs as if fully set forth herein.

[33] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.

784. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

785. There is an actual case or controversy such that the Court may entertain Gilead'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.

786. Laurus has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Laurus Labs's Second VEMLIDY Notice Letter, Laurus Labs intends to manufacture, use, offer for sale, sell, and/or import its VEMLIDY ANDA Product within the United States.

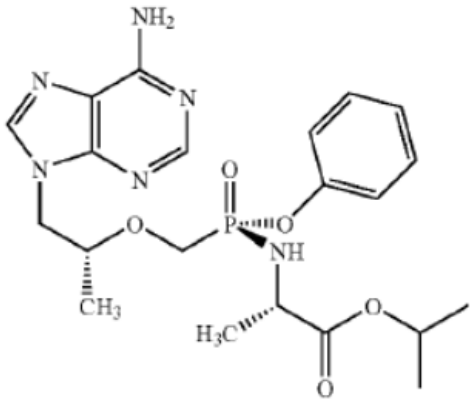
787. While the FDA has not yet approved Laurus Labs's VEMLIDY ANDA, Laurus has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import its VEMLIDY ANDA Product.

788. Laurus Labs's actions indicate that it does not intend to change its course of conduct.

789. On information and belief, upon FDA approval of Laurus Labs's VEMLIDY ANDA, Laurus will infringe one or more claims of the '791 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[34] by making, using, offering to sell, and/or selling Laurus Labs's VEMLIDY ANDA Product in the United States and/or importing said product into the United States under 35 U.S.C. § 271(a), unless enjoined by the Court.

790. On information and belief, for example, Laurus Labs's VEMLIDY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:

[34] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

791. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's VEMLIDY ANDA Product by Laurus prior to the expiration of the '791 patent will constitute direct infringement of the '791 patent.

792. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

793. Unless and until Laurus Labs is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

DESCOVY Counts

Count XXXV: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Laurus Labs's DESCOVY ANDA Product

794. Gilead realleges the foregoing paragraphs as if fully set forth herein.

795. Pursuant to 35 U.S.C. § 271(e)(2)(A), Laurus Labs has committed an act of infringement of the '065 patent by submitting Laurus Labs's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of

Laurus Labs's DESCOVY ANDA Product in the United States prior to the expiration of the '065 patent.

796. Laurus Labs's commercial manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's DESCOVY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[35]

797. On information and belief, for example, Laurus Labs's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

798. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

799. Unless and until Laurus Labs is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXXVI: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Laurus Labs's DESCOVY ANDA Product

800. Gilead realleges the foregoing paragraphs as if fully set forth herein.

801. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

802. There is an actual case or controversy such that the Court may entertain Gilead'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.

[35] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

803. Laurus Labs has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Laurus Labs's First DESCOVY Notice Letter, Laurus Labs intends to manufacture, use, offer for sale, sell, and/or import Laurus Labs's DESCOVY ANDA Product within the United States.

804. While the FDA has not yet approved Laurus Labs's DESCOVY ANDA, Laurus Labs has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Laurus Labs's DESCOVY ANDA Product.

805. Laurus Labs's actions indicate that it does not intend to change its course of conduct.

806. On information and belief, upon FDA approval of Laurus Labs's DESCOVY ANDA, Laurus Labs will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[36] by making, using, offering to sell, and/or selling Laurus Labs's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

807. On information and belief, for example, Laurus Labs's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

808. Laurus Labs has actual knowledge of the '065 patent.

809. On information and belief, Laurus Labs became aware of the '065 patent no later

[36] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

810. On information and belief, Laurus Labs's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Laurus Labs's First DESCOVY Notice Letter, which does not contest infringement of at least claim 1 of the '065 patent, except on the basis that the claim is allegedly invalid.

811. On information and belief, Laurus Labs's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Laurus Labs in the United States by it or on its behalf.

812. On information and belief, Laurus Labs's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Laurus Labs's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '065 patent.

813. On information and belief, physicians and healthcare providers will administer Laurus Labs's DESCOVY ANDA Product in the United States according to the directions and instructions in Laurus Labs's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

814. On information and belief, at least through its Proposed DESCOVY Label, Laurus Labs will encourage physicians and healthcare providers to administer Laurus Labs's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods

described/claimed in the ’065 patent, and Laurus Labs will know or should know that such conduct will occur.

815. On information and belief, Laurus Labs will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the ’065 patent.

816. Through at least the foregoing actions, Laurus Labs will actively induce the infringement of at least one claim of the ’065 patent.

817. On information and belief, Laurus Labs knows or should know that Laurus Labs’s DESCOVY ANDA Product will be especially made or adapted for use in infringing the ’065 patent and that Laurus Labs’s DESCOVY ANDA Product is not suitable for substantial non-infringing use.

818. The commercial manufacture, use, sale, offer for sale, and/or importation of Laurus Labs’s DESCOVY ANDA Product will contribute to the actual infringement of the ’065 patent.

819. On information and belief, Laurus Labs knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the ’065 patent.

820. Through at least the foregoing actions, Laurus Labs will contribute to the infringement of at least one claim of the ’065 patent.

821. On information and belief, if Laurus Labs’s DESCOVY ANDA is approved by the FDA, Laurus Labs will make its DESCOVY ANDA Product using a process covered by one or more claims of the ’065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

822. On information and belief, Laurus Labs’s DESCOVY ANDA Product will not be

materially changed by a subsequent process nor will Laurus Labs's DESCOVY ANDA Product become a trivial and nonessential component of another product.

823. Through at least the foregoing actions, Laurus Labs will infringe at least one claim of the '065 patent under 35 U.S.C. § 271(g).

824. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's DESCOVY ANDA Product by Laurus Labs prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

825. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

826. Unless and until Laurus Labs is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXXVII: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Laurus Labs's DESCOVY ANDA Product

827. Gilead realleges the foregoing paragraphs as if fully set forth herein.

828. Pursuant to 35 U.S.C. § 271(e)(2)(A), Laurus Labs has committed an act of infringement of the '769 patent by submitting Laurus Labs's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's DESCOVY ANDA Product in the United States prior to the expiration of the '769 patent.

829. Laurus Labs's commercial manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's DESCOVY ANDA Product prior to the expiration of the '769 patent, and its

inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[37]

830. On information and belief, for example, Laurus Labs's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

831. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

832. Unless and until Laurus Labs is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XXXVIII: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Laurus Labs's DESCOVY ANDA Product

833. Gilead realleges the foregoing paragraphs as if fully set forth herein.

834. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

835. There is an actual case or controversy such that the Court may entertain Gilead'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.

836. Laurus Labs has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Laurus Labs's First DESCOVY Notice Letter, Laurus Labs

[37] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

intends to manufacture, use, offer for sale, sell, and/or import Laurus Labs's DESCOVY ANDA Product within the United States.

837. While the FDA has not yet approved Laurus Labs's DESCOVY ANDA, Laurus Labs has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Laurus Labs's DESCOVY ANDA Product.

838. Laurus Labs's actions indicate that it does not intend to change its course of conduct.

839. On information and belief, upon FDA approval of Laurus Labs's DESCOVY ANDA, Laurus Labs will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[38] by making, using, offering to sell, and/or selling Laurus Labs's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

840. On information and belief, for example, Laurus Labs's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

841. Laurus Labs has actual knowledge of the '769 patent.

[38] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

842. On information and belief, Laurus Labs became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

843. On information and belief, Laurus Labs's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent. On information and belief, this knowledge is reflected through, among other things, Laurus Labs's First DESCOVY Notice Letter, which does not contest infringement of at least claim 1 of the '769 patent, except on the basis that the claim is allegedly invalid.

844. On information and belief, Laurus Labs's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Laurus Labs in the United States by it or on its behalf.

845. On information and belief, Laurus Labs's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Laurus Labs's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent.

846. On information and belief, physicians and healthcare providers will administer Laurus Labs's DESCOVY ANDA Product in the United States according to the directions and instructions in Laurus Labs's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

847. On information and belief, at least through its Proposed DESCOVY Label, Laurus Labs will encourage physicians and healthcare providers to administer Laurus Labs's DESCOVY

ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent, and Laurus Labs will know or should know that such conduct will occur.

848. On information and belief, Laurus Labs will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

849. Through at least the foregoing actions, Laurus Labs will actively induce the infringement of at least one claim of the '769 patent.

850. On information and belief, Laurus Labs knows or should know that Laurus Labs's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Laurus Labs's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

851. The commercial manufacture, use, sale, offer for sale, and/or importation of Laurus Labs's DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

852. On information and belief, Laurus Labs knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

853. Through at least the foregoing actions, Laurus Labs will contribute to the infringement of at least one claim of the '769 patent.

854. On information and belief, if Laurus Labs's DESCOVY ANDA is approved by the FDA, Laurus Labs will make its DESCOVY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

855. On information and belief, Laurus Labs's DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Laurus Labs's DESCOVY ANDA Product become a trivial and nonessential component of another product.

856. Through at least the foregoing actions, Laurus Labs will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

857. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's DESCOVY ANDA Product by Laurus Labs prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

858. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

859. Unless and until Laurus Labs is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

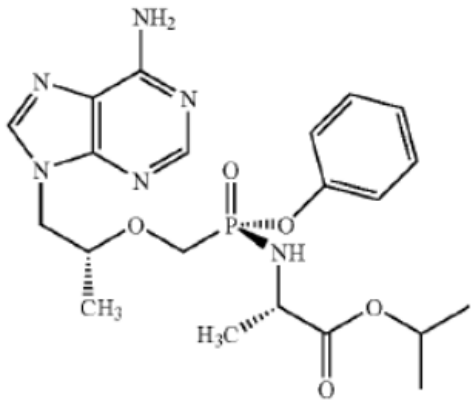
Count XXXIX: Infringement of the '791 Patent under 35 U.S.C. § 271(e)(2) by Laurus Labs's DESCOVY ANDA Product

860. Gilead realleges the foregoing paragraphs as if fully set forth herein.

861. Pursuant to 35 U.S.C. § 271(e)(2)(A), Laurus Labs has committed an act of infringement of the '791 patent by submitting Laurus Labs's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's DESCOVY ANDA Product in the United States prior to the expiration of the '791 patent.

862. Laurus Labs's commercial manufacture, use, offer for sale, sale, and/or importation of its DESCOVY ANDA Product prior to the expiration of the '791 patent would constitute infringement of at least one of the claims of the '791 patent, including but not limited to claim 7.[39]

863. On information and belief, for example, Laurus Labs's DESCOVY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

864. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

865. Unless and until Laurus Labs is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XL: Declaratory Judgment of Infringement of the '791 Patent under 35 U.S.C. § 271(a) by Laurus Labs's DESCOVY ANDA Product

866. Gilead realleges the foregoing paragraphs as if fully set forth herein.

[39] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.

867. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

868. There is an actual case or controversy such that the Court may entertain Gilead'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.

869. Laurus has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Laurus Labs's Second DESCOVY Notice Letter, Laurus Labs intends to manufacture, use, offer for sale, sell, and/or import its DESCOVY ANDA Product within the United States.

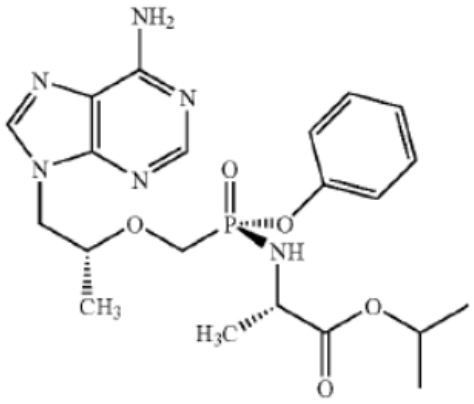
870. While the FDA has not yet approved Laurus Labs's DESCOVY ANDA, Laurus has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import its DESCOVY ANDA Product.

871. Laurus Labs's actions indicate that it does not intend to change its course of conduct.

872. On information and belief, upon FDA approval of Laurus Labs's DESCOVY ANDA, Laurus will infringe one or more claims of the '791 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[40] by making, using, offering to sell, and/or selling Laurus Labs's DESCOVY ANDA Product in the United States and/or importing said product into the United States under 35 U.S.C. § 271(a), unless enjoined by the Court.

873. On information and belief, for example, Laurus Labs's DESCOVY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:

[40] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

874. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Laurus Labs's DESCOVY ANDA Product by Laurus prior to the expiration of the '791 patent will constitute direct infringement of the '791 patent.

875. The commercial manufacture, importation, use, sale, or offer for sale of Laurus Labs's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

876. Unless and until Laurus Labs is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

COUNTS XLI-XLIV AGAINST SHILPA

VEMLIDY Counts

Count XLI: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Shilpa's VEMLIDY ANDA Product

877. Gilead realleges the foregoing paragraphs as if fully set forth herein.

878. Pursuant to 35 U.S.C. § 271(e)(2)(A), Shilpa has committed an act of infringement of the '065 patent by submitting Shilpa's VEMLIDY ANDA to obtain approval to engage in the

commercial manufacture, use, offer for sale, sale, and/or importation of Shilpa's VEMLIDY ANDA Product in the United States prior to the expiration of the '065 patent.

879. Shilpa's commercial manufacture, use, offer for sale, sale, and/or importation of Shilpa's VEMLIDY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[41]

880. On information and belief, for example, Shilpa's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

881. The commercial manufacture, importation, use, sale, or offer for sale of Shilpa's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

882. Unless and until Shilpa is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XLII: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Shilpa's VEMLIDY ANDA Product

883. Gilead realleges the foregoing paragraphs as if fully set forth herein.

884. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

885. There is an actual case or controversy such that the Court may entertain Gilead'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.

[41] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

886. Shilpa has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Shilpa's VEMLIDY Notice Letter, Shilpa intends to manufacture, use, offer for sale, sell, and/or import Shilpa's VEMLIDY ANDA Product within the United States.

887. While the FDA has not yet approved Shilpa's VEMLIDY ANDA, Shilpa has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Shilpa's VEMLIDY ANDA Product.

888. Shilpa's actions indicate that it does not intend to change its course of conduct.

889. On information and belief, upon FDA approval of Shilpa's VEMLIDY ANDA, Shilpa will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[42] by making, using, offering to sell, and/or selling Shilpa's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

890. On information and belief, for example, Shilpa's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

891. Shilpa has actual knowledge of the '065 patent.

892. On information and belief, Shilpa became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

[42] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

893. On information and belief, Shilpa's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Shilpa's VEMLIDY Notice Letter, which does not contest infringement of at least claim 1 of the '065 patent, except on the basis that the claim is allegedly invalid.

894. On information and belief, Shilpa's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Shilpa in the United States by it or on its behalf.

895. On information and belief, Shilpa's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Shilpa's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent.

896. On information and belief, physicians and healthcare providers will administer Shilpa's VEMLIDY ANDA Product in the United States according to the directions and instructions in Shilpa's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

897. On information and belief, at least through its Proposed VEMLIDY Label, Shilpa will encourage physicians and healthcare providers to administer Shilpa's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent, and Shilpa will know or should know that such conduct will occur.

898. On information and belief, Shilpa will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

899. Through at least the foregoing actions, Shilpa will actively induce the infringement of at least one claim of the '065 patent.

900. On information and belief, Shilpa knows or should know that Shilpa's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the '065 patent and that Shilpa's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

901. The commercial manufacture, use, sale, offer for sale, and/or importation of Shilpa's VEMLIDY ANDA Product will contribute to the actual infringement of the '065 patent.

902. On information and belief, Shilpa knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the '065 patent.

903. Through at least the foregoing actions, Shilpa will contribute to the infringement of at least one claim of the '065 patent.

904. On information and belief, if Shilpa's VEMLIDY ANDA is approved by the FDA, Shilpa will make its VEMLIDY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

905. On information and belief, Shilpa's VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Shilpa's VEMLIDY ANDA Product become a trivial and nonessential component of another product.

906. Through at least the foregoing actions, Shilpa will infringe at least one claim of the

'065 patent under 35 U.S.C. § 271(g).

907. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Shilpa's VEMLIDY ANDA Product by Shilpa prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

908. The commercial manufacture, importation, use, sale, or offer for sale of Shilpa's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

909. Unless and until Shilpa is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XLIII: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Shilpa's VEMLIDY ANDA Product

910. Gilead realleges the foregoing paragraphs as if fully set forth herein.

911. Pursuant to 35 U.S.C. § 271(e)(2)(A), Shilpa has committed an act of infringement of the '769 patent by submitting Shilpa's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Shilpa's VEMLIDY ANDA Product in the United States prior to the expiration of the '769 patent.

912. Shilpa's commercial manufacture, use, offer for sale, sale, and/or importation of Shilpa's VEMLIDY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[43]

[43] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

913. On information and belief, for example, Shilpa's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

914. The commercial manufacture, importation, use, sale, or offer for sale of Shilpa's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

915. Unless and until Shilpa is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XLIV: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Shilpa's VEMLIDY ANDA Product

916. Gilead realleges the foregoing paragraphs as if fully set forth herein.

917. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

918. There is an actual case or controversy such that the Court may entertain Gilead'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.

919. Shilpa has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Shilpa's VEMLIDY Notice Letter, Shilpa intends to manufacture, use, offer for sale, sell, and/or import Shilpa's VEMLIDY ANDA Product within the United States.

920. While the FDA has not yet approved Shilpa's VEMLIDY ANDA, Shilpa has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Shilpa's VEMLIDY ANDA Product.

921. Shilpa's actions indicate that it does not intend to change its course of conduct.

922. On information and belief, upon FDA approval of Shilpa's VEMLIDY ANDA, Shilpa will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[44] by making, using, offering to sell, and/or selling Shilpa's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

923. On information and belief, for example, Shilpa's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

924. Shilpa has actual knowledge of the '769 patent.

925. On information and belief, Shilpa became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

926. On information and belief, Shilpa's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent. On information and belief, this knowledge is reflected through, among other things, Shilpa's VEMLIDY Notice Letter, which

[44] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

does not contest infringement of at least claim 1 of the '769 patent, except on the basis that the claim is allegedly invalid.

927. On information and belief, Shilpa's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Shilpa in the United States by it or on its behalf.

928. On information and belief, Shilpa's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Shilpa's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent.

929. On information and belief, physicians and healthcare providers will administer Shilpa's VEMLIDY ANDA Product in the United States according to the directions and instructions in Shilpa's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

930. On information and belief, at least through its Proposed VEMLIDY Label, Shilpa will encourage physicians and healthcare providers to administer Shilpa's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent, and Shilpa will know or should know that such conduct will occur.

931. On information and belief, Shilpa will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

932. Through at least the foregoing actions, Shilpa will actively induce the infringement of at least one claim of the '769 patent.

933. On information and belief, Shilpa knows or should know that Shilpa's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Shilpa's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

934. The commercial manufacture, use, sale, offer for sale, and/or importation of Shilpa's VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

935. On information and belief, Shilpa knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

936. Through at least the foregoing actions, Shilpa will contribute to the infringement of at least one claim of the '769 patent.

937. On information and belief, if Shilpa's VEMLIDY ANDA is approved by the FDA, Shilpa will make its VEMLIDY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

938. On information and belief, Shilpa's VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Shilpa's VEMLIDY ANDA Product become a trivial and nonessential component of another product.

939. Through at least the foregoing actions, Shilpa will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

940. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Shilpa's VEMLIDY ANDA Product by Shilpa prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

941. The commercial manufacture, importation, use, sale, or offer for sale of Shilpa's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

942. Unless and until Shilpa is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

COUNTS XLV-XLVIII AGAINST SUNSHINE LAKE

VEMLIDY Counts

Count XLV: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Sunshine Lake's VEMLIDY ANDA Product

943. Gilead realleges the foregoing paragraphs as if fully set forth herein.

944. Pursuant to 35 U.S.C. § 271(e)(2)(A), Sunshine Lake has committed an act of infringement of the '065 patent by submitting Sunshine Lake's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Sunshine Lake's VEMLIDY ANDA Product in the United States prior to the expiration of the '065 patent.

945. Sunshine Lake's commercial manufacture, use, offer for sale, sale, and/or importation of Sunshine Lake's VEMLIDY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[45]

946. On information and belief, for example, Sunshine Lake's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

[45] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

947. The commercial manufacture, importation, use, sale, or offer for sale of Sunshine Lake's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

948. Unless and until Sunshine Lake is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XLVI: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Sunshine Lake's VEMLIDY ANDA Product

949. Gilead realleges the foregoing paragraphs as if fully set forth herein.

950. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

951. There is an actual case or controversy such that the Court may entertain Gilead'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.

952. Sunshine Lake has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Sunshine Lake's VEMLIDY Notice Letter, Sunshine Lake intends to manufacture, use, offer for sale, sell, and/or import Sunshine Lake's VEMLIDY ANDA Product within the United States.

953. While the FDA has not yet approved Sunshine Lake's VEMLIDY ANDA, Sunshine Lake has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Sunshine Lake's VEMLIDY ANDA Product.

954. Sunshine Lake's actions indicate that it does not intend to change its course of conduct.

955. On information and belief, upon FDA approval of Sunshine Lake's VEMLIDY ANDA, Sunshine Lake will infringe one or more claims of the '065 patent, either literally or under

the doctrine of equivalents, including but not limited to claim 1,[46] by making, using, offering to sell, and/or selling Sunshine Lake's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

956. On information and belief, for example, Sunshine Lake's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

957. Sunshine Lake has actual knowledge of the '065 patent.

958. On information and belief, Sunshine Lake became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

959. On information and belief, Sunshine Lake's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Sunshine Lake's VEMLIDY Notice Letter, which does not contest infringement of at least claim 1 of the '065 patent, except on the basis that the claim is allegedly invalid.

[46] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

960. On information and belief, Sunshine Lake's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Sunshine Lake in the United States by it or on its behalf.

961. On information and belief, Sunshine Lake's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Sunshine Lake's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent.

962. On information and belief, physicians and healthcare providers will administer Sunshine Lake's VEMLIDY ANDA Product in the United States according to the directions and instructions in Sunshine Lake's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

963. On information and belief, at least through its Proposed VEMLIDY Label, Sunshine Lake will encourage physicians and healthcare providers to administer Sunshine Lake's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent, and Sunshine Lake will know or should know that such conduct will occur.

964. On information and belief, Sunshine Lake will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

965. Through at least the foregoing actions, Sunshine Lake will actively induce the infringement of at least one claim of the '065 patent.

966. On information and belief, Sunshine Lake knows or should know that Sunshine Lake's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the

'065 patent and that Sunshine Lake's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

967. The commercial manufacture, use, sale, offer for sale, and/or importation of Sunshine Lake's VEMLIDY ANDA Product will contribute to the actual infringement of the '065 patent.

968. On information and belief, Sunshine Lake knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the '065 patent.

969. Through at least the foregoing actions, Sunshine Lake will contribute to the infringement of at least one claim of the '065 patent.

970. On information and belief, if Sunshine Lake's VEMLIDY ANDA is approved by the FDA, Sunshine Lake will make its VEMLIDY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

971. On information and belief, Sunshine Lake's VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Sunshine Lake's VEMLIDY ANDA Product become a trivial and nonessential component of another product.

972. Through at least the foregoing actions, Sunshine Lake will infringe at least one claim of the '065 patent under 35 U.S.C. § 271(g).

973. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Sunshine Lake's VEMLIDY ANDA Product by Sunshine Lake prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

974. The commercial manufacture, importation, use, sale, or offer for sale of Sunshine Lake's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

975. Unless and until Sunshine Lake is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XLVII: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Sunshine Lake's VEMLIDY ANDA Product

976. Gilead realleges the foregoing paragraphs as if fully set forth herein.

977. Pursuant to 35 U.S.C. § 271(e)(2)(A), Sunshine Lake has committed an act of infringement of the '769 patent by submitting Sunshine Lake's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Sunshine Lake's VEMLIDY ANDA Product in the United States prior to the expiration of the '769 patent.

978. Sunshine Lake's commercial manufacture, use, offer for sale, sale, and/or importation of Sunshine Lake's VEMLIDY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[47]

979. On information and belief, for example, Sunshine Lake's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

[47] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

980. The commercial manufacture, importation, use, sale, or offer for sale of Sunshine Lake's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

981. Unless and until Sunshine Lake is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count XLVIII: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Sunshine Lake's VEMLIDY ANDA Product

982. Gilead realleges the foregoing paragraphs as if fully set forth herein.

983. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

984. There is an actual case or controversy such that the Court may entertain Gilead'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.

985. Sunshine Lake has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Sunshine Lake's VEMLIDY Notice Letter, Sunshine Lake intends to manufacture, use, offer for sale, sell, and/or import Sunshine Lake's VEMLIDY ANDA Product within the United States.

986. While the FDA has not yet approved Sunshine Lake's VEMLIDY ANDA, Sunshine Lake has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Sunshine Lake's VEMLIDY ANDA Product.

987. Sunshine Lake's actions indicate that it does not intend to change its course of conduct.

988. On information and belief, upon FDA approval of Sunshine Lake's VEMLIDY ANDA, Sunshine Lake will infringe one or more claims of the '769 patent, either literally or under

the doctrine of equivalents, including but not limited to claim 1,[48] by making, using, offering to sell, and/or selling Sunshine Lake's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

989. On information and belief, for example, Sunshine Lake's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

990. Sunshine Lake has actual knowledge of the '769 patent.

991. On information and belief, Sunshine Lake became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

992. On information and belief, Sunshine Lake's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent. On information and belief, this knowledge is reflected through, among other things, Sunshine Lake's VEMLIDY Notice Letter, which does not contest infringement of at least claim 1 of the '769 patent, except on the basis that the claim is allegedly invalid.

[48] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

993. On information and belief, Sunshine Lake's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Sunshine Lake in the United States by it or on its behalf.

994. On information and belief, Sunshine Lake's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Sunshine Lake's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent.

995. On information and belief, physicians and healthcare providers will administer Sunshine Lake's VEMLIDY ANDA Product in the United States according to the directions and instructions in Sunshine Lake's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

996. On information and belief, at least through its Proposed VEMLIDY Label, Sunshine Lake will encourage physicians and healthcare providers to administer Sunshine Lake's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent, and Sunshine Lake will know or should know that such conduct will occur.

997. On information and belief, Sunshine Lake will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

998. Through at least the foregoing actions, Sunshine Lake will actively induce the infringement of at least one claim of the '769 patent.

999. On information and belief, Sunshine Lake knows or should know that Sunshine Lake's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the

'769 patent and that Sunshine Lake's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

1000. The commercial manufacture, use, sale, offer for sale, and/or importation of Sunshine Lake's VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

1001. On information and belief, Sunshine Lake knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

1002. Through at least the foregoing actions, Sunshine Lake will contribute to the infringement of at least one claim of the '769 patent.

1003. On information and belief, if Sunshine Lake's VEMLIDY ANDA is approved by the FDA, Sunshine Lake will make its VEMLIDY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1004. On information and belief, Sunshine Lake's VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Sunshine Lake's VEMLIDY ANDA Product become a trivial and nonessential component of another product.

1005. Through at least the foregoing actions, Sunshine Lake will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

1006. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Sunshine Lake's VEMLIDY ANDA Product by Sunshine Lake prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

1007. The commercial manufacture, importation, use, sale, or offer for sale of Sunshine Lake's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1008. Unless and until Sunshine Lake is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

COUNTS XLIX-LIV AGAINST NATCO

DESCOVY Counts

Count XLIX: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Natco's DESCOVY ANDA Product

1009. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1010. Pursuant to 35 U.S.C. § 271(e)(2)(A), Natco has committed an act of infringement of the '065 patent by submitting Natco's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Natco's DESCOVY ANDA Product in the United States prior to the expiration of the '065 patent.

1011. Natco's commercial manufacture, use, offer for sale, sale, and/or importation of Natco's DESCOVY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[49]

1012. On information and belief, for example, Natco's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

1013. The commercial manufacture, importation, use, sale, or offer for sale of Natco's

[49] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1014. Unless and until Natco is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count L: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Natco's DESCOVY ANDA Product

1015. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1016. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1017. There is an actual case or controversy such that the Court may entertain Gilead'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.

1018. Natco has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Natco's First DESCOVY Notice Letter, Natco intends to manufacture, use, offer for sale, sell, and/or import Natco's DESCOVY ANDA Product within the United States.

1019. While the FDA has not yet approved Natco's DESCOVY ANDA, Natco has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Natco's DESCOVY ANDA Product.

1020. Natco's actions indicate that it does not intend to change its course of conduct.

1021. On information and belief, upon FDA approval of Natco's DESCOVY ANDA, Natco will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[50] by making, using, offering to sell, and/or selling

[50] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

Natco's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1022. On information and belief, for example, Natco's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

1023. Natco has actual knowledge of the '065 patent.

1024. On information and belief, Natco became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

1025. On information and belief, Natco's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Natco's First DESCOVY Notice Letter, which does not contest infringement of at least claim 1 of the '065 patent, except on the basis that the claim is allegedly invalid.

1026. On information and belief, Natco's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Natco in the United States by it or on its behalf.

1027. On information and belief, Natco's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Natco's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with

the methods described/claimed in the ’065 patent.

1028. On information and belief, physicians and healthcare providers will administer Natco’s DESCOVY ANDA Product in the United States according to the directions and instructions in Natco’s Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the ’065 patent.

1029. On information and belief, at least through its Proposed DESCOVY Label, Natco will encourage physicians and healthcare providers to administer Natco’s DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the ’065 patent, and Natco will know or should know that such conduct will occur.

1030. On information and belief, Natco will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the ’065 patent.

1031. Through at least the foregoing actions, Natco will actively induce the infringement of at least one claim of the ’065 patent.

1032. On information and belief, Natco knows or should know that Natco’s DESCOVY ANDA Product will be especially made or adapted for use in infringing the ’065 patent and that Natco’s DESCOVY ANDA Product is not suitable for substantial non-infringing use.

1033. The commercial manufacture, use, sale, offer for sale, and/or importation of Natco’s DESCOVY ANDA Product will contribute to the actual infringement of the ’065 patent.

1034. On information and belief, Natco knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the ’065 patent.

1035. Through at least the foregoing actions, Natco will contribute to the infringement of at least one claim of the ’065 patent.

1036. On information and belief, if Natco’s DESCOVY ANDA is approved by the FDA, Natco will make its DESCOVY ANDA Product using a process covered by one or more claims of the ’065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1037. On information and belief, Natco’s DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Natco’s DESCOVY ANDA Product become a trivial and nonessential component of another product.

1038. Through at least the foregoing actions, Natco will infringe at least one claim of the ’065 patent under 35 U.S.C. § 271(g).

1039. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Natco’s DESCOVY ANDA Product by Natco prior to the expiration of the ’065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the ’065 patent.

1040. The commercial manufacture, importation, use, sale, or offer for sale of Natco’s DESCOVY ANDA Product in violation of Gilead’s patent rights will cause harm to Gilead for which damages are inadequate.

1041. Unless and until Natco is enjoined from infringing the ’065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LI: Infringement of the ’769 Patent under 35 U.S.C. § 271(e)(2) by Natco’s DESCOVY ANDA Product

1042. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1043. Pursuant to 35 U.S.C. § 271(e)(2)(A), Natco has committed an act of infringement of the '769 patent by submitting Natco's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Natco's DESCOVY ANDA Product in the United States prior to the expiration of the '769 patent.

1044. Natco's commercial manufacture, use, offer for sale, sale, and/or importation of Natco's DESCOVY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[51]

1045. On information and belief, for example, Natco's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1046. The commercial manufacture, importation, use, sale, or offer for sale of Natco's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1047. Unless and until Natco is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LII: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Natco's DESCOVY ANDA Product

1048. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1049. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

[51] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

1050. There is an actual case or controversy such that the Court may entertain Gilead'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.

1051. Natco has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Natco's First DESCOVY Notice Letter, Natco intends to manufacture, use, offer for sale, sell, and/or import Natco's DESCOVY ANDA Product within the United States.

1052. While the FDA has not yet approved Natco's DESCOVY ANDA, Natco has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Natco's DESCOVY ANDA Product.

1053. Natco's actions indicate that it does not intend to change its course of conduct.

1054. On information and belief, upon FDA approval of Natco's DESCOVY ANDA, Natco will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[52] by making, using, offering to sell, and/or selling Natco's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1055. On information and belief, for example, Natco's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls

[52] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1056. Natco has actual knowledge of the '769 patent.

1057. On information and belief, Natco became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

1058. On information and belief, Natco's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent. On information and belief, this knowledge is reflected through, among other things, Natco's First DESCOVY Notice Letter, which does not contest infringement of at least claim 1 of the '769 patent, except on the basis that the claim is allegedly invalid.

1059. On information and belief, Natco's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Natco in the United States by it or on its behalf.

1060. On information and belief, Natco's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Natco's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent.

1061. On information and belief, physicians and healthcare providers will administer Natco's DESCOVY ANDA Product in the United States according to the directions and instructions in Natco's Proposed DESCOVY Label, and such administration will constitute direct

infringement of at least one claim of the '769 patent.

1062. On information and belief, at least through its Proposed DESCOVY Label, Natco will encourage physicians and healthcare providers to administer Natco's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent, and Natco will know or should know that such conduct will occur.

1063. On information and belief, Natco will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

1064. Through at least the foregoing actions, Natco will actively induce the infringement of at least one claim of the '769 patent.

1065. On information and belief, Natco knows or should know that Natco's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Natco's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

1066. The commercial manufacture, use, sale, offer for sale, and/or importation of Natco's DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

1067. On information and belief, Natco knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

1068. Through at least the foregoing actions, Natco will contribute to the infringement of at least one claim of the '769 patent.

1069. On information and belief, if Natco's DESCOVY ANDA is approved by the FDA, Natco will make its DESCOVY ANDA Product using a process covered by one or more claims of

the ’769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1070. On information and belief, Natco’s DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Natco’s DESCOVY ANDA Product become a trivial and nonessential component of another product.

1071. Through at least the foregoing actions, Natco will infringe at least one claim of the ’769 patent under 35 U.S.C. § 271(g).

1072. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Natco’s DESCOVY ANDA Product by Natco prior to the expiration of the ’769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the ’769 patent.

1073. The commercial manufacture, importation, use, sale, or offer for sale of Natco’s DESCOVY ANDA Product in violation of Gilead’s patent rights will cause harm to Gilead for which damages are inadequate.

1074. Unless and until Natco is enjoined from infringing the ’769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

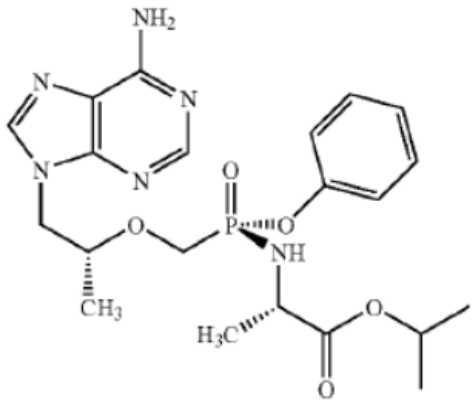
Count LIII: Infringement of the ’791 Patent under 35 U.S.C. § 271(e)(2) by Natco’s DESCOVY ANDA Product

1075. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1076. Pursuant to 35 U.S.C. § 271(e)(2)(A), Natco has committed an act of infringement of the ’791 patent by submitting Natco’s DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Natco’s DESCOVY ANDA Product in the United States prior to the expiration of the ’791 patent.

1077. Natco's commercial manufacture, use, offer for sale, sale, and/or importation of its DESCOVY ANDA Product prior to the expiration of the '791 patent would constitute infringement of at least one of the claims of the '791 patent, including but not limited to claim 7.[53]

1078. On information and belief, for example, Natco's DESCOVY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

1079. The commercial manufacture, importation, use, sale, or offer for sale of Natco's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1080. Unless and until Natco is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LIV: Declaratory Judgment of Infringement of the '791 Patent under 35 U.S.C. § 271(a) by Natco's DESCOVY ANDA Product

1081. Gilead realleges the foregoing paragraphs as if fully set forth herein.

[53] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.

1082. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1083. There is an actual case or controversy such that the Court may entertain Gilead'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.

1084. Natco has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Natco's Third DESCOVY Notice Letter, Natco intends to manufacture, use, offer for sale, sell, and/or import its DESCOVY ANDA Product within the United States.

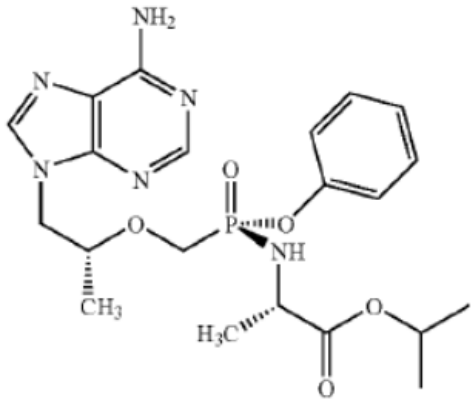
1085. While the FDA has not yet approved Natco's DESCOVY ANDA, Natco has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import its DESCOVY ANDA Product.

1086. Natco's actions indicate that it does not intend to change its course of conduct.

1087. On information and belief, upon FDA approval of Natco's DESCOVY ANDA, Natco will infringe one or more claims of the '791 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[54] by making, using, offering to sell, and/or selling Natco's DESCOVY ANDA Product in the United States and/or importing said product into the United States under 35 U.S.C. § 271(a), unless enjoined by the Court.

1088. On information and belief, for example, Natco's DESCOVY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:

[54] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

1089. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Natco's DESCOVY ANDA Product by Natco prior to the expiration of the '791 patent will constitute direct infringement of the '791 patent.

1090. The commercial manufacture, importation, use, sale, or offer for sale of Natco's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1091. Unless and until Natco is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

COUNTS LV-LXX AGAINST CIPLA

DESCOVY Counts

Count LV: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Cipla's DESCOVY ANDA Product

1092. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1093. Pursuant to 35 U.S.C. § 271(e)(2)(A), Cipla has committed an act of infringement of the '065 patent by submitting Cipla's DESCOVY ANDA to obtain approval to engage in the

commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's DESCOVY ANDA Product in the United States prior to the expiration of the '065 patent.

1094. Cipla's commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's DESCOVY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[55]

1095. On information and belief, for example, Cipla's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

1096. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1097. Unless and until Cipla is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LVI: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Cipla's DESCOVY ANDA Product

1098. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1099. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1100. There is an actual case or controversy such that the Court may entertain Gilead'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.

[55] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

1101. Cipla has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Cipla's DESCOVY Notice Letter, Cipla intends to manufacture, use, offer for sale, sell, and/or import Cipla's DESCOVY ANDA Product within the United States.

1102. While the FDA has not yet approved Cipla's DESCOVY ANDA, Cipla has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Cipla's DESCOVY ANDA Product.

1103. Cipla's actions indicate that it does not intend to change its course of conduct.

1104. On information and belief, upon FDA approval of Cipla's DESCOVY ANDA, Cipla will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[56] by making, using, offering to sell, and/or selling Cipla's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1105. On information and belief, for example, Cipla's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

1106. Cipla has actual knowledge of the '065 patent.

1107. On information and belief, Cipla became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

[56] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

1108. On information and belief, Cipla's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Cipla's DESCOVY Notice Letter, which does not contest infringement of at least claim 1 of the '065 patent, except on the basis that the claim is allegedly invalid.

1109. On information and belief, Cipla's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Cipla in the United States by it or on its behalf.

1110. On information and belief, Cipla's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Cipla's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '065 patent.

1111. On information and belief, physicians and healthcare providers will administer Cipla's DESCOVY ANDA Product in the United States according to the directions and instructions in Cipla's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

1112. On information and belief, at least through its Proposed DESCOVY Label, Cipla will encourage physicians and healthcare providers to administer Cipla's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '065 patent, and Cipla will know or should know that such conduct will occur.

1113. On information and belief, Cipla will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

1114. Through at least the foregoing actions, Cipla will actively induce the infringement of at least one claim of the '065 patent.

1115. On information and belief, Cipla knows or should know that Cipla's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '065 patent and that Cipla's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

1116. The commercial manufacture, use, sale, offer for sale, and/or importation of Cipla's DESCOVY ANDA Product will contribute to the actual infringement of the '065 patent.

1117. On information and belief, Cipla knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '065 patent.

1118. Through at least the foregoing actions, Cipla will contribute to the infringement of at least one claim of the '065 patent.

1119. On information and belief, if Cipla's DESCOVY ANDA is approved by the FDA, Cipla will make its DESCOVY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1120. On information and belief, Cipla's DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Cipla's DESCOVY ANDA Product become a trivial and nonessential component of another product.

1121. Through at least the foregoing actions, Cipla will infringe at least one claim of the

'065 patent under 35 U.S.C. § 271(g).

1122. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Cipla's DESCOVY ANDA Product by Cipla prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

1123. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1124. Unless and until Cipla is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LVII: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Cipla's DESCOVY ANDA Product

1125. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1126. Pursuant to 35 U.S.C. § 271(e)(2)(A), Cipla has committed an act of infringement of the '769 patent by submitting Cipla's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's DESCOVY ANDA Product in the United States prior to the expiration of the '769 patent.

1127. Cipla's commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's DESCOVY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[57]

[57] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

1128. On information and belief, for example, Cipla's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1129. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1130. Unless and until Cipla is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LVIII: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Cipla's DESCOVY ANDA Product

1131. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1132. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1133. There is an actual case or controversy such that the Court may entertain Gilead'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.

1134. Cipla has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Cipla's DESCOVY Notice Letter, Cipla intends to manufacture, use, offer for sale, sell, and/or import Cipla's DESCOVY ANDA Product within the United States.

1135. While the FDA has not yet approved Cipla's DESCOVY ANDA, Cipla has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Cipla's DESCOVY ANDA Product.

1136. Cipla's actions indicate that it does not intend to change its course of conduct.

1137. On information and belief, upon FDA approval of Cipla's DESCOVY ANDA, Cipla will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[58] by making, using, offering to sell, and/or selling Cipla's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1138. On information and belief, for example, Cipla's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1139. Cipla has actual knowledge of the '769 patent.

1140. On information and belief, Cipla became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

1141. On information and belief, Cipla's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent.

[58] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

1142. On information and belief, Cipla's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Cipla in the United States by it or on its behalf.

1143. On information and belief, Cipla's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Cipla's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent.

1144. On information and belief, physicians and healthcare providers will administer Cipla's DESCOVY ANDA Product in the United States according to the directions and instructions in Cipla's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

1145. On information and belief, at least through its Proposed DESCOVY Label, Cipla will encourage physicians and healthcare providers to administer Cipla's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent, and Cipla will know or should know that such conduct will occur.

1146. On information and belief, Cipla will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

1147. Through at least the foregoing actions, Cipla will actively induce the infringement of at least one claim of the '769 patent.

1148. On information and belief, Cipla knows or should know that Cipla's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that

Cipla's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

1149. The commercial manufacture, use, sale, offer for sale, and/or importation of Cipla's DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

1150. On information and belief, Cipla knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

1151. Through at least the foregoing actions, Cipla will contribute to the infringement of at least one claim of the '769 patent.

1152. On information and belief, if Cipla's DESCOVY ANDA is approved by the FDA, Cipla will make its DESCOVY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1153. On information and belief, Cipla's DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Cipla's DESCOVY ANDA Product become a trivial and nonessential component of another product.

1154. Through at least the foregoing actions, Cipla will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

1155. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Cipla's DESCOVY ANDA Product by Cipla prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

1156. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for

which damages are inadequate.

1157. Unless and until Cipla is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LIX: Infringement of the '791 Patent under 35 U.S.C. § 271(e)(2) by Cipla's DESCOVY ANDA Product

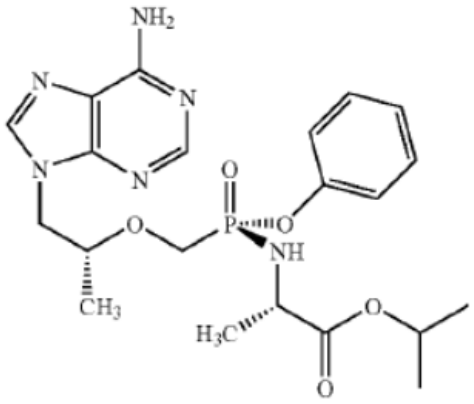
1158. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1159. Pursuant to 35 U.S.C. § 271(e)(2)(A), Cipla has committed an act of infringement of the '791 patent by submitting Cipla's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's DESCOVY ANDA Product in the United States prior to the expiration of the '791 patent.

1160. Cipla's commercial manufacture, use, offer for sale, sale, and/or importation of the DESCOVY ANDA Product prior to the expiration of the '791 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '791 patent, including but not limited to claim 7.[59]

1161. On information and belief, for example, Cipla's DESCOVY ANDA Product contains diastereomerically enriched compound, which can be represented by the following formula:

[59] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

1162. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1163. Unless and until Cipla is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LX: Declaratory Judgment of Infringement of the '791 Patent under 35 U.S.C. § 271(a) by Cipla's DESCOVY ANDA Product

1164. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1165. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1166. There is an actual case or controversy such that the Court may entertain Gilead'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.

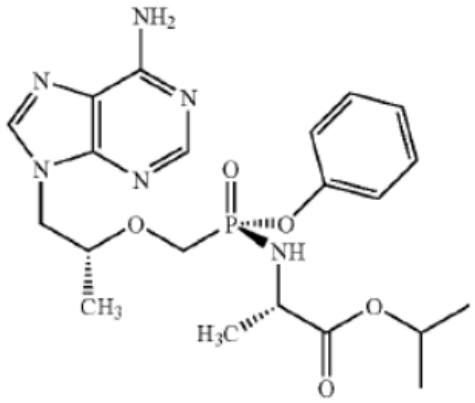
1167. Cipla has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Cipla's DESCOVY Notice Letter, Cipla intends to manufacture, use, offer for sale, sell, and/or import its DESCOVY ANDA Product within the United States.

1168. While the FDA has not yet approved Cipla's DESCOVY ANDA, Cipla has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import its DESCOVY ANDA Product.

1169. Cipla's actions indicate that it does not intend to change its course of conduct.

1170. On information and belief, upon FDA approval of Cipla's DESCOVY ANDA, Cipla will infringe one or more claims of the '791 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[60] by making, using, offering to sell, and/or selling Cipla's DESCOVY ANDA Product in the United States and/or importing said product into the United States under 35 U.S.C. § 271(a), unless enjoined by the Court.

1171. On information and belief, for example, Cipla's DESCOVY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

1172. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for

[60] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.

sale, sale, and/or importation of Cipla's DESCOVY ANDA Product by Cipla prior to the expiration of the '791 patent will constitute direct infringement of the '791 patent.

1173. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1174. Unless and until Cipla is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXI: Infringement of the '788 Patent under 35 U.S.C. § 271(e)(2) by Cipla's DESCOVY ANDA Product

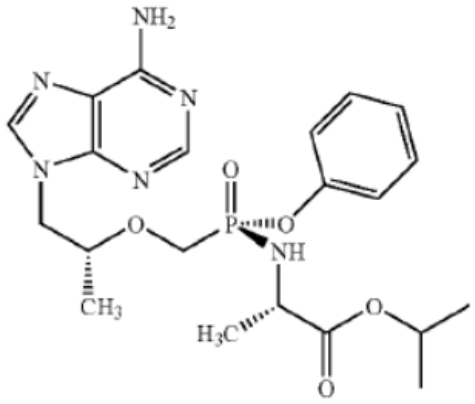
1175. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1176. Pursuant to 35 U.S.C. § 271(e)(2)(A), Cipla has committed an act of infringement of the '788 patent by submitting Cipla's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's DESCOVY ANDA Product in the United States prior to the expiration of the '788 patent.

1177. Cipla's commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's DESCOVY ANDA Product prior to the expiration of the '788 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '788 patent, including but not limited to claim 7.[61]

1178. On information and belief, for example, Cipla's DESCOVY ANDA Product, in accordance with Cipla's Proposed DESCOVY Label, will be used in antiviral therapy comprising administering a therapeutically effective amount of a diastereomerically enriched compound, which can be represented by the following formula:

[61] Gilead will identify all asserted claims of the '788 patent in accordance with this Court's Local Rules and/or scheduling order.



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '788 patent, either literally or under the doctrine of equivalents.

1179. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1180. Unless and until Cipla is enjoined from infringing the '788 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXII: Declaratory Judgment of Infringement of the '788 Patent under 35 U.S.C. §§ 271(a)-(c) by Cipla's DESCOVY ANDA Product

1181. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1182. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1183. There is an actual case or controversy such that the Court may entertain Gilead'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.

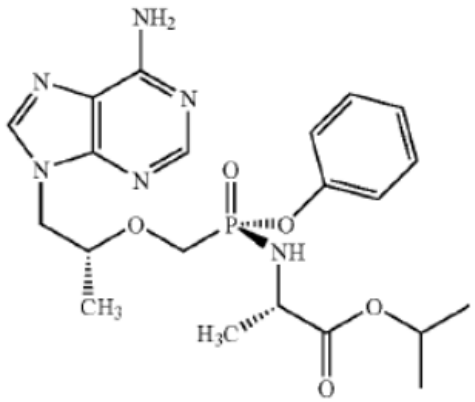
1184. Cipla has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Cipla's DESCOVY Notice Letter, Cipla intends to manufacture, use, offer for sale, sell, and/or import Cipla's DESCOVY ANDA Product within the United States.

1185. While the FDA has not yet approved Cipla's DESCOVY ANDA, Cipla has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Cipla's DESCOVY ANDA Product.

1186. Cipla's actions indicate that it does not intend to change its course of conduct.

1187. On information and belief, upon FDA approval of Cipla's DESCOVY ANDA, Cipla will infringe one or more claims of the '788 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[62] by making, using, offering to sell, and/or selling Cipla's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '788 patent by others, under 35 U.S.C. §§ 271(a), (b) and/or (c), unless enjoined by the Court.

1188. On information and belief, for example, Cipla's DESCOVY ANDA Product, in accordance with Cipla's Proposed DESCOVY Label, will be used in antiviral therapy comprising administering a therapeutically effective amount of a diastereomerically enriched compound, which can be represented by the following formula:



[62] Gilead will identify all asserted claims of the '788 patent in accordance with this Court's Local Rules and/or scheduling order.

and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '788 patent, either literally or under the doctrine of equivalents.

1189. Cipla has actual knowledge of the '788 patent.

1190. On information and belief, Cipla became aware of the '788 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

1191. On information and belief, Cipla's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '788 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '788 patent. On information and belief, this knowledge is reflected through, among other things, Cipla's DESCOVY Notice Letter, which does not contest infringement of any claim of the '788 patent, except on the basis that those claims are allegedly invalid.

1192. On information and belief, Cipla's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Cipla in the United States by it or on its behalf.

1193. On information and belief, Cipla's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Cipla's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '788 patent.

1194. On information and belief, physicians and healthcare providers will administer Cipla's DESCOVY ANDA Product in the United States according to the directions and instructions in Cipla's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '788 patent.

1195. On information and belief, at least through its Proposed DESCOVY Label, Cipla will encourage physicians and healthcare providers to administer Cipla's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '788 patent, and Cipla will know or should know that such conduct will occur.

1196. On information and belief, Cipla will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '788 patent.

1197. Through at least the foregoing actions, Cipla will actively induce the infringement of at least one claim of the '788 patent.

1198. On information and belief, Cipla knows or should know that Cipla's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '788 patent and that Cipla's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

1199. The commercial manufacture, use, sale, offer for sale, and/or importation of Cipla's DESCOVY ANDA Product will contribute to the actual infringement of the '788 patent.

1200. On information and belief, Cipla knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '788 patent.

1201. Through at least the foregoing actions, Cipla will contribute to the infringement of at least one claim of the '788 patent.

1202. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Cipla's DESCOVY ANDA Product by Cipla prior to the expiration of the '788 patent will constitute direct infringement and/or will induce and/or

contribute to the actual and direct infringement of the '788 patent.

1203. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1204. Unless and until Cipla is enjoined from infringing the '788 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

ODEFSEY Counts

Count LXIII: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Cipla's ODEFSEY ANDA Product

1205. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1206. Pursuant to 35 U.S.C. § 271(e)(2)(A), Cipla has committed an act of infringement of the '065 patent by submitting Cipla's ODEFSEY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product in the United States prior to the expiration of the '065 patent.

1207. Cipla's commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[63]

1208. On information and belief, for example, Cipla's ODEFSEY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

1209. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's

[63] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1210. Unless and until Cipla is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXIV: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Cipla's ODEFSEY ANDA Product

1211. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1212. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1213. There is an actual case or controversy such that the Court may entertain Gilead'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.

1214. Cipla has submitted an ANDA for a generic version of Gilead's ODEFSEY pharmaceutical product. According to Cipla's ODEFSEY Notice Letter, Cipla intends to manufacture, use, offer for sale, sell, and/or import Cipla's ODEFSEY ANDA Product within the United States.

1215. While the FDA has not yet approved Cipla's ODEFSEY ANDA, Cipla has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Cipla's ODEFSEY ANDA Product.

1216. Cipla's actions indicate that it does not intend to change its course of conduct.

1217. On information and belief, upon FDA approval of Cipla's ODEFSEY ANDA, Cipla will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[64] by making, using, offering to sell, and/or selling

[64] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

Cipla's ODEFSEY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1218. On information and belief, for example, Cipla's ODEFSEY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

1219. Cipla has actual knowledge of the '065 patent.

1220. On information and belief, Cipla became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's ODEFSEY product.

1221. On information and belief, Cipla's efforts to make, use, sell, offer for sell, and/or import its ODEFSEY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Cipla's ODEFSEY Notice Letter, which does not contest infringement of at least claim 1 of the '065 patent, except on the basis that the claim is allegedly invalid.

1222. On information and belief, Cipla's ODEFSEY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Cipla in the United States by it or on its behalf.

1223. On information and belief, Cipla's Proposed ODEFSEY Label will include directions and instructions that instruct physicians and healthcare providers to administer Cipla's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the

methods described/claimed in the ’065 patent.

1224. On information and belief, physicians and healthcare providers will administer Cipla’s ODEFSEY ANDA Product in the United States according to the directions and instructions in Cipla’s Proposed ODEFSEY Label, and such administration will constitute direct infringement of at least one claim of the ’065 patent.

1225. On information and belief, at least through its Proposed ODEFSEY Label, Cipla will encourage physicians and healthcare providers to administer Cipla’s ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the ’065 patent, and Cipla will know or should know that such conduct will occur.

1226. On information and belief, Cipla will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the ’065 patent.

1227. Through at least the foregoing actions, Cipla will actively induce the infringement of at least one claim of the ’065 patent.

1228. On information and belief, Cipla knows or should know that Cipla’s ODEFSEY ANDA Product will be especially made or adapted for use in infringing the ’065 patent and that Cipla’s ODEFSEY ANDA Product is not suitable for substantial non-infringing use.

1229. The commercial manufacture, use, sale, offer for sale, and/or importation of Cipla’s ODEFSEY ANDA Product will contribute to the actual infringement of the ’065 patent.

1230. On information and belief, Cipla knows or should know that its offer for sale, sale and/or importation of its ODEFSEY ANDA Product will contribute to the actual infringement of the ’065 patent.

1231. Through at least the foregoing actions, Cipla will contribute to the infringement of at least one claim of the '065 patent.

1232. On information and belief, if Cipla's ODEFSEY ANDA is approved by the FDA, Cipla will make its ODEFSEY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1233. On information and belief, Cipla's ODEFSEY ANDA Product will not be materially changed by a subsequent process nor will Cipla's ODEFSEY ANDA Product become a trivial and nonessential component of another product.

1234. Through at least the foregoing actions, Cipla will infringe at least one claim of the '065 patent under 35 U.S.C. § 271(g).

1235. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product by Cipla prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

1236. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1237. Unless and until Cipla is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXV: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Cipla's ODEFSEY ANDA Product

1238. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1239. Pursuant to 35 U.S.C. § 271(e)(2)(A), Cipla has committed an act of infringement of the '769 patent by submitting Cipla's ODEFSEY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product in the United States prior to the expiration of the '769 patent.

1240. Cipla's commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[65]

1241. On information and belief, for example, Cipla's ODEFSEY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1242. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1243. Unless and until Cipla is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXVI: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Cipla's ODEFSEY ANDA Product

1244. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1245. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

[65] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

1246. There is an actual case or controversy such that the Court may entertain Gilead'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.

1247. Cipla has submitted an ANDA for a generic version of Gilead's ODEFSEY pharmaceutical product. According to Cipla's ODEFSEY Notice Letter, Cipla intends to manufacture, use, offer for sale, sell, and/or import Cipla's ODEFSEY ANDA Product within the United States.

1248. While the FDA has not yet approved Cipla's ODEFSEY ANDA, Cipla has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Cipla's ODEFSEY ANDA Product.

1249. Cipla's actions indicate that it does not intend to change its course of conduct.

1250. On information and belief, upon FDA approval of Cipla's ODEFSEY ANDA, Cipla will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[66] by making, using, offering to sell, and/or selling Cipla's ODEFSEY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1251. On information and belief, for example, Cipla's ODEFSEY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls

[66] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1252. Cipla has actual knowledge of the '769 patent.

1253. On information and belief, Cipla became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's ODEFSEY product.

1254. On information and belief, Cipla's efforts to make, use, sell, offer for sell, and/or import its ODEFSEY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent.

1255. On information and belief, Cipla's ODEFSEY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Cipla in the United States by it or on its behalf.

1256. On information and belief, Cipla's Proposed ODEFSEY Label will include directions and instructions that instruct physicians and healthcare providers to administer Cipla's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '769 patent.

1257. On information and belief, physicians and healthcare providers will administer Cipla's ODEFSEY ANDA Product in the United States according to the directions and instructions in Cipla's Proposed ODEFSEY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

1258. On information and belief, at least through its Proposed ODEFSEY Label, Cipla will encourage physicians and healthcare providers to administer Cipla's ODEFSEY ANDA

Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '769 patent, and Cipla will know or should know that such conduct will occur.

1259. On information and belief, Cipla will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

1260. Through at least the foregoing actions, Cipla will actively induce the infringement of at least one claim of the '769 patent.

1261. On information and belief, Cipla knows or should know that Cipla's ODEFSEY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Cipla's ODEFSEY ANDA Product is not suitable for substantial non-infringing use.

1262. The commercial manufacture, use, sale, offer for sale, and/or importation of Cipla's ODEFSEY ANDA Product will contribute to the actual infringement of the '769 patent.

1263. On information and belief, Cipla knows or should know that its offer for sale, sale and/or importation of its ODEFSEY ANDA Product will contribute to the actual infringement of the '769 patent.

1264. Through at least the foregoing actions, Cipla will contribute to the infringement of at least one claim of the '769 patent.

1265. On information and belief, if Cipla's ODEFSEY ANDA is approved by the FDA, Cipla will make its ODEFSEY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1266. On information and belief, Cipla's ODEFSEY ANDA Product will not be

materially changed by a subsequent process nor will Cipla's ODEFSEY ANDA Product become a trivial and nonessential component of another product.

1267. Through at least the foregoing actions, Cipla will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

1268. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product by Cipla prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

1269. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1270. Unless and until Cipla is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXVII: Infringement of the '791 Patent under 35 U.S.C. § 271(e)(2) by Cipla's ODEFSEY ANDA Product

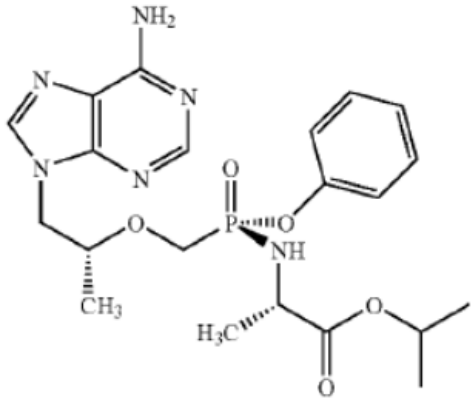
1271. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1272. Pursuant to 35 U.S.C. § 271(e)(2)(A), Cipla has committed an act of infringement with respect to the '791 patent by submitting Cipla's ODEFSEY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product in the United States prior to the expiration of the '791 patent.

1273. Cipla's commercial manufacture, use, offer for sale, sale, and/or importation of the ODEFSEY ANDA Product prior to the expiration of the '791 patent, and its inducement of

and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '791 patent, including but not limited to claim 7.[67]

1274. On information and belief, for example, Cipla's ODEFSEY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

1275. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1276. Unless and until Cipla is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXVIII: Declaratory Judgment of Infringement of the '791 Patent under 35 U.S.C. § 271(a) by Cipla's ODEFSEY ANDA Product

1277. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1278. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

[67] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.

1279. There is an actual case or controversy such that the Court may entertain Gilead'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.

1280. Cipla has submitted an ANDA for a generic version of Gilead's ODEFSEY pharmaceutical product. According to Cipla's ODEFSEY Notice Letter, Cipla intends to manufacture, use, offer for sale, sell, and/or import its ODEFSEY ANDA Product within the United States.

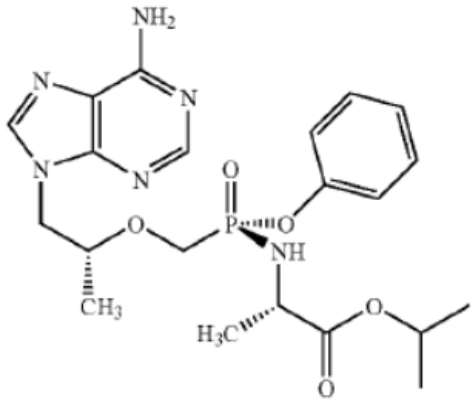
1281. While the FDA has not yet approved Cipla's ODEFSEY ANDA, Cipla has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import its ODEFSEY ANDA Product.

1282. Cipla's actions indicate that it does not intend to change its course of conduct.

1283. On information and belief, upon FDA approval of Cipla's ODEFSEY ANDA, Cipla will infringe one or more claims of the '791 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[68] by making, using, offering to sell, and/or selling Cipla's ODEFSEY ANDA Product in the United States and/or importing said product into the United States under 35 U.S.C. § 271(a), unless enjoined by the Court.

1284. On information and belief, for example, Cipla's ODEFSEY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:

[68] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

1285. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product by Cipla prior to the expiration of the '791 patent will constitute direct infringement of the '791 patent.

1286. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1287. Unless and until Cipla is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

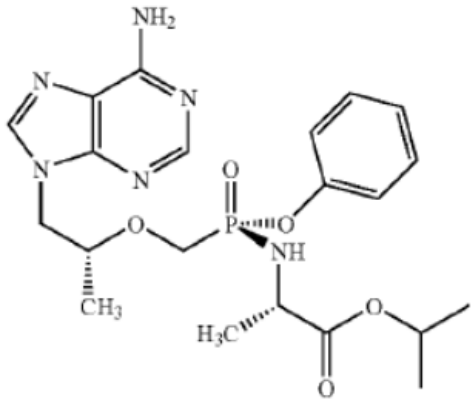
Count LXIX: Infringement of the '788 Patent under 35 U.S.C. § 271(e)(2) by Cipla's ODEFSEY ANDA Product

1288. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1289. Pursuant to 35 U.S.C. § 271(e)(2)(A), Cipla has committed an act of infringement with respect to the '788 patent by submitting Cipla's ODEFSEY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product in the United States prior to the expiration of the '788 patent.

1290. Cipla's commercial manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product prior to the expiration of the '788 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '788 patent, including but not limited to claim 7.[69]

1291. On information and belief, for example, Cipla's ODEFSEY ANDA Product, in accordance with Cipla's Proposed ODEFSEY Label, will be used in antiviral therapy comprising administering a therapeutically effective amount of a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '788 patent, either literally or under the doctrine of equivalents.

1292. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1293. Unless and until Cipla is enjoined from infringing the '788 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

[69] Gilead will identify all asserted claims of the '788 patent in accordance with this Court's Local Rules and/or scheduling order.

Count LXX: Declaratory Judgment of Infringement of the '788 Patent under 35 U.S.C. §§ 271(a)-(c) by Cipla's ODEFSEY ANDA Product

1294. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1295. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1296. There is an actual case or controversy such that the Court may entertain Gilead'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.

1297. Cipla has submitted an ANDA for a generic version of Gilead's ODEFSEY pharmaceutical product. According to Cipla's ODEFSEY Notice Letter, Cipla intends to manufacture, use, offer for sale, sell, and/or import Cipla's ODEFSEY ANDA Product within the United States.

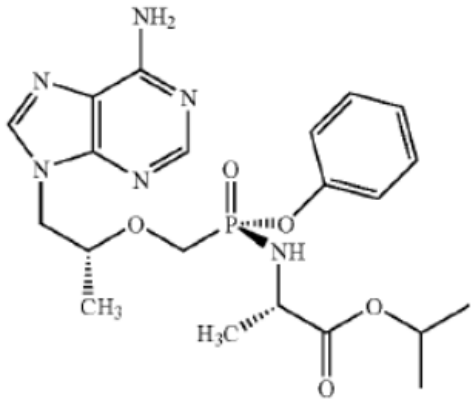
1298. While the FDA has not yet approved Cipla's ODEFSEY ANDA, Cipla has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Cipla's ODEFSEY ANDA Product.

1299. Cipla's actions indicate that it does not intend to change its course of conduct.

1300. On information and belief, upon FDA approval of Cipla's ODEFSEY ANDA, Cipla will infringe one or more claims of the '788 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[70] by making, using, offering to sell, and/or selling Cipla's ODEFSEY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '788 patent by others, under 35 U.S.C. §§ 271(a), (b) and/or (c), unless enjoined by the Court.

[70] Gilead will identify all asserted claims of the '788 patent in accordance with this Court's Local Rules and/or scheduling order.

1301. On information and belief, for example, Cipla's ODEFSEY ANDA Product, in accordance with Cipla's Proposed ODEFSEY Label, will be used in antiviral therapy comprising administering a therapeutically effective amount of a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '788 patent, either literally or under the doctrine of equivalents.

1302. Cipla has actual knowledge of the '788 patent.

1303. On information and belief, Cipla became aware of the '788 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's ODEFSEY product.

1304. On information and belief, Cipla's efforts to make, use, sell, offer for sell, and/or import its ODEFSEY ANDA Product have been made and will be made with full knowledge of the '788 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '788 patent. On information and belief, this knowledge is reflected through, among other things, Cipla's ODEFSEY Notice Letter, which does not contest infringement of any claims of the '788 patent, except on the basis that those claims are allegedly invalid.

1305. On information and belief, Cipla's ODEFSEY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Cipla in the United States by it or on its behalf.

1306. On information and belief, Cipla's Proposed ODEFSEY Label will include directions and instructions that instruct physicians and healthcare providers to administer Cipla's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '788 patent.

1307. On information and belief, physicians and healthcare providers will administer Cipla's ODEFSEY ANDA Product in the United States according to the directions and instructions in Cipla's Proposed ODEFSEY Label, and such administration will constitute direct infringement of at least one claim of the '788 patent.

1308. On information and belief, at least through its Proposed ODEFSEY Label, Cipla will encourage physicians and healthcare providers to administer Cipla's ODEFSEY ANDA Product in order to treat, *inter alia*, HIV-1 infection in accordance with the methods described/claimed in the '788 patent, and Cipla will know or should know that such conduct will occur.

1309. On information and belief, Cipla will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '788 patent.

1310. Through at least the foregoing actions, Cipla will actively induce the infringement at least one claim of the '788 patent.

1311. On information and belief, Cipla knows or should know that Cipla's ODEFSEY ANDA Product will be especially made or adapted for use in infringing the '788 patent and that

Cipla's ODEFSEY ANDA Product is not suitable for substantial non-infringing use.

1312. The commercial manufacture, use, sale, offer for sale, and/or importation of Cipla's ODEFSEY ANDA Product will contribute to the actual infringement of the '788 patent.

1313. On information and belief, Cipla knows or should know that its offer for sale, sale and/or importation of its ODEFSEY ANDA Product will contribute to the actual infringement of the '788 patent.

1314. Through at least the foregoing actions, Cipla will contribute to the infringement of at least one claim of the '788 patent.

1315. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Cipla's ODEFSEY ANDA Product by Cipla prior to the expiration of the '788 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '788 patent.

1316. The commercial manufacture, importation, use, sale, or offer for sale of Cipla's ODEFSEY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1317. Unless and until Cipla is enjoined from infringing the '788 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

COUNTS LXXI-LXXIV AGAINST MACLEODS

DESCOVY Counts

Count LXXI: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Macleods's DESCOVY ANDA Product

1318. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1319. Pursuant to 35 U.S.C. § 271(e)(2)(A), Macleods has committed an act of infringement of the '065 patent by submitting Macleods's DESCOVY ANDA to obtain approval

to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Macleods's DESCOVY ANDA Product in the United States prior to the expiration of the '065 patent.

1320. Macleods's commercial manufacture, use, offer for sale, sale, and/or importation of Macleods's DESCOVY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[71]

1321. On information and belief, for example, Macleods's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

1322. The commercial manufacture, importation, use, sale, or offer for sale of Macleods's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1323. Unless and until Macleods is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXII: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Macleods's DESCOVY ANDA Product

1324. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1325. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1326. There is an actual case or controversy such that the Court may entertain Gilead'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.

[71] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

1327. Macleods has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Macleods's DESCOVY Notice Letter, Macleods intends to manufacture, use, offer for sale, sell, and/or import Macleods's DESCOVY ANDA Product within the United States.

1328. While the FDA has not yet approved Macleods's DESCOVY ANDA, Macleods has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Macleods's DESCOVY ANDA Product.

1329. Macleods's actions indicate that it does not intend to change its course of conduct.

1330. On information and belief, upon FDA approval of Macleods's DESCOVY ANDA, Macleods will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[72] by making, using, offering to sell, and/or selling Macleods's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1331. On information and belief, for example, Macleods's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

1332. Macleods has actual knowledge of the '065 patent.

1333. On information and belief, Macleods became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

[72] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

1334. On information and belief, Macleods's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent.

1335. On information and belief, Macleods's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Macleods in the United States by it or on its behalf.

1336. On information and belief, Macleods's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Macleods's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '065 patent.

1337. On information and belief, physicians and healthcare providers will administer Macleods's DESCOVY ANDA Product in the United States according to the directions and instructions in Macleods's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

1338. On information and belief, at least through its Proposed DESCOVY Label, Macleods will encourage physicians and healthcare providers to administer Macleods's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '065 patent, and Macleods will know or should know that such conduct will occur.

1339. On information and belief, Macleods will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

1340. Through at least the foregoing actions, Macleods will actively induce the infringement of at least one claim of the ’065 patent.

1341. On information and belief, Macleods knows or should know that Macleods’s DESCOVY ANDA Product will be especially made or adapted for use in infringing the ’065 patent and that Macleods’s DESCOVY ANDA Product is not suitable for substantial non-infringing use.

1342. The commercial manufacture, use, sale, offer for sale, and/or importation of Macleods’s DESCOVY ANDA Product will contribute to the actual infringement of the ’065 patent.

1343. On information and belief, Macleods knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the ’065 patent.

1344. Through at least the foregoing actions, Macleods will contribute to the infringement of at least one claim of the ’065 patent.

1345. On information and belief, if Macleods’s DESCOVY ANDA is approved by the FDA, Macleods will make its DESCOVY ANDA Product using a process covered by one or more claims of the ’065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1346. On information and belief, Macleods’s DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Macleods’s DESCOVY ANDA Product become a trivial and nonessential component of another product.

1347. Through at least the foregoing actions, Macleods will infringe at least one claim of the ’065 patent under 35 U.S.C. § 271(g).

1348. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Macleods's DESCOVY ANDA Product by Macleods prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

1349. The commercial manufacture, importation, use, sale, or offer for sale of Macleods's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1350. Unless and until Macleods is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXIII: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Macleods's DESCOVY ANDA Product

1351. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1352. Pursuant to 35 U.S.C. § 271(e)(2)(A), Macleods has committed an act of infringement of the '769 patent by submitting Macleods's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Macleods's DESCOVY ANDA Product in the United States prior to the expiration of the '769 patent.

1353. Macleods's commercial manufacture, use, offer for sale, sale, and/or importation of Macleods's DESCOVY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[73]

[73] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

1354. On information and belief, for example, Macleods's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1355. The commercial manufacture, importation, use, sale, or offer for sale of Macleods's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1356. Unless and until Macleods is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXIV: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Macleods's DESCOVY ANDA Product

1357. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1358. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1359. There is an actual case or controversy such that the Court may entertain Gilead'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.

1360. Macleods has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Macleods's DESCOVY Notice Letter, Macleods intends to manufacture, use, offer for sale, sell, and/or import Macleods's DESCOVY ANDA Product within the United States.

1361. While the FDA has not yet approved Macleods's DESCOVY ANDA, Macleods has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Macleods's DESCOVY ANDA Product.

1362. Macleods's actions indicate that it does not intend to change its course of conduct.

1363. On information and belief, upon FDA approval of Macleods's DESCOVY ANDA, Macleods will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[74] by making, using, offering to sell, and/or selling Macleods's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1364. On information and belief, for example, Macleods's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1365. Macleods has actual knowledge of the '769 patent.

1366. On information and belief, Macleods became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

1367. On information and belief, Macleods's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent.

[74] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

1368. On information and belief, Macleods's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Macleods in the United States by it or on its behalf.

1369. On information and belief, Macleods's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Macleods's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 in accordance with the methods described/claimed in the '769 patent.

1370. On information and belief, physicians and healthcare providers will administer Macleods's DESCOVY ANDA Product in the United States according to the directions and instructions in Macleods's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

1371. On information and belief, at least through its Proposed DESCOVY Label, Macleods will encourage physicians and healthcare providers to administer Macleods's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent, and Macleods will know or should know that such conduct will occur.

1372. On information and belief, Macleods will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

1373. Through at least the foregoing actions by Macleods will constitute active inducement of the infringement of the '769 patent.

1374. On information and belief, Macleods knows or should know that Macleods's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '769 patent

and that Macleods's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

1375. The commercial manufacture, use, sale, offer for sale, and/or importation of Macleods's DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

1376. On information and belief, Macleods knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

1377. Through at least the foregoing actions, Macleods will contribute to the infringement of at least one claim of the '769 patent.

1378. On information and belief, if Macleods's DESCOVY ANDA is approved by the FDA, Macleods will make its DESCOVY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1379. On information and belief, Macleods's DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Macleods's DESCOVY ANDA Product become a trivial and nonessential component of another product.

1380. Through at least the foregoing actions, Macleods will infringe at least one claim of the '769 patent under 35 U.S.C. § 271(g).

1381. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Macleods's DESCOVY ANDA Product by Macleods prior to the expiration of the '769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '769 patent.

1382. The commercial manufacture, importation, use, sale, or offer for sale of Macleods's

DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1383. Unless and until Macleods is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

COUNTS LXXV-LXXXVI AGAINST HETERO

VEMLIDY Counts

Count LXXV: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Hetero's VEMLIDY ANDA Product

1384. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1385. Pursuant to 35 U.S.C. § 271(e)(2)(A), Hetero has committed an act of infringement of the '065 patent by submitting Hetero's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Hetero's VEMLIDY ANDA Product in the United States prior to the expiration of the '065 patent.

1386. Hetero's commercial manufacture, use, offer for sale, sale, and/or importation of Hetero's VEMLIDY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[75]

1387. On information and belief, for example, Hetero's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

[75] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

1388. If Hetero's marketing and sale of Hetero's VEMLIDY ANDA Product prior to expiration of the '065 patent and all other relevant exclusivities is not enjoined, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

1389. The commercial manufacture, importation, use, sale, or offer for sale of Hetero's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1390. Unless and until Hetero is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXVI: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Hetero's VEMLIDY ANDA Product

1391. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1392. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1393. There is an actual case or controversy such that the Court may entertain Gilead'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.

1394. Hetero has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Hetero's First VEMLIDY Notice Letter, Hetero intends to manufacture, use, offer for sale, sell, and/or import Hetero's VEMLIDY ANDA Product within the United States.

1395. While the FDA has not yet approved Hetero's VEMLIDY ANDA, Hetero has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Hetero's VEMLIDY ANDA Product.

1396. Hetero's actions indicate that it does not intend to change its course of conduct.

1397. On information and belief, upon FDA approval of Hetero's VEMLIDY ANDA,

Hetero will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[76] by making, using, offering to sell, and/or selling Hetero's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1398. On information and belief, for example, Hetero's VEMLIDY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

1399. Hetero has actual knowledge of the '065 patent.

1400. On information and belief, Hetero became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

1401. On information and belief, Hetero's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Hetero's First VEMLIDY Notice Letter, which does not contest infringement of any claim of the '065 patent, except on the basis that those claims are allegedly invalid.

[76] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

1402. On information and belief, Hetero's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Hetero in the United States by it or on its behalf.

1403. On information and belief, Hetero's Proposed VEMLIDY Label will include directions and instructions that instruct physicians and healthcare providers to administer Hetero's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent.

1404. On information and belief, physicians and healthcare providers will administer Hetero's VEMLIDY ANDA Product in the United States according to the directions and instructions in Hetero's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

1405. On information and belief, at least through its Proposed VEMLIDY Label, Hetero will encourage physicians and healthcare providers to administer Hetero's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '065 patent, and Hetero will know or should know that such conduct will occur.

1406. On information and belief, Hetero will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

1407. Through at least the foregoing actions, Hetero will actively induce the infringement of at least one claim of the '065 patent.

1408. On information and belief, Hetero knows or should know that Hetero's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the '065 patent and that Hetero's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

1409. The commercial manufacture, use, sale, offer for sale, and/or importation of Hetero's VEMLIDY ANDA Product will contribute to the actual infringement of the '065 patent.

1410. On information and belief, Hetero knows or should know that its offer for sale, sale and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the '065 patent.

1411. Through at least the foregoing actions, Hetero will contribute to the infringement of at least one claim of the '065 patent.

1412. On information and belief, if Hetero's VEMLIDY ANDA is approved by the FDA, Hetero will make its VEMLIDY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1413. On information and belief, Hetero's VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Hetero's VEMLIDY ANDA Product become a trivial and nonessential component of another product.

1414. Through at least the foregoing actions, Hetero will infringe at least one claim of the '065 patent under 35 U.S.C. § 271(g).

1415. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Hetero's VEMLIDY ANDA Product by Hetero prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

1416. The commercial manufacture, importation, use, sale, or offer for sale of Hetero's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1417. Unless and until Hetero is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXVII: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Hetero's VEMLIDY ANDA Product

1418. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1419. Pursuant to 35 U.S.C. § 271(e)(2)(A), Hetero has committed an act of infringement of the '769 patent by submitting Hetero's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Hetero's VEMLIDY ANDA Product in the United States prior to the expiration of the '769 patent.

1420. Hetero's commercial manufacture, use, offer for sale, sale, and/or importation of Hetero's VEMLIDY ANDA Product prior to the expiration of the '769 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[77]

1421. On information and belief, for example, Hetero's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1422. The commercial manufacture, importation, use, sale, or offer for sale of Hetero's

[77] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1423. Unless and until Hetero is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXVIII: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Hetero's VEMLIDY ANDA Product

1424. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1425. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1426. There is an actual case or controversy such that the Court may entertain Gilead'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.

1427. Hetero has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Hetero's First VEMLIDY Notice Letter, Hetero intends to manufacture, use, offer for sale, sell, and/or import Hetero's VEMLIDY ANDA Product within the United States.

1428. While the FDA has not yet approved Hetero's VEMLIDY ANDA, Hetero has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Hetero's VEMLIDY ANDA Product.

1429. Hetero's actions indicate that it does not intend to change its course of conduct.

1430. On information and belief, upon FDA approval of Hetero's VEMLIDY ANDA, Hetero will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[78] by making, using, offering to sell, and/or selling

[78] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

Hetero's VEMLIDY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1431. On information and belief, for example, Hetero's VEMLIDY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1432. Hetero has actual knowledge of the '769 patent.

1433. On information and belief, Hetero became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's VEMLIDY product.

1434. On information and belief, Hetero's efforts to make, use, sell, offer for sell, and/or import its VEMLIDY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent. On information and belief, this knowledge is reflected through, among other things, Hetero's First VEMLIDY Notice Letter, which does not contest infringement of any claim of the '769 patent, except on the basis that those claims are allegedly invalid.

1435. On information and belief, Hetero's VEMLIDY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Hetero in the United States by it or on its behalf.

1436. On information and belief, Hetero's Proposed VEMLIDY Label will include

directions and instructions that instruct physicians and healthcare providers to administer Hetero's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent.

1437. On information and belief, physicians and healthcare providers will administer Hetero's VEMLIDY ANDA Product in the United States according to the directions and instructions in Hetero's Proposed VEMLIDY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

1438. On information and belief, at least through its Proposed VEMLIDY Label, Hetero will encourage physicians and healthcare providers to administer Hetero's VEMLIDY ANDA Product in order to treat, *inter alia*, hepatitis B infection in accordance with the methods described/claimed in the '769 patent, and Hetero will know or should know that such conduct will occur.

1439. On information and belief, Hetero will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

1440. Through at least the foregoing actions, Hetero will actively induce the infringement of at least one claim of the '769 patent.

1441. On information and belief, Hetero knows or should know that Hetero's VEMLIDY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Hetero's VEMLIDY ANDA Product is not suitable for substantial non-infringing use.

1442. The commercial manufacture, use, sale, offer for sale, and/or importation of Hetero's VEMLIDY ANDA Product will contribute to the actual infringement of the '769 patent.

1443. On information and belief, Hetero knows or should know that its offer for sale, sale

and/or importation of its VEMLIDY ANDA Product will contribute to the actual infringement of the ’769 patent.

1444. Through at least the foregoing actions, Hetero will contribute to the infringement of at least one claim of the ’769 patent.

1445. On information and belief, if Hetero’s VEMLIDY ANDA is approved by the FDA, Hetero will make its VEMLIDY ANDA Product using a process covered by one or more claims of the ’769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1446. On information and belief, Hetero’s VEMLIDY ANDA Product will not be materially changed by a subsequent process nor will Hetero’s VEMLIDY ANDA Product become a trivial and nonessential component of another product.

1447. Through at least the foregoing actions, Hetero will infringe at least one claim of the ’769 patent under 35 U.S.C. § 271(g).

1448. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Hetero’s VEMLIDY ANDA Product by Hetero prior to the expiration of the ’769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the ’769 patent.

1449. The commercial manufacture, importation, use, sale, or offer for sale of Hetero’s VEMLIDY ANDA Product in violation of Gilead’s patent rights will cause harm to Gilead for which damages are inadequate.

1450. Unless and until Hetero is enjoined from infringing the ’769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

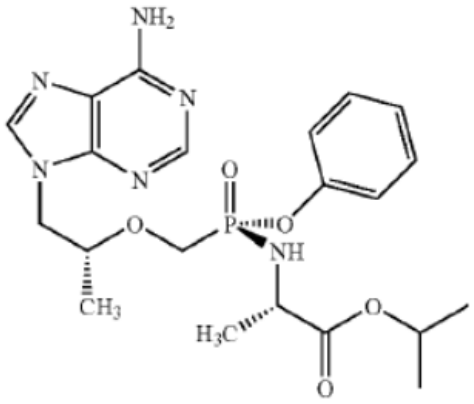
Count LXXIX: Infringement of the '791 Patent under 35 U.S.C. § 271(e)(2) by Hetero's VEMLIDY ANDA Product

1451. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1452. Pursuant to 35 U.S.C. § 271(e)(2)(A), Hetero has committed an act of infringement of the '791 patent by submitting Hetero's VEMLIDY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Hetero's VEMLIDY ANDA Product in the United States prior to the expiration of the '791 patent.

1453. Hetero's commercial manufacture, use, offer for sale, sale, and/or importation of the VEMLIDY ANDA Product prior to the expiration of the '791 patent would constitute infringement of at least one of the claims of the '791 patent, including but not limited to claim 7.[79]

1454. On information and belief, for example, Hetero's VEMLIDY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

1455. The commercial manufacture, importation, use, sale, or offer for sale of Hetero's

[79] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.

VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1456. Unless and until Hetero is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXX: Declaratory Judgment of Infringement of the '791 Patent under 35 U.S.C. § 271(a) by Hetero's VEMLIDY ANDA Product

1457. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1458. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1459. There is an actual case or controversy such that the Court may entertain Gilead'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.

1460. Hetero has submitted an ANDA for a generic version of Gilead's VEMLIDY pharmaceutical product. According to Hetero's Second VEMLIDY Notice Letter, Hetero intends to manufacture, use, offer for sale, sell, and/or import its VEMLIDY ANDA Product within the United States.

1461. While the FDA has not yet approved Hetero's VEMLIDY ANDA, Hetero has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import its VEMLIDY ANDA Product.

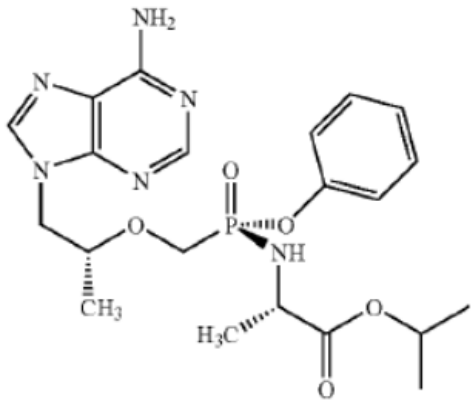
1462. Hetero's actions indicate that it does not intend to change its course of conduct.

1463. On information and belief, upon FDA approval of Hetero's VEMLIDY ANDA, Hetero will infringe one or more claims of the '791 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[80] by making, using, offering to sell, and/or selling

[80] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.

Hetero's VEMLIDY ANDA Product in the United States and/or importing said product into the United States under 35 U.S.C. § 271(a), unless enjoined by the Court.

1464. On information and belief, for example, Hetero's VEMLIDY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

1465. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Hetero's VEMLIDY ANDA Product by Hetero prior to the expiration of the '791 patent will constitute direct infringement of the '791 patent.

1466. The commercial manufacture, importation, use, sale, or offer for sale of Hetero's VEMLIDY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1467. Unless and until Hetero is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

DESCOVY Counts

Count LXXXI: Infringement of the '065 Patent under 35 U.S.C. § 271(e)(2) by Hetero's DESCOVY ANDA Product

1468. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1469. Pursuant to 35 U.S.C. § 271(e)(2)(A), Hetero has committed an act of infringement of the '065 patent by submitting Hetero's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Hetero's DESCOVY ANDA Product in the United States prior to the expiration of the '065 patent.

1470. Hetero's commercial manufacture, use, offer for sale, sale, and/or importation of Hetero's DESCOVY ANDA Product prior to the expiration of the '065 patent, and its inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '065 patent, including but not limited to claim 1.[81]

1471. On information and belief, for example, Hetero's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

1472. The commercial manufacture, importation, use, sale, or offer for sale of Hetero's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1473. Unless and until Hetero is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXXII: Declaratory Judgment of Infringement of the '065 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Hetero's DESCOVY ANDA Product

1474. Gilead realleges the foregoing paragraphs as if fully set forth herein.

[81] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

1475. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1476. There is an actual case or controversy such that the Court may entertain Gilead'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.

1477. Hetero has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Hetero's First DESCOVY Notice Letter, Hetero intends to manufacture, use, offer for sale, sell, and/or import Hetero's DESCOVY ANDA Product within the United States.

1478. While the FDA has not yet approved Hetero's DESCOVY ANDA, Hetero has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Hetero's DESCOVY ANDA Product.

1479. Hetero's actions indicate that it does not intend to change its course of conduct.

1480. On information and belief, upon FDA approval of Hetero's DESCOVY ANDA, Hetero will infringe one or more claims of the '065 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[82] by making, using, offering to sell, and/or selling Hetero's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '065 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1481. On information and belief, for example, Hetero's DESCOVY ANDA Product contains tenofovir alafenamide hemifumarate and thus falls within the scope of at least claim 1 of the '065 patent, either literally or under the doctrine of equivalents.

[82] Gilead will identify all asserted claims of the '065 patent in accordance with this Court's Local Rules and/or scheduling order.

1482. Hetero has actual knowledge of the '065 patent.

1483. On information and belief, Hetero became aware of the '065 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

1484. On information and belief, Hetero's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '065 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '065 patent. On information and belief, this knowledge is reflected through, among other things, Hetero's First DESCOVY Notice Letter, which does not contest infringement of any claim of the '065 patent, except on the basis that those claims are allegedly invalid.

1485. On information and belief, Hetero's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Hetero in the United States by it or on its behalf.

1486. On information and belief, Hetero's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Hetero's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '065 patent.

1487. On information and belief, physicians and healthcare providers will administer Hetero's DESCOVY ANDA Product in the United States according to the directions and instructions in Hetero's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '065 patent.

1488. On information and belief, at least through its Proposed DESCOVY Label, Hetero

will encourage physicians and healthcare providers to administer Hetero's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '065 patent, and Hetero will know or should know that such conduct will occur.

1489. On information and belief, Hetero will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '065 patent.

1490. Through at least the foregoing actions, Hetero will actively induce the infringement of at least one claim of the '065 patent.

1491. On information and belief, Hetero knows or should know that Hetero's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '065 patent and that Hetero's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

1492. The commercial manufacture, use, sale, offer for sale, and/or importation of Hetero's DESCOVY ANDA Product will contribute to the actual infringement of the '065 patent.

1493. On information and belief, Hetero knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '065 patent.

1494. Through at least the foregoing actions, Hetero will contribute to the infringement of at least one claim of the '065 patent.

1495. On information and belief, if Hetero's DESCOVY ANDA is approved by the FDA, Hetero will make its DESCOVY ANDA Product using a process covered by one or more claims of the '065 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1496. On information and belief, Hetero's DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Hetero's DESCOVY ANDA Product become a trivial and nonessential component of another product.

1497. Through at least the foregoing actions, Hetero will infringe at least one claim of the '065 patent under 35 U.S.C. § 271(g).

1498. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Hetero's DESCOVY ANDA Product by Hetero prior to the expiration of the '065 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the '065 patent.

1499. The commercial manufacture, importation, use, sale, or offer for sale of Hetero's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1500. Unless and until Hetero is enjoined from infringing the '065 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXXIII: Infringement of the '769 Patent under 35 U.S.C. § 271(e)(2) by Hetero's DESCOVY ANDA Product

1501. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1502. Pursuant to 35 U.S.C. § 271(e)(2)(A), Hetero has committed an act of infringement of the '769 patent by submitting Hetero's DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Hetero's DESCOVY ANDA Product in the United States prior to the expiration of the '769 patent.

1503. Hetero's commercial manufacture, use, offer for sale, sale, and/or importation of Hetero's DESCOVY ANDA Product prior to the expiration of the '769 patent, and its

inducement of and/or contribution to such conduct, would constitute infringement of at least one of the claims of the '769 patent, including but not limited to claim 1.[83]

1504. On information and belief, for example, Hetero's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1505. The commercial manufacture, importation, use, sale, or offer for sale of Hetero's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1506. Unless and until Hetero is enjoined from infringing the '769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXXIV: Declaratory Judgment of Infringement of the '769 Patent under 35 U.S.C. §§ 271(a)-(c), (g) by Hetero's DESCOVY ANDA Product

1507. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1508. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1509. There is an actual case or controversy such that the Court may entertain Gilead'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.

1510. Hetero has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Hetero's First DESCOVY Notice Letter, Hetero intends to

[83] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

manufacture, use, offer for sale, sell, and/or import Hetero's DESCOVY ANDA Product within the United States.

1511. While the FDA has not yet approved Hetero's DESCOVY ANDA, Hetero has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import Hetero's DESCOVY ANDA Product.

1512. Hetero's actions indicate that it does not intend to change its course of conduct.

1513. On information and belief, upon FDA approval of Hetero's DESCOVY ANDA, Hetero will infringe one or more claims of the '769 patent, either literally or under the doctrine of equivalents, including but not limited to claim 1,[84] by making, using, offering to sell, and/or selling Hetero's DESCOVY ANDA Product in the United States and/or importing said product into the United States and/or by actively inducing and contributing to infringement of the '769 patent by others, under 35 U.S.C. §§ 271(a), (b), (c) and/or (g), unless enjoined by the Court.

1514. On information and belief, for example, Hetero's DESCOVY ANDA Product contains a composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate, and thus falls within the scope of at least claim 1 of the '769 patent, either literally or under the doctrine of equivalents.

1515. Hetero has actual knowledge of the '769 patent.

1516. On information and belief, Hetero became aware of the '769 patent no later than the date on which that patent was issued by the Patent Office and/or listed in the Orange Book for Gilead's DESCOVY product.

[84] Gilead will identify all asserted claims of the '769 patent in accordance with this Court's Local Rules and/or scheduling order.

1517. On information and belief, Hetero's efforts to make, use, sell, offer for sell, and/or import its DESCOVY ANDA Product have been made and will be made with full knowledge of the '769 patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the '769 patent. On information and belief, this knowledge is reflected through, among other things, Hetero's First DESCOVY Notice Letter, which does not contest infringement of any claim of the '769 patent, except on the basis that those claims are allegedly invalid.

1518. On information and belief, Hetero's DESCOVY ANDA Product, if FDA-approved, will be commercially manufactured, used, imported, offered for sale, and/or sold by Hetero in the United States by it or on its behalf.

1519. On information and belief, Hetero's Proposed DESCOVY Label will include directions and instructions that instruct physicians and healthcare providers to administer Hetero's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent.

1520. On information and belief, physicians and healthcare providers will administer Hetero's DESCOVY ANDA Product in the United States according to the directions and instructions in Hetero's Proposed DESCOVY Label, and such administration will constitute direct infringement of at least one claim of the '769 patent.

1521. On information and belief, at least through its Proposed DESCOVY Label, Hetero will encourage physicians and healthcare providers to administer Hetero's DESCOVY ANDA Product for, *inter alia*, the treatment of HIV-1 infection in accordance with the methods described/claimed in the '769 patent, and Hetero will know or should know that such conduct will occur.

1522. On information and belief, Hetero will actively induce, encourage, aid, and abet that conduct by physicians and healthcare providers with knowledge and specific intent that the conduct infringe the '769 patent.

1523. Through at least the foregoing actions, Hetero will actively induce the infringement of at least one claim of the '769 patent.

1524. On information and belief, Hetero knows or should know that Hetero's DESCOVY ANDA Product will be especially made or adapted for use in infringing the '769 patent and that Hetero's DESCOVY ANDA Product is not suitable for substantial non-infringing use.

1525. The commercial manufacture, use, sale, offer for sale, and/or importation of Hetero's DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

1526. On information and belief, Hetero knows or should know that its offer for sale, sale and/or importation of its DESCOVY ANDA Product will contribute to the actual infringement of the '769 patent.

1527. Through at least the foregoing actions, Hetero will contribute to the infringement of at least one claim of the '769 patent.

1528. On information and belief, if Hetero's DESCOVY ANDA is approved by the FDA, Hetero will make its DESCOVY ANDA Product using a process covered by one or more claims of the '769 patent and import that product into the United States and/or offer to sell, sell or use that product in the United States.

1529. On information and belief, Hetero's DESCOVY ANDA Product will not be materially changed by a subsequent process nor will Hetero's DESCOVY ANDA Product become a trivial and nonessential component of another product.

1530. Through at least the foregoing actions, Hetero will infringe at least one claim of

the ’769 patent under 35 U.S.C. § 271(g).

1531. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Hetero’s DESCOVY ANDA Product by Hetero prior to the expiration of the ’769 patent will constitute direct infringement and/or will induce and/or contribute to the actual and direct infringement of the ’769 patent.

1532. The commercial manufacture, importation, use, sale, or offer for sale of Hetero’s DESCOVY ANDA Product in violation of Gilead’s patent rights will cause harm to Gilead for which damages are inadequate.

1533. Unless and until Hetero is enjoined from infringing the ’769 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXXV: Infringement of the ’791 Patent under 35 U.S.C. § 271(e)(2) by Hetero’s DESCOVY ANDA Product

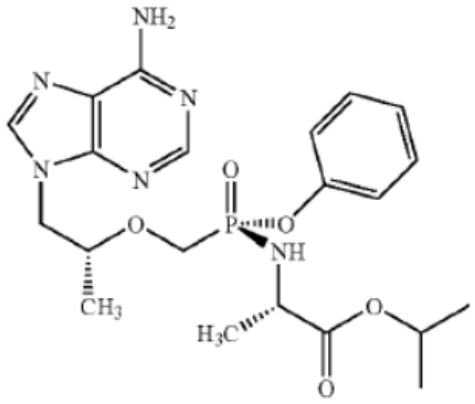
1534. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1535. Pursuant to 35 U.S.C. § 271(e)(2)(A), Hetero has committed an act of infringement of the ’791 patent by submitting Hetero’s DESCOVY ANDA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Hetero’s DESCOVY ANDA Product in the United States prior to the expiration of the ’791 patent.

1536. Hetero’s commercial manufacture, use, offer for sale, sale, and/or importation of the DESCOVY ANDA Product prior to the expiration of the ’791 patent would constitute infringement of at least one of the claims of the ’791 patent, including but not limited to claim 7.[85]

[85] Gilead will identify all asserted claims of the ’791 patent in accordance with this Court’s Local Rules and/or scheduling order.

1537. On information and belief, for example, Hetero's DESCOVY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

1538. The commercial manufacture, importation, use, sale, or offer for sale of Hetero's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1539. Unless and until Hetero is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

Count LXXXVI: Declaratory Judgment of Infringement of the '791 Patent under 35 U.S.C. § 271(a) by Hetero's DESCOVY ANDA Product

1540. Gilead realleges the foregoing paragraphs as if fully set forth herein.

1541. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

1542. There is an actual case or controversy such that the Court may entertain Gilead'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.

1543. Hetero has submitted an ANDA for a generic version of Gilead's DESCOVY pharmaceutical product. According to Hetero's Second DESCOVY Notice Letter, Hetero intends to manufacture, use, offer for sale, sell, and/or import its DESCOVY ANDA Product within the United States.

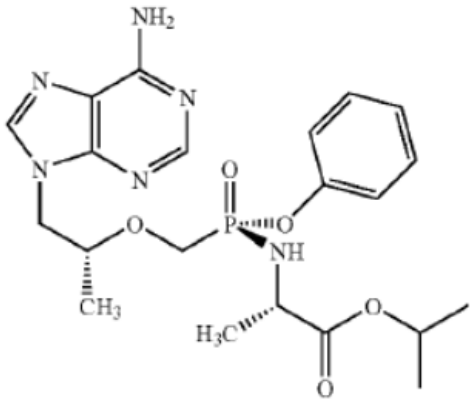
1544. While the FDA has not yet approved Hetero's DESCOVY ANDA, Hetero has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import its DESCOVY ANDA Product.

1545. Hetero's actions indicate that it does not intend to change its course of conduct.

1546. On information and belief, upon FDA approval of Hetero's DESCOVY ANDA, Hetero will infringe one or more claims of the '791 patent, either literally or under the doctrine of equivalents, including but not limited to claim 7,[86] by making, using, offering to sell, and/or selling Hetero's DESCOVY ANDA Product in the United States and/or importing said product into the United States under 35 U.S.C. § 271(a), unless enjoined by the Court.

1547. On information and belief, for example, Hetero's DESCOVY ANDA Product contains a diastereomerically enriched compound, which can be represented by the following formula:

[86] Gilead will identify all asserted claims of the '791 patent in accordance with this Court's Local Rules and/or scheduling order.



and/or its salts, tautomers, free base and solvates, and thus falls within the scope of at least claim 7 of the '791 patent, either literally or under the doctrine of equivalents.

1548. Gilead is entitled to a declaratory judgment that future manufacture, use, offer for sale, sale, and/or importation of Hetero's DESCOVY ANDA Product by Hetero prior to the expiration of the '791 patent will constitute direct infringement of the '791 patent.

1549. The commercial manufacture, importation, use, sale, or offer for sale of Hetero's DESCOVY ANDA Product in violation of Gilead's patent rights will cause harm to Gilead for which damages are inadequate.

1550. Unless and until Hetero is enjoined from infringing the '791 patent, Gilead will suffer substantial and irreparable harm for which there is no remedy at law.

EXCEPTIONAL CASE

1551. Defendants were aware of the Patents-In-Suit prior to filing of an ANDA for a generic version of Gilead's VEMLIDY, DESCOVY, and/or ODEFSEY, and sending Notice Letters to Gilead.

1552. The actions of Defendants render this an exceptional case under 35 U.S.C. § 285.

JURY TRIAL DEMAND

Pursuant to Federal Rule of Civil Procedure 38(b), Gilead hereby demands a trial by jury of all issues that are or may become so triable.

PRAYER FOR RELIEF

WHEREFORE, Gilead prays that this Court grant the following relief:

A) A judgment that each Defendant has infringed the '065 patent, the '769 patent, the '791 patent, and/or the '788 patent by submitting its respective ANDA(s) under Section 505(j) of the FFDCA, and that the making, using, offering to sell, and/or selling within the United States, and/or importation into the United States of Defendants' VEMLIDY, DESCOVY, and/or ODEFSEY ANDA Products will constitute an infringement of the '065 patent, the '769 patent, the '791 patent, and/or the '788 patent;

B) A judgment entered declaring that the Patents-In-Suit have not been proven invalid or unenforceable;

C) An order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any FDA approval of Defendants' VEMLIDY, DESCOVY, and/or ODEFSEY ANDAs shall be a date which is not earlier than the latest expiration date of the Patents-In-Suit as extended by any applicable periods of exclusivity to which Gilead is or will be entitled;

D) An order under 35 U.S.C. § 271(e)(4)(B) and/or 35 U.S.C. § 283 permanently enjoining Defendants, their affiliates, subsidiaries, and each of their officers, agents, servants and employees and those acting in privity or concert with them, from making, using, offering to sell, and/or selling in the United States, and/or importing into the United States any of Defendants' VEMLIDY, DESCOVY, and/or ODEFSEY ANDA Products until after the latest expiration date

of the Patents-In-Suit, including any extensions and/or additional periods of exclusivity to which Gilead is or will be entitled;

E) An order pursuant to 28 U.S.C. §§ 2201 and 2202 declaring that Defendants' commercial manufacture, use, offer for sell, sale, and/or importation of Defendants' VEMLIDY, DESCOVY, and/or ODEFSEY ANDA Products in or into the United States prior to the expiration of the Patents-In-Suit (including such actions by their officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with Defendants or acting on Defendants' behalf) will constitute infringement of the Patents-In-Suit under 35 U.S.C. §§ 271 (a), (b), (c), and/or (g) and providing any further necessary or proper relief based on the Court's declaratory judgment or decree;

F) Damages or other monetary relief under 35 U.S.C. §§ 271(a), (b), (c) and (e)(4)(c), and/or 35 U.S.C. § 284, including costs, fees, pre- and post-judgment interest, to Gilead if Defendants engage in commercial manufacture, use, offers to sell, sale, and/or importation in or into the United States of any of Defendants' VEMLIDY, DESCOVY, and/or ODEFSEY ANDA Products prior to the latest expiration date of the Patents-In-Suit, including any extensions and/or additional periods of exclusivity to which Gilead is or will be entitled;

G) An order that this case is exceptional under 35 U.S.C. § 285, and that Gilead be awarded reasonable attorneys' fees and costs; and

H) Such further and other relief as this Court deems proper and just, including any appropriate relief under 35 U.S.C. § 285.

Dated: October 15, 2021

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Exhibit A

US007390791B2

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

(10) **Patent No.: US 7,390,791 B2**
(45) **Date of Patent: Jun. 24, 2008**

(54) **PRODRUGS OF PHOSPHONATE NUCLEOTIDE ANALOGUES**

(75) Inventors: **Mark W. Becker**, Belmont, CA (US); **Harlan H. Chapman**, La Honda, CA (US); **Tomas Cihlar**, Foster City, CA (US); **Eugene J. Eisenberg**, San Carlos, CA (US); **Gong-Xin He**, Fremont, CA (US); **Michael R. Kernan**, Pacifica, CA (US); **William A. Lee**, Los Altos, CA (US); **Ernest J. Prisbe**, Los Altos, CA (US); **John C. Rohloff**, Mountain View, CA (US); **Mark L. Sparacino**, Morgan Hill, CA (US)

(73) Assignee: **Gilead Sciences, Inc.**, Foster City, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 291 days.

(21) Appl. No.: **10/798,692**

(22) Filed: **Mar. 11, 2004**

(65) **Prior Publication Data**

US 2005/0009043 A1 Jan. 13, 2005

Related U.S. Application Data

(63) Continuation of application No. 10/354,207, filed on Jan. 28, 2003, now abandoned, which is a continuation of application No. 09/909,560, filed on Jul. 20, 2001, now abandoned.

(60) Provisional application No. 60/220,021, filed on Jul. 21, 2000.

(51) **Int. Cl.**
A01N 43/48 (2006.01)
A61K 3/1675 (2006.01)
C07F 9/6512 (2006.01)

(52) **U.S. Cl.** **514/44**; 514/7; 514/81

(58) **Field of Classification Search** 435/4, 435/7.1, 9.1; 514/44, 7, 81, 85
See application file for complete search history.

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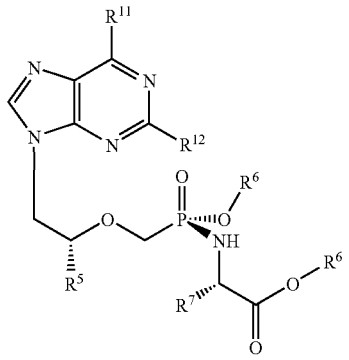
(Continued)

Primary Examiner—Jon Weber
Assistant Examiner—Kailash Srivastava
(74) *Attorney, Agent, or Firm*—Max D. Hensley

(57) **ABSTRACT**

A novel method has led to the identification of novel mixed ester-amidates of PMPA for retroviral or hepadnaviral therapy, including compounds of structure (5a)

(5a)



having substituent groups as defined herein. Compositions of these novel compounds in pharmaceutically acceptable excipients and their use in therapy and prophylaxis are provided.

13 Claims, 3 Drawing Sheets

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Figure 1. HPLC/C-14 Traces of PBMC Extracts from Human Blood Incubated for 1 h at 37°C with TDF, GS-7340 or PMPA.

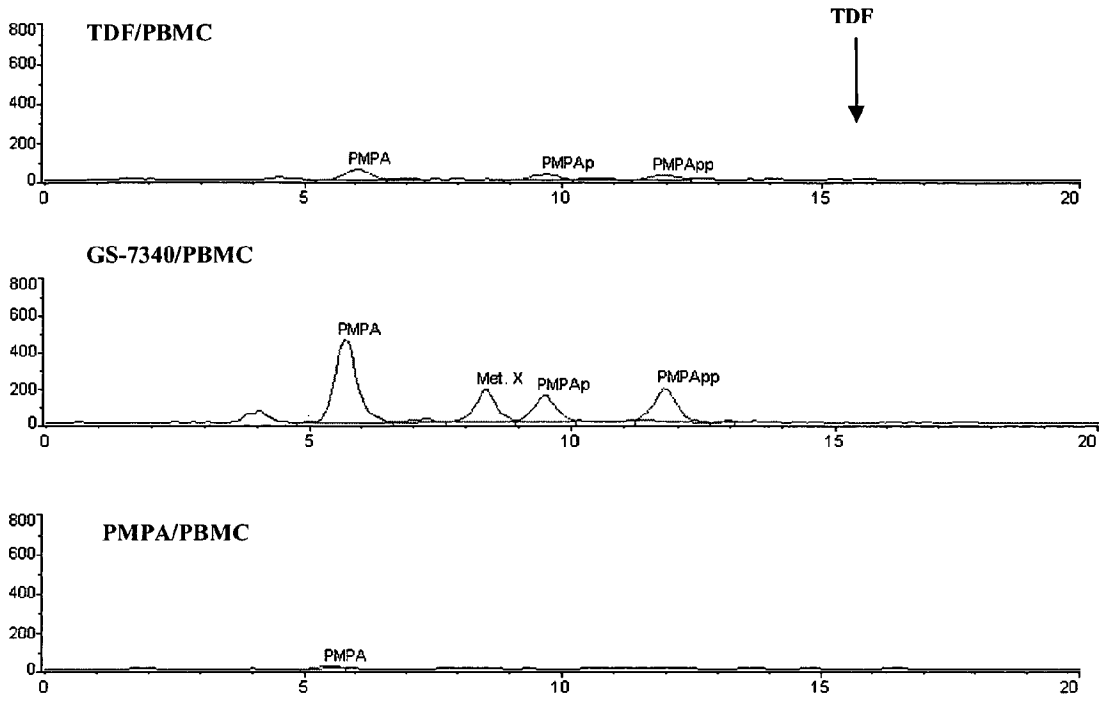


Figure 2. PMPA and Prodrug Concentration in Plasma and PBMCs Following Oral Administration of GS 7340-2 to Dogs at 10 mg-eq/kg.

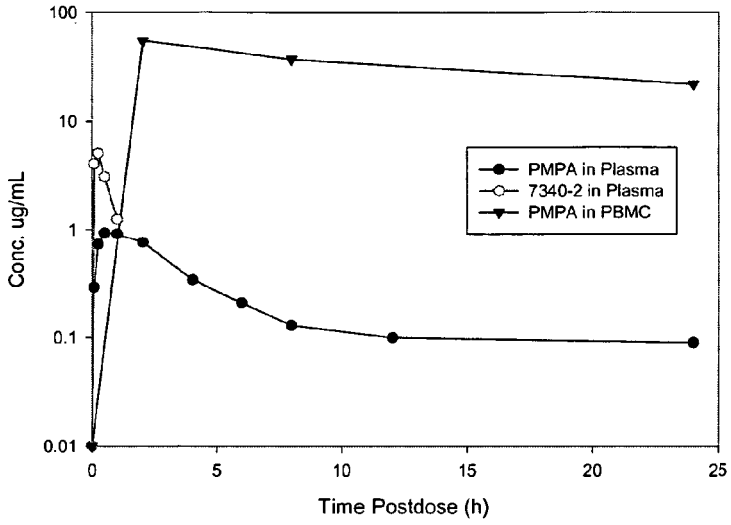
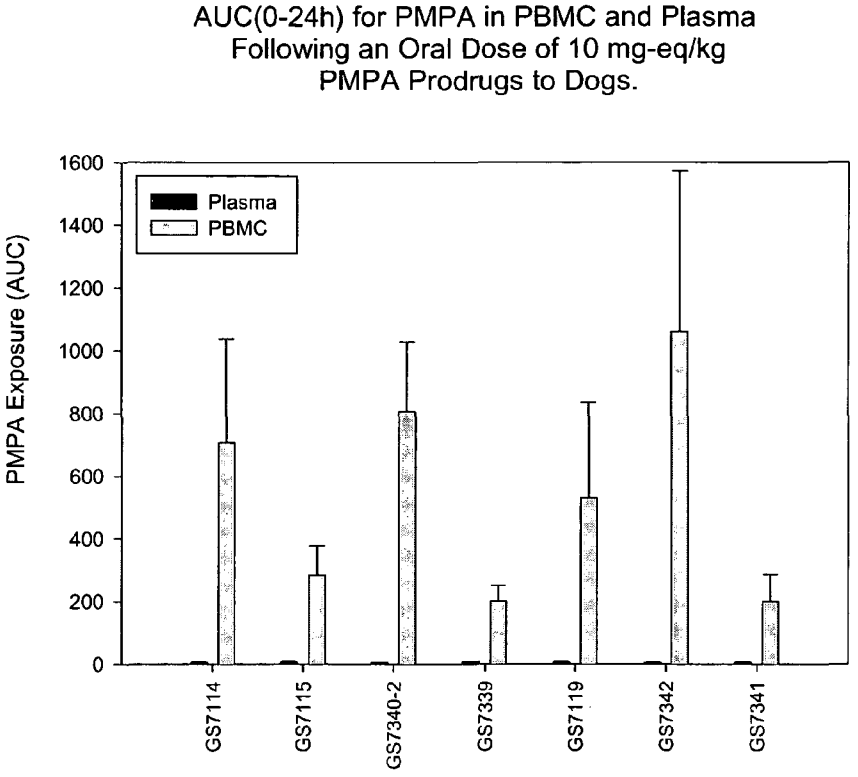


Figure 3. Depicts Tenofovir Exposure in PBMCs and Plasma Upon Administration of 10 mg-eq/kg in dogs



PRODRUGS OF PHOSPHONATE NUCLEOTIDE ANALOGUES

This non-provisional application is a continuation application of application Ser. No. 10/354,207, filed Jan. 28, 2003, now abandoned, which is a continuation application of application Ser. No. 09/909,560, filed Jul. 20, 2001, now abandoned, which is a regular utility application of provisional application 60/220,021, filed Jul. 21, 2000, now abandoned, all of which are incorporated herein by reference.

This application relates to prodrugs of methoxyphosphonate nucleotide analogues. In particular it relates to improved methods for making and identifying such prodrugs.

Many methoxyphosphonate nucleotide analogues are known. In general, such compounds have the structure A-$OCH_2P(O)(OR)_2$ where A is the residue of a nucleoside analogue and R independently is hydrogen or various protecting or prodrug functionalities. See U.S. Pat. Nos. 5,663,159, 5,977,061 and 5,798,340, Oliyai et al, "Pharmaceutical Research" 16(11):1687-1693 (1999), Stella et al., "J. Med. Chem." 23(12):1275-1282 (1980), Aarons, L., Boddy, A. and Petrak, K. (1989) *Novel Drug Delivery and Its Therapeutic Application* (Prescott, L. F. and Nimmo, W. S., ed.), pp. 121-126; Bundgaard, H. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 70-74 and 79-92; Banerjee, P. K. and Amidon, G. L. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 118-121; Notari, R. E. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 135-156; Stella, V. J. and Himmelstein, K. J. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 177-198; Jones, G. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 199-241; Connors, T. A. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 291-316. All literature and patent citations herein are expressly incorporated by reference.

SUMMARY OF THE INVENTION

Prodrugs of methoxyphosphonate nucleotide analogues intended for antiviral or antitumor therapy, while known, traditionally have been selected for their systemic effect. For example, such prodrugs have been selected for enhanced bioavailability, i.e., ability to be absorbed from the gastrointestinal tract and converted rapidly to parent drug to ensure that the parent drug is available to all tissues. However, applicants now have found that it is possible to select prodrugs that become enriched at therapeutic sites, as illustrated by the studies described herein where the analogues are enriched at localized focal sites of HIV infection. The objective of this invention is, among other advantages, to produce less toxicity to bystander tissues and greater potency of the parental drug in tissues which are the targets of therapy with the parent methoxyphosphonate nucleotide analogue.

Accordingly, pursuant to these observations, a screening method is provided for identifying a methoxyphosphonate nucleotide analogue prodrug conferring enhanced activity in a target tissue comprising:

(a) providing at least one of said prodrugs;

(b) selecting at least one therapeutic target tissue and at least one non-target tissue;

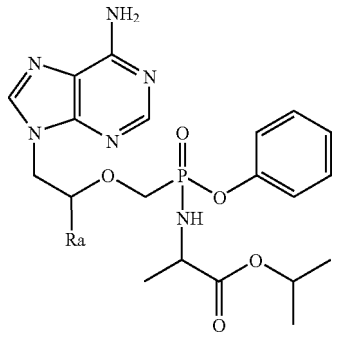
(c) administering the prodrug to the target tissue and to said at least one non-target tissue; and

(d) determining the relative antiviral activity conferred by the prodrug in the tissues in step (c).

In preferred embodiments, the target tissue are sites where HIV is actively replicated and/or which serve as an HIV reservoir, and the non-target tissue is an intact animal. Unexpectedly, we found that selecting lymphoid tissue as the target tissue for the practice of this method for HIV led to identification of prodrugs that enhance the delivery of active drug to such tissues.

A preferred compound of this invention, which has been identified by this method has the structure (1),

(1)

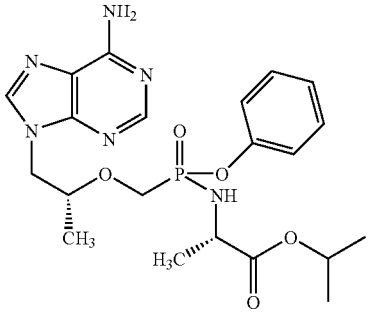


where Ra is H or methyl,

and chirally enriched compositions thereof, salts, their free base and solvates thereof.

A preferred compound of this invention has the structure (2)

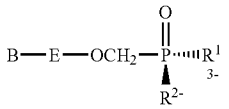
(2)



and its enriched diasteromers, salts, free base and solvates.

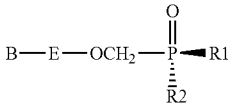
In addition, we unexpectedly found that the chirality of substituents on the phosphorous atom and/or the amidate substituent are influential in the enrichment observed in the practice of this invention. Thus, in another embodiment of this invention, we provide diastereomerically enriched compounds of this invention having the structure (3)

(3)



which are substantially free of the diastereomer (4)

(4)



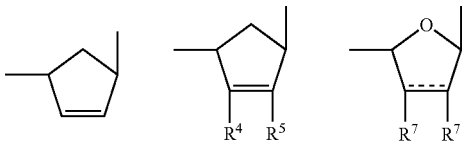
wherein

R^1 is an oxyester which is hydrolyzable in vivo, or hydroxyl;

B is a heterocyclic base;

R^2 is hydroxyl, or the residue of an amino acid bonded to the P atom through an amino group of the amino acid and having each carboxy substituent of the amino acid optionally esterified, but not both of R^1 and R^2 are hydroxyl;

E is —$(CH_2)_2$—, —$CH(CH_3)CH_2$—, —$CH(CH_2F)CH_2$—, —$CH(CH_2OH)CH_2$—, —$CH(CH{=}CH_2)CH_2$—, —$CH(C{\equiv}CH)CH_2$—, —$CH(CH_2N_3)CH_2$—,



—$CH(R^6)OCH(R^{6'})$—, —$CH(R^9)CH_2O$— or —$CH(R^8)O$—, wherein the right hand bond is linked to the heterocyclic base;

the broken line represents an optional double bond;

R^4 and R^5 are independently hydrogen, hydroxy, halo, amino or a substituent having 1-5 carbon atoms selected from acyloxy, alkyoxy, alkylthio, alkylamino and dialkylamino;

R^6 and $R^{6'}$ are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_2-C_7 alkanoyl;

R^7 is independently H, C_1-C_6 alkyl, or are taken together to form —O— or —CH_2—;

R^8 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl or C_1-C_6 haloalkyl; and

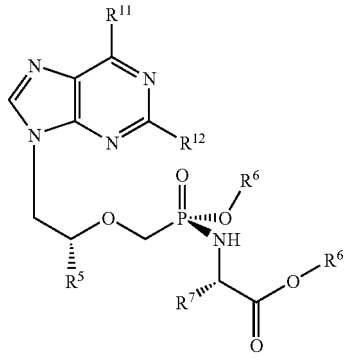
R^9 is H, hydroxymethyl or acyloxymethyl;

and their salts, free base, and solvates.

The diastereomers of structure (3) are designated the (5) isomers at the phosphorus chiral center.

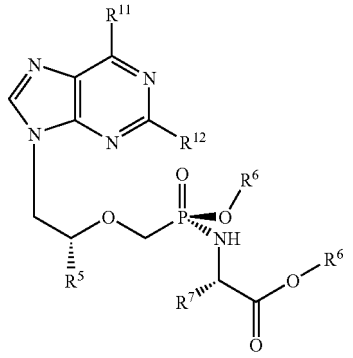
Preferred embodiments of this invention are the diastereomerically enriched compounds having the structure (5a)

(5a)



which is substantially free of diastereomer (5b)

(5b)



wherein

R^5 is methyl or hydrogen;

R^6 independently is H, alkyl, alkenyl, alkynyl, aryl or arylalkyl, or R^6 independently is alkyl, alkenyl, alkynyl, aryl or arylalkyl which is substituted with from 1 to 3 substituents selected from alkylamino, alkylaminoalkyl, dialkylaminoalkyl, dialkylamino, hydroxyl, oxo, halo, amino, alkylthio, alkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylalkoxyalkyl, haloalkyl, nitro, nitroalkyl, azido, azidoalkyl, alkylacyl, alkylacylalkyl, carboxyl, or alkylacylamino;

R^7 is the side chain of any naturally-occurring or pharmaceutically acceptable amino acid and which, if the side chain comprises carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group;

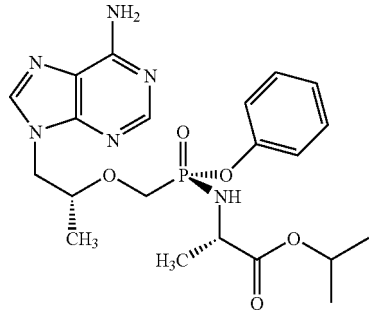
R^{11} is amino, alkylamino, oxo, or dialkylamino; and

R^{12} is amino or H;

and its salts, tautomers, free base and solvates.

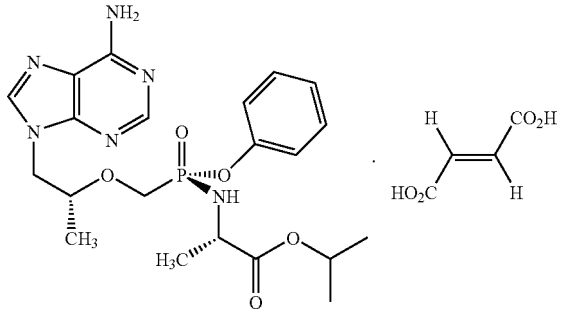
A preferred embodiment of this invention is the compound of structure (6), 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine, also designated herein GS-7340

(6)



Another preferred embodiment of this invention is the fumarate salt of structure (5) (structure (7)),9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine fumarate (1:1), also designated herein GS-7340-2

(7)



The compounds of structures (1)-(7) optionally are formulated into compositions containing pharmaceutically acceptable excipients. Such compositions are used in effective doses in the therapy or prophylaxis of viral (particularly HIV or hepadnaviral) infections.

In a further embodiment, a method is provided for the facile manufacture of 9-[2-(phosphonomethoxy)propyl]adenine (hereinafter "PMPA" or 9-[2-(phosphonomethoxy)ethyl] adenine (hereinafter "PMEA") using magnesium alkoxide, which comprises combining 9-(2-hydroxypropyl)adenine or 9-(2-hydroxyethyl)adenine, protected p-toluenesulfonyloxymethylphosphonate and magnesium alkoxide, and recovering PMPA or PMEA, respectively.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows HPLC/C-14 traces of PBMC extracts from human blood incubated for 1 h at 37° C. with TDF, GS-7340 and PMPA.

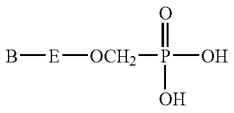
FIG. **2** shows PMPA and Prodrug concentration in plasma and PBMCs following oral administration of GS 7340-2 to Dogs at 10 mg-eq/kg.

FIG. **3** depicts Tenofovir exposure in PBMCs and plasma upon administration of 10 mg-eq/kg in dogs.

DETAILED DESCRIPTION OF THE INVENTION

The methoxyphosphonate nucleotide analogue parent drugs for use in this screening method are compounds having the structure A-$OCH_2P(O)(OH)_2$ wherein A is the residue of a nucleoside analogue. These compounds are known

(7a)



per se and are not part of this invention. More particularly, the parent compounds comprise a heterocyclic base B and an aglycon E, in general having the structure wherein the group B is defined below and group E is defined above. Examples are described in U.S. Pat. Nos. 4,659,825, 4,808,716, 4,724,233, 5,142,051, 5,130,427, 5,650,510, 5,663,159, 5,302,585, 5,476,938, 5,696,263, 5,744,600, 5,688,778, 5,386,030, 5,733,896, 5,352,786, and 5,798,340, and EP 821,690 and 654,037.

The prodrugs for use in the screening method of this invention are covalently modified analogues of the parent methoxyphosphonate nucleotide analogues described in the preceding paragraph. In general, the phosphorus atom of the parent drug is the preferred site for prodrug modification, but other sites are found on the heterocyclic base B or the aglycon E. Many such prodrugs are already known. Primarily, they are esters or amidates of the phosphorus atom, but also include substitutions on the base and aglycon. None of these modifications per se is part of this invention and none are to be considered limiting on the scope of the invention herein.

The phosphorus atom of the methoxyphosphonate nucleotide analogues contains two valences for covalent modification such as amidation or esterification (unless one phosphoryl hydroxyl is esterified to an aglycon E hydroxyl substituent, whereupon only one phosphorus valence is free for substitution). The esters typically are aryloxy. The amidates ordinarily are naturally occurring monoamino acids having free carboxyl group(s) esterified with an alkyl or aryl group, usually phenyl, cycloalkyl, or t-, n- or s- alkyl groups. Suitable prodrugs for use in the screening method of this invention are disclosed for example in U.S. Pat. No. 5,798,340. However, any prodrug which is potentially believed to be capable of being converted in vivo within target tissue cells to the free methoxyphosphonate nucleotide analogue parent drug, e.g., whether by hydrolysis, oxidation, or other covalent transformation resulting from exposure to biological tissues, is suitable for use in the method of this invention. Such prodrugs may not be known at this time but are identified in the future and thus become suitable candidates available for testing in the method of this invention. Since the prodrugs are simply candidates for screening in the methods their structures are not relevant to practicing or enabling the screening method, although of course their structures ultimately are dispositive of whether or not a prodrug will be shown to be selective in the assay.

The pro-moieties bound to the parent drug may be the same or different. However, each prodrug to be used in the screening assay will differ structurally from the other prodrugs to be tested. Distinct, i.e. structurally different, prodrugs generally are selected on the basis of either their stereochemistry or their covalent structure, or these features are varied in combination. Each prodrug tested, however, desirably is structurally and stereochemically substantially pure, else the output of the screening assay will be less useful. It is of course within the scope of this invention to test only a single prodrug in an individual embodiment of the method of this invention, although typically then one would compare the results with prior studies with other prodrugs.

We have found that the stereochemistry of the prodrugs is capable of influencing the enrichment in target tissues. Chiral sites are at the phosphorus atom and are also found in its substituents. For example, amino acid used in preparing amidates may be D or L forms, and the phosphonate esters or the amino acid esters can contain chiral centers as well. Chiral sites also are found on the nucleoside analogue portion of the molecules, but these typically are already dictated by the stereochemistry of the parent drug and will not be varied as part of the screen. For example the R isomer of PMPA is preferred as it is more active than the corresponding S isomer. Typically these diasteromers or enantiomers will be chirally enriched if not pure at each site so that the results of the screen will be more meaningful. As noted, distinctiveness of stereoisomers is conferred by enriching or purifying the stereoisomer (typically this will be a diastereomer rather than an enantiomer in the case of most methoxyphosphonate nucleotide analogues) free of other stereoisomers at the chiral center in question, so that each test compound is substantially homogeneous. By substantially homogeneous or chirally enriched, we mean that the desired stereoisomer constitutes greater than about 60% by weight of the compound, ordinarily greater than about 80% and preferably greater than about 95%.

Novel Screening Method

Once at least one candidate prodrug has been selected, the remaining steps of the screening method of this invention are used to identify a prodrug possessing the required selectivity for the target tissue. Most conveniently the prodrugs are labeled with a detectable group, e.g. radiolabeled, in order to facilitate detection later in tissues or cells. However, a label is not required since other suitable assays for the prodrug or its metabolites (including the parent drug) can also be employed. These assays could include mass spectrometry, HPLC, bioassays or immunoassays for instance. The assay may detect the prodrug and any one or more of its metabolites, but preferably the assay is conducted to detect only the generation of the parent drug. This is based on the assumption (which may not be warranted in all cases) that the degree and rate of conversion of prodrug to antivirally active parent diphosphate is the same across all tissues tested. Otherwise, one can test for the diphosphate.

The target tissue preferably will be lymphoid tissue when screening for prodrugs useful in the treatment of HIV infection. Lymphoid tissue will be known to the artisan and includes CD4 cells, lymphocytes, lymph nodes, macrophages and macrophage-like cells including monocytes such as peripheral blood monocytic cells (PBMCs) and glial cells. Lymphoid tissue also includes non-lymphoid tissues that are enriched in lymphoid tissues or cells, e.g. lung, skin and

spleen. Other targets for other antiviral drugs of course will be the primary sites of replication or latency for the particular virus concerned, e.g., liver for hepatitis and peripheral nerves for HSV. Similarly, target tissues for tumors will in fact be the tumors themselves. These tissues are all well-known to the artisan and would not require undue experimentation to select. When screening for antiviral compounds, target tissue can be infected by the virus.

Non-target tissues or cells also are screened as part of the method herein. Any number or identity of such tissues or cells can be employed in this regard. In general, tissues for which the parent drug is expected to be toxic will be used as non-target tissues. The selection of a non-target tissue is entirely dependent upon the nature of the prodrug and the activity of the parent. For example, non-hepatic tissues would be selected for prodrugs against hepatitis, and untransformed cells of the same tissue as the tumor will suffice for the antitumor-selective prodrug screen.

It should be noted that the method of this invention is distinct from studies typically undertaken to determine oral bioavailability of prodrugs. In oral bioavailability studies, the objective is to identify a prodrug which passes into the systemic circulation substantially converted to parent drug. In the present invention, the objective is to find prodrugs that are not metabolized in the gastrointestinal tract or circulation. Thus, target tissues to be evaluated in the method of this invention generally do not include the small intestines or, if the intestines are included, then the tissues also include additional tissues other than the small intestines.

The target and non-target tissues used in the screening method of this invention typically will be in an intact living animal. Prodrugs containing esters are more desirably tested in dogs, monkeys or other animals than rodents; mice and rat plasma contains high circulating levels of esterases that may produce a misleading result if the desired therapeutic subject is a human or higher mammal.

It is not necessary to practice this method with intact animals. It also is within the scope of this invention to employ perfused organs, in vitro culture of organs (e.g. skin grafts) or cell lines maintained in various forms of cell culture, e.g. roller bottles or zero gravity suspension systems. For example, MT-2 cells can be used as a target tissue for selecting HIV prodrugs. Thus, the term "tissue" shall not be construed to require organized cellular structures, or the structures of tissues as they may be found in nature, although such would be preferred. Rather, the term "tissue" shall be construed to be synonymous with cells of a particular source, origin or differentiation stage.

The target and non-target tissue may in fact be the same tissue, but the tissues will be in different biological status. For example, the method herein could be used to select for prodrugs that confer activity in virally-infected tissue (target tissue) but which remain substantially inactive in virally-uninfected cells (corresponding non-target tissue). The same strategy would be employed to select prophylactic prodrugs, i.e., prodrugs metabolized to antivirally active forms incidental to viral infection but which remain substantially unmetabolized in uninfected cells. Similarly, prodrugs could be screened in transformed cells and the untransformed counterpart tissue. This would be particularly useful in comparative testing to select prodrugs for the treatment of hematological malignancies, e.g. leukemias.

Without being limited by any particular theory of operation, tissue selective prodrugs are thought to be selectively taken up by target cells and/or selectively metabolized within the cell, as compared to other tissues or cells. The unique advantage of the methoxyphosphonate prodrugs herein is that their metabolism to the dianion at physiological pH ensures that they will be unable to diffuse back out of the cell. They therefore remain effective for lengthy periods of time and are maintained at elevated intracellular concentrations, thereby exhibiting increased potency. The mechanisms for enhanced activity in the target tissue are believed to include enhanced uptake by the target cells, enhanced intracellular retention, or both mechanisms working together. However, the manner in which selectivity or enhanced delivery occurs in the target tissue is not important. It also is not important that all of the metabolic conversion of the prodrug to the parent compound occurs within the target tissue. Only the final drug activity-conferring conversion need occur in the target tissue; metabolism in other tissues may provide intermediates finally converted to antiviral forms in the target tissue.

The degree of selectivity or enhanced delivery that is desired will vary with the parent compound and the manner in which it is measured (% dose distribution or parent drug concentration). In general, if the parent drug already possess a generous therapeutic window, a low degree of selectivity may be sufficient for the desired prodrug. On the other hand, toxic compounds may require more extensive screening to identify selective prodrugs. The relative expense of the method of this invention can be reduced by screening only in the target tissue and tissues against which the parent compound is known to be relatively toxic, e.g. for PMEA, which is nephrotoxic at higher doses, the primary focus will be on kidney and lymphoid tissues.

The step of determining the relative antiviral activity of a prodrug in the selected tissues ordinarily is accomplished by assaying target and non-target tissues for the relative presence or activity of a metabolite of the prodrug, which metabolite is known to have, or is converted to, a metabolite having antiviral or antitumor activity.

Thus, typically one would determine the relative amount of the parent drug in the tissues over substantially the same time course in order to identify prodrugs that are preferentially metabolized in the target tissue to an antivirally or antitumor active metabolite or precursor thereof which in the target tissue ultimately produces the active metabolite. In the case of antiviral compounds, the active metabolite is the diphosphate of the phosphonate parent compounds. It is this metabolite that is incorporated into the viral nucleic acid, thereby truncating the elongating nucleic acid strand and halting viral replication. Metabolites of the prodrug can be anabolic metabolites, catabolic metabolites, or the product of anabolism and catabolism together. The manner in which the metabolite is produced is not important in the practice of the method of this invention.

The method of this invention is not limited to assaying a metabolite which per se possesses antiviral or antitumor activity. Instead, one can assay inactive precursors of the active metabolites. Precursors of the antivirally active diphosphate metabolite include the monophosphate of the parent drug, monophosphates of other metabolites of the parent drug (e.g., an intermediate modification of a substituent on the heterocyclic base), the parent itself and metabolites generated by the cell in converting the prodrug to the parent prior to phosphorylation. The precursor structures may vary considerably as they are the result of cellular metabolism. However, this information is already known or could be readily determined by one skilled in the art.

If the prodrug being assayed does not exhibit antitumor or antiviral activity per se then adjustments to the raw assay results may be required. For example, if the intracellular processing of the inactive metabolite to an active metabolite occurs at different rates among the tissues being tested, the

raw assay results with the inactive metabolite would need to be adjusted to take account of the differences among the cell types because the relevant parameter is the generation of activity in the target tissue, not accumulation of inactive metabolites. However, determining the proper adjustments would be within the ordinary skill. Thus, when step (d) of the method herein calls for determining the activity, activity can be either measured directly or extrapolated. It does not mean that the method herein is limited to only assaying intermediates that are active per se. For instance, the absence or decline of the prodrug in the test tissues also could be assayed. Step (d) only requires assessment of the activity conferred by the prodrug as it interacts with the tissue concerned, and this may be based on extrapolation or other indirect measurement.

Step (d) of the method of this invention calls for determining the "relative" activity of the prodrug. It will be understood that this does not require that each and every assay or series of assays necessarily must also contain runs with the selected non-target tissue. On the contrary, it is within the scope of this invention to employ historical controls of the non-target tissue or tissues, or algorithms representing results to be expected from such non-target tissues, in order to provide the benchmark non-target activity.

The results obtained in step (d) are then used optimally to select or identify a prodrug which produces greater antiviral activity in the target tissue than in the non-target tissue. It is this prodrug that is selected for further development.

It will be appreciated that some preassessment of prodrug candidates can be undertaken before the practice of the method of this invention. For example, the prodrug will need to be capable of passing largely unmetabolized through the gastrointestinal tract, it will need to be substantially stable in blood, and it should be able to permeate cells at least to some degree. In most cases it also will need to complete a first pass of the hepatic circulation without substantial metabolism. Such prestudies are optional, and are well-known to those skilled in the art.

The same reasoning as is described above for antiviral activity is applicable to antitumor prodrugs of methoxyphosphonate nucleotide analogues as well. These include, for example, prodrugs of PMEG, the guanyl analogue of PMEA. In this case, cytotoxic phosphonates such as PMEG are worthwhile candidates to pursue as their cytotoxicity in fact confers their antitumor activity.

A compound identified by this novel screening method then can be entered into a traditional preclinical or clinical program to confirm that the desired objectives have been met. Typically, a prodrug is considered to be selective if the activity or concentration of parent drug in the target tissue (% dose distribution) is greater than 2×, and preferably 5×, that of the parent compound in non-target tissue. Alternatively, a prodrug candidate can be compared against a benchmark prodrug. In this case, selectivity is relative rather than absolute. Selective prodrugs will be those resulting in greater than about 10× concentration or activity in the target tissue as compared with the prototype, although the degree of selectivity is a matter of discretion.

Novel Method for Preparation of Starting Materials or Intermediates

Also included herein is an improved method for manufacture of preferred starting materials (parent drugs) of this invention, PMEA and (R)-PMPA. Typically, this method comprises reacting 9-(2-hydroxypropyl)adenine (HPA) or 9-(2-hydroxyethyl)adenine (HEA) with a magnesium alkoxide, thereafter adding the protected aglycon synthon p-toluene-sulfonyloxymethylphosphonate (tosylate) to the reaction mixture, and recovering PMPA or PMEA, respectively.

Preferably, HPA is the enriched or isolated R enantiomer. If a chiral HPA mixture is used, R-PMPA can be isolated from the chiral PMPA mixture after the synthesis is completed.

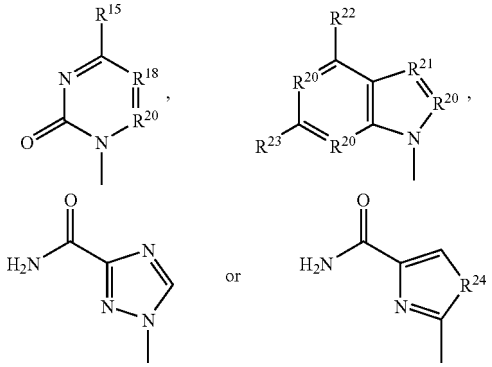
Typically the tosylate is protected by lower alkyl groups, but other suitable groups will be apparent to the artisan. It may be convenient to employ the tosylate presubstituted with the prodrug phosphonate substituents which are capable of acting as protecting groups in the tosylation reaction, thereby allowing one to bypass the deprotection step and directly recover prodrug or an intermediate therefore.

The alkyl group of the magnesium alkoxide is not critical and can be any C_1-C_6 branched or normal alkyl, but is preferably t-butyl (for PMPA) or isopropyl (for PMEA). The reaction conditions also are not critical, but preferably comprise heating the reaction mixture at about 70-75° C. with stirring or other moderate agitation.

If there is no interest in retaining the phosphonate substituents, the product is deprotected (usually with bromotrimethylsilane where the tosylate protecting group is alkyl), and the product then recovered by crystallization or other conventional method as will be apparent to the artisan.

Heterocyclic Base

In the compounds of this invention depicted in structures (3) and (4), the heterocyclic base B is selected from the structures



wherein

R^{15} is H, OH, F, Cl, Br, I, OR^{16}, SH, SR^{16}, NH_2, or NHR^{17};

R^{16} is C_1-C_6 alkyl or C_2-C_6 alkenyl including —CH_3, —CH_2CH_3, —$CH_2C{\equiv}CH$, —$CH_2CH{=}CH_2$ and —C_3H_7;

R^{17} is C_1-C_6 alkyl or C_2-C_6 alkenyl including —CH_3, —CH_2CH_3, —$CH_2C{\equiv}CH$, —$CH_2CH{=}CH_2$, and —C_3H_7;

R^{18} is N, CF, CCl, CBr, CI, CR^{19}, CSR^{19}, or COR^{19};

R^{19} is H, C_1-C_9 alkyl, C_2-C_9 alkenyl, C_2-C_9 alkynyl, C_1-C_9 alkyl-C_1-C_9 alkoxy, or C_7-C_9 aryl-alkyl unsubstituted or substituted by OH, F, Cl, Br or I, R^{19} therefore including —CH_3, —CH_2CH_3, —$CHCH_2$, —CHCHBr, —CH_2CH_2Cl, —CH_2CH_2F, —CH_2CCH, —CH_2CHCH_2, —C_3H_7, —CH_2OH, —CH_2OCH_3, —$CH_2OC_2H_5$, —CH_2OCCH, —$CH_2OCH_2CHCH_2$, —$CH_2C_3H_7$, —CH_2CH_2OH, —$CH_2CH_2OCH_3$, —$CH_2CH_2OC_2H_5$, —CH_2CH_2OCCH, —$CH_2CH_2OCH_2CHCH_2$, and —$CH_2CH_2OC_3H_7$;

R^{20} is N or CH;

R^{21} is N, CH, CCN, CCF_3, $CC{\equiv}CH$ or $CC(O)NH_2$;

R^{22} is H, OH, NH_2, SH, SCH_3, SCH_2CH_3, $SCH_2C{\equiv}CH$, $SCH_2CH{=}CH_2$, SC_3H_7, $NH(CH_3)$, $N(CH_3)_2$, $NH(CH_2CH_3)$, $N(CH_2CH_3)_2$, $NH(CH_2C{\equiv}CH)$, $NH(CH_2CHCH_2)$, $NH(C_3H_7)$, halogen (F, Cl, Br or I) or X wherein X is $—(CH_2)_m(O)_n(CH_2)_mN(R^{10})_2$ wherein each m is independently 0-2, n is 0-1, and

R^{10} independently is H,

C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_6-C_{15} arylalkynyl, C_2-C_{15} alkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroaralkyl, C_5-C_6 aryl, C_2-C_6 het-

erocycloalkyl, C_2-C_{15} alkyl, C_3-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_3-C_{15} alkynyl, C_7-C_{15} arylalkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroalkyl or C_3-C_6 heterocycloalkyl wherein methylene in the alkyl moiety not adjacent to N^6 has been replaced by —O—,

optionally both R^{10} are joined together with N to form a saturated or unsaturated C_2-C_5 heterocycle containing one or two N heteroatoms and optionally an additional O or S heteroatom,

or one of the foregoing R^{10} groups which is substituted with 1 to 3 halo, CN or N_3; but optionally at least one R^{10} group is not H;

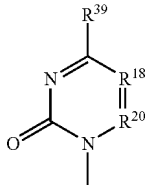
R^{23} is H, OH, F, Cl, Br, I, SCH_3, SCH_2CH_3, $SCH_2C{\equiv}CH$, SCH_2CHCH_2, SC_3H_7, OR^{16}, NH_2, NHR^{17} or R_{22}; and

R^{24} is O, S or Se.

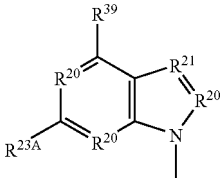
B also includes both protected and unprotected heterocyclic bases, particularly purine and pyrimidine bases. Protecting groups for exocyclic amines and other labile groups are known (Greene et al. "Protective Groups in Organic Synthesis") and include N-benzoyl, isobutyryl, 4,4'-dimethoxytrityl (DMT) and the like. The selection of protecting group will be apparent to the ordinary artisan and will depend upon the nature of the labile group and the chemistry which the protecting group is expected to encounter, e.g. acidic, basic, oxidative, reductive or other conditions. Exemplary protected species are N^4-benzoylcytosine, N^6-benzoyladenine, N^2-isobutyrylguanine and the like.

Protected bases have the formulas Xa.1, XIa.1, XIb.1, XIIa.1 or XIIIa.1

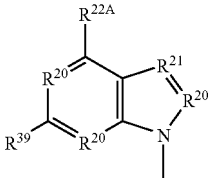
(Xa.1)



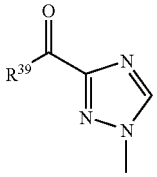
(XIa.1)



(XIb.1)



(XIIa.1)



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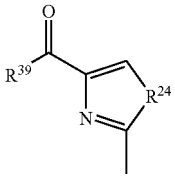
(XIIIa.1)



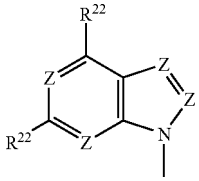
wherein R^{18}, R^{20}, R^{21}, R^{24} have the meanings previously defined; R^{22A} is R^{39} or R^{22} provided that R^{22} is not NH_2; R^{23A} is R^{39} or R^{23} provided that R^{23} is not NH_2; R^{39} is NHR^{40}, $NHC(O)R^{36}$ or $CR^{41}N(R^{38})_2$ wherein R^{36} is C_1-C_{19} alkyl, C_1-C_{19} alkenyl, C_3-C_{10} aryl, adamantoyl, alkylanyl, or C_3-C_{10} aryl substituted with 1 or 2 atoms or groups selected from halogen, methyl, ethyl, methoxy, ethoxy, hydroxy and cyano; R^{38} is C_1-C_{10} alkyl, or both R^{38} together are 1-morpholino, 1-piperidine or 1-pyrrolidine; R^{40} is C_1-C_{1a} alkyl, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, octyl and decanyl; and R^{41} is hydrogen or CH_3.

For bases of structures XIa.1 and XIb.1, if R^{39} is present at R^{22A} or R^{23A}, both R^{39} groups on the same base will generally be the same. Exemplary R^{36} are phenyl, phenyl substituted with one of the foregoing R^{36} aryl substituents, $—C_{10}H_{15}$ (where $C_{10}H_{15}$ is 2-adamantoyl), $—CH_2—C_6H_5$, $—C_6H_5$, $—CH(CH_3)_2$, $—CH_2CH_3$, methyl, butyl, t-butyl, heptanyl, nonanyl, undecanyl, or undecenyl.

Specific bases include hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil and 5-propynyluracil.

Preferably, B is a 9-purinyl residue selected from guanyl, 3-deazaguanyl, 1-deazaguanyl, 8-azaguanyl, 7-deazaguanyl, adenyl, 3-deazaadenyl, 1-dezazadenyl, 8-azaadenyl, 7-deazaadenyl, 2,6-diaminopurinyl, 2-aminopurinyl, 6-chloro-2-aminopurinyl and 6-thio-2-aminopurinyl, or a B' is a 1-pyrimidinyl residue selected from cytosinyl, 5-halocytosinyl, and 5-(C_1-C_3-alkyl)cytosinyl.

Preferred B groups have the formula



wherein

R^{22} independently is halo, oxygen, NH_2, X or H, but optionally at least one R^{22} is X;

X is $—(CH_2)_m(O)_n(CH_2)_mN(R^{10})_2$ wherein m is 0-2, n is 0-1, and

R^{10} independently is H,

C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_6-C_1 arylalkynyl, C_2-C_{15} alkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroaralkyl, C_5-C_6 aryl, C_2-C_6 heterocycloalkyl,

C_2-C_{15} alkyl, C_3-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_3-C_{15} alkynyl, C_7-C_{15} arylalkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroalkyl or C_3-C_6 heterocycloalkyl wherein methylene in the alkyl moiety not adjacent to N^6 has been replaced by —O—,

optionally both R^{10} are joined together with N to form a saturated or unsaturated C_2-C_5 heterocycle containing one or two N heteroatoms and optionally an additional O or S heteroatom,

or one of the foregoing R^{10} groups is substituted with 1 to 3 halo, CN or N_3; but optionally at least one R^{10} group is not H; and

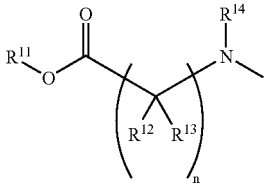
Z is N or CH, provided that the heterocyclic nucleus varies from purine by no more than one Z.

E groups represent the aglycons employed in the methoxyphosphonate nucleotide analogues. Preferably, the E group is $—CH(CH_3)CH_2—$ or $—CH_2CH_2—$. Also, it is preferred that the side groups at chiral centers in the aglycon be substantially solely in the (R) configuration (except for hydroxymethyl, which is the enriched (S) enantiomer).

R^1 is an in vivo hydrolyzable oxyester having the structure $—OR^{35}$ or $—OR^6$ wherein R^{35} is defined in column 64, line 49 of U.S. Pat. No. 5,798,340, herein incorporated by reference, and R^6 is defined above. Preferably R^1 is aryloxy, ordinarily unsubstituted or para-substituted (as defined in R^6) phenoxy.

R^2 is an amino acid residue, optionally provided that any carboxy group linked by less than about 5 atoms to the amidate N is esterified. R^2 typically has the structure

(8)



wherein

n is 1 or 2;

R^{11} is R^6 or H; preferably R^6═C_3-C_9 alkyl; C_3-C_9 alkyl substituted independently with OH, halogen, O or N; C_3-C_6 aryl; C_3-C_6 aryl which is independently substituted with OH, halogen, O or N; or C_3-C_6 arylalkyl which is independently substituted with OH, halogen, O or N;

R^{12} independently is H or C_1-C_9 alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen; C_3-C_6 aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen; or C_3-C_9 aryl-alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen;

R^{13} independently is C(O)—OR^{11}; amino; amide; guanidinyl; imidazolyl; indolyl; sulfoxide; phosphoryl; C_1-C_3 alkylamino; C_1-C_3 alkyldiamino; C_1-C_6 alkenylamino; hydroxy; thiol; C_1-C_3 alkoxy; C_1-C_3 alkthiol; $(CH_2)_nCOOR^{11}$; C_1-C_6 alkyl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; C_2-C_6 alkenyl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; and C_6-C_{12} aryl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; and

R^{14} is H or C_1-C_9 alkyl or C_1-C_9 alkyl independently substituted with OH, halogen, $COOR^{11}$, O or N; C_3-C_6 aryl; C_3-C_6 aryl which is independently substituted with OH, halogen, $COOR^{11}$, O or N; or C_3-C_6 arylalkyl which is independently substituted with OH, halogen, $COOR^{11}$, O or N.

Preferably, R^{11} is C_1-C_6 alkyl, most preferably isopropyl, R^{13} is the side chain of a naturally occurring amino acid, n=1, R^{12} is H and R^{14} is H. In the compound of structure (2), the invention includes metabolites in which the phenoxy and isopropyl esters have been hydrolyzed to —OH. Similarly, the de-esterified enriched phosphonoamidate metabolites of compounds (5a), 5(b) and (6) are included within the scope of this invention.

Aryl and "O" or "N" substitution are defined in column 16, lines 42-58, of U.S. Pat. No. 5,798,340.

Typically, the amino acids are in the natural or l amino acids. Suitable specific examples are set forth in U.S. Pat. No. 5,798,340, for instance Table 4 and col. 8-10 therein.

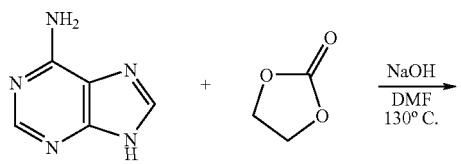
Alkyl as used herein, unless stated to the contrary, is a normal, secondary, tertiary or cyclic hydrocarbon. Unless stated to the contrary alkyl is C_1-C_{12}. Examples are $—CH_3$, $—CH_2CH_3$, $—CH_2CH_2CH_3$, $—CH(CH_3)_2$, $—CH_2CH_2CH_2CH_3$), $—CH_2CH(CH_3)_2$, $—CH(CH_3)CH_2CH_3$, $—C(CH_3)_3$, $—CH_2CH_2CH_2CH_2CH_3$, $—CH(CH_3)CH_2CH_2CH_3$, $—CH(CH_2CH_3)_2$, $—C(CH_3)_2CH_2CH_3$), $—CH(CH_3)CH(CH_3)_2$, $—CH_2CH_2CH(CH_3)_2$), $—CH_2CH(CH_3)CH_2CH_3$, $—CH_2CH_2CH_2CH_2CH_2CH_3$, $—CH(CH_3)CH_2CH_2CH_2CH_3$, $—CH(CH_2CH_3)(CH_2CH_2CH_3)$, $—C(CH_3)_2CH_2CH_2CH_3$, $—CH(CH_3)CH(CH_3)CH_2CH_3$, $—CH(CH_3)CH_2CH(CH_3)_2$, $—C(CH_3)(CH_2CH_3)_2$, $—CH(CH_2CH_3)CH(CH_3)_2$, $—C(CH_3)_2CH(CH_3)_2$, and $—CH(CH_3)C(CH_3)_3$. Alkenyl and alkynyl are defined in the same fashion, but contain at least one double or triple bond, respectively.

Where enol or keto groups are disclosed, the corresponding tautomers are to be construed as taught as well.

The prodrug compounds of this invention are provided in the form of free base or the various salts enumerated in U.S. Pat. No. 5,798,340, and are formulated with pharmaceutically acceptable excipients or solvating diluents for use as pharmaceutical products also as set forth in U.S. Pat. No. 5,798,340. These prodrugs have the antiviral and utilities already established for the parent drugs (see U.S. Pat. No. 5,798,340 and other citations relating to the methoxyphosphonate nucleotide analogues). It will be understood that the diastereomer of structure (4) at least is useful as an intermediate in the chemical production of the parent drug by hydrolysis in vitro, regardless of its relatively unselective character as revealed in the studies herein.

The invention will be more fully understood by reference to the following examples:

EXAMPLE 1a



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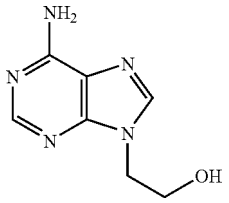
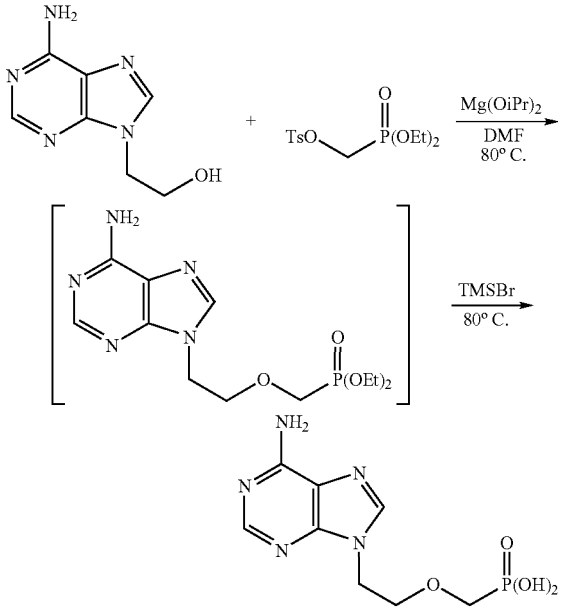
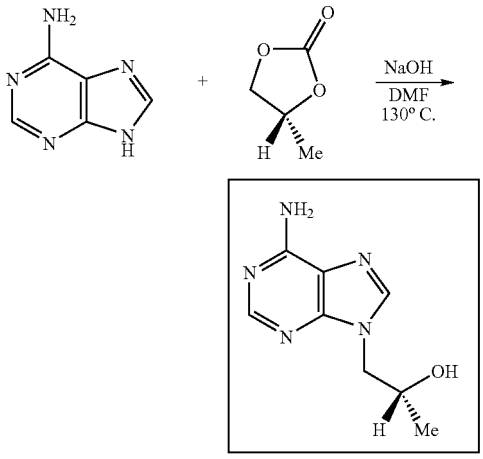


Adenine to PMEA using Magnesium Isopropoxide. To a suspension of adenine (16.8 g, 0.124 mol) in DMF (41.9 ml) was added ethylene carbonate (12.1 g, 0.137 mol) and sodium hydroxide (.100 g, 0.0025 mol). The mixture was heated at 130° C. overnight. The reaction was cooled to below 50° C. and toluene (62.1 ml) was added. The slurry was further cooled to 5° C. for 2 hours, filtered, and rinsed with toluene (2×). The wet solid was dried in vacuo at 65° C. to yield 20.0 g (90%) of 9-(2-hydroxyethyl)adenine as an off-white solid. Mp: 238-240° C.

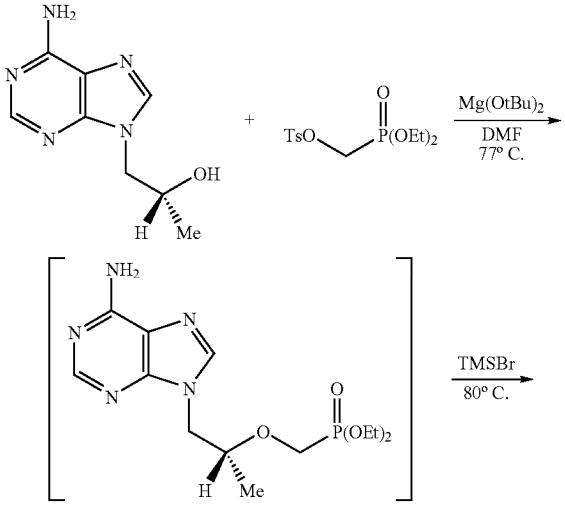


9-(2-Hydroxyethyl)adenine (HEA) (20.0 g, 0.112 mol) was suspended in DMF (125 ml) and heated to 80° C. Magnesium isopropoxide (11.2 g, 0.0784 mol), or alternatively magnesium t-butoxide, was added to the mixture followed by diethyl p-toluenesulfonyloxymethylphosphonate (66.0 g, 0.162 mol) over one hour. The mixture was stirred at 80° C. for 7 hours. 30 ml of volatiles were removed via vacuum distillation and the reaction was recharged with 30 ml of fresh DMF. After cooling to room temperature, bromotrimethylsilane (69.6 g, 0.450 mol) was added and the mixture heated to 80° C. for 6 hours. The reaction was concentrated to yield a thick gum. The gum was dissolved into 360 ml water, extracted with 120 ml dichloromethane, adjusted to pH 3.2 with sodium hydroxide, and the resulting slurry stirred at room temperature overnight. The slurry was cooled to 4° C. for one hour. The solids were isolated by filtration, washed with water (2×), and dried in vacuo at 56° C. to yield 20 g (65.4%) of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) as a white solid. Mp:>200° C. dec. ^{1}H NMR (D_2O) δ 3.49 (t, 2H); 3.94 (t, 2H); 4.39 (t, 2H); 8.13 (s, 1H); 8.22 (s, 1H).

EXAMPLE 1b



Adenine to PMPA using Magnesium t-Butoxide. To a suspension of adenine (40 g, 0.296 mol) in DMF (41.9 ml) was added (R)-propylene carbonate (34.5 g, 0.338 mol) and sodium hydroxide (0.480 g, 0.012 mol). The mixture was heated at 130° C. overnight. The reaction was cooled to 100° C. and toluene (138 ml) was added followed by methanesulfonic acid (4.7 g, 0.049 mol) while maintaining the reaction temperature between 100-110° C. Additional toluene (114 ml) was added to create a homogeneous solution. The solution was cooled to 3° C. over 7 hours and then held at 3° C. for one hour. The resulting solid was isolated by filtration and rinsed with acetone (2×). The wet solid was dried in vacuo at 80° C. to yield 42.6 g (75%) of (R)-9-[2-(hydroxy)propyl] adenine (HPA) as an off-white solid. Mp: 188-190° C.



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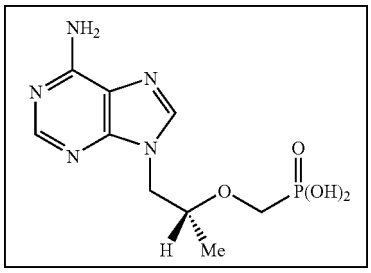


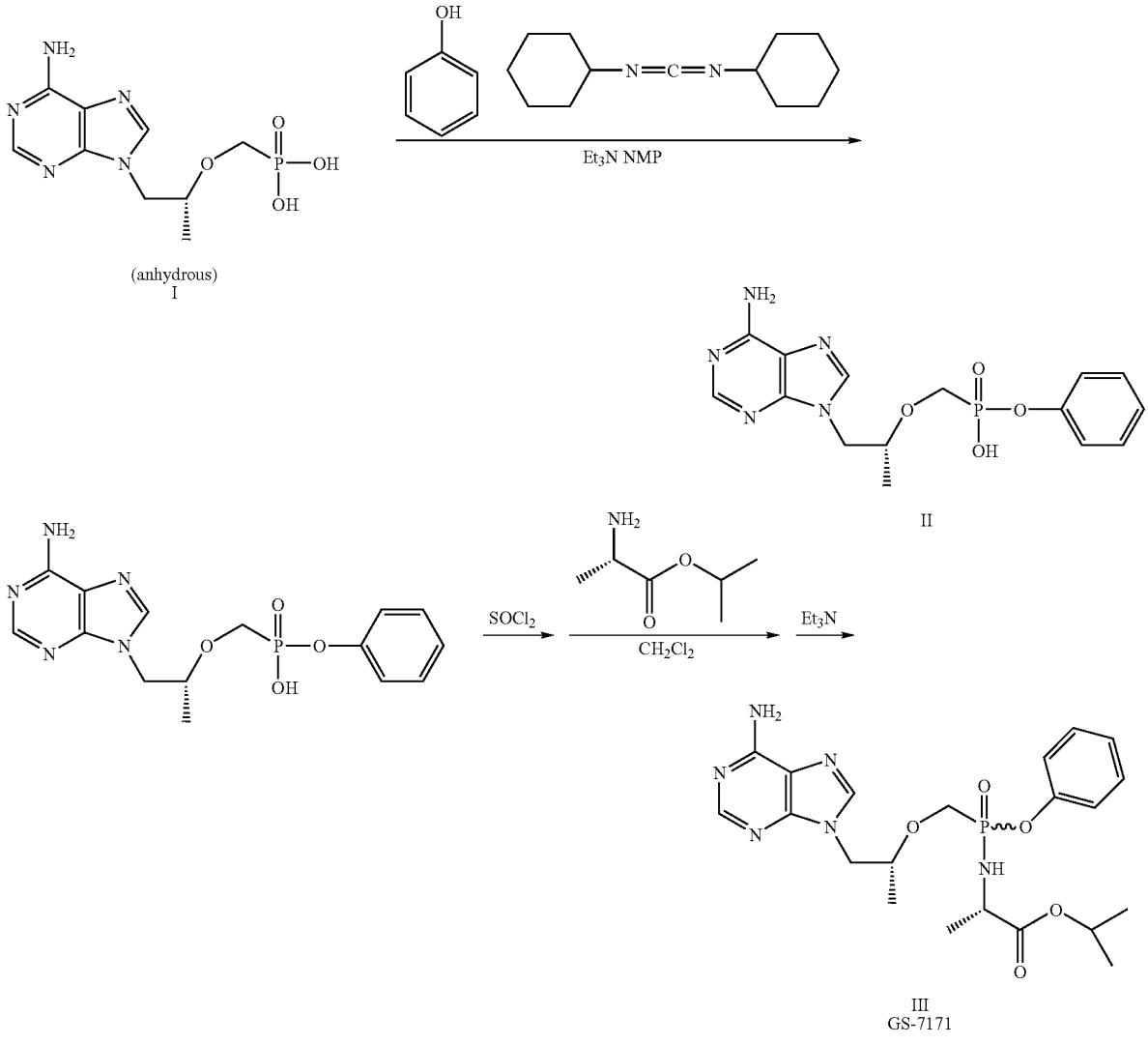
(R)-9-[2-(hydroxy)propyl]adenine (HPA) (20.0 g, 0.104 mol) was suspended in DMF (44.5 ml) and heated to 65° C. Magnesium t-butoxide (14.2 g, 0.083 mol), or alternatively magnesium isopropoxide, was added to the mixture over one hour followed by diethyl p-toluenesulfonyloxymethylphosphonate (66.0 g, 0.205 mol) over two hours while the temperature was kept at 78° C. The mixture was stirred at 75° C. for 4 hours. After cooling to below 50° C., bromotrimethylsilane (73.9 g, 0.478 mol) was added and the mixture heated to 77° C. for 3 hours. When complete, the reaction was heated to 80° C. and volatiles were removed via atmospheric distillation. The residue was dissolved into water (120 ml) at 50° C. and then extracted with ethyl acetate (101 ml). The pH of the aqueous phase was adjusted to pH 1.1 with sodium hydroxide, seeded with authentic (R)-PMPA, and the pH of the aqueous layer was readjusted to pH 2.1 with sodium hydroxide. The resulting slurry was stirred at room temperature overnight. The slurry was cooled to 4° C. for three hours. The solid was isolated by filtration, washed with water (60 ml), and dried in vacuo at 50° C. to yield 18.9 g (63.5%) of crude(R)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA) as an off-white solid.

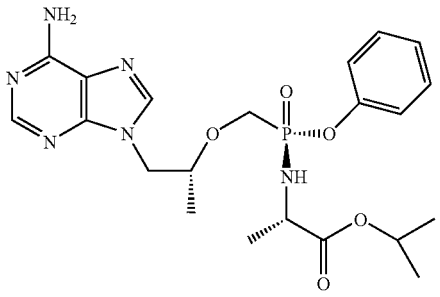
The crude(R)-9-[2-(phosphonomethoxy)propyl]adenine was heated at reflux in water (255 ml) until all solids dissolved. The solution was cooled to room temperature over 4 hours. The resulting slurry was cooled at 4° C. for three hours. The solid was isolated by filtration, washed with water (56 ml) and acetone (56 ml), and dried in vacuo at 50° C. to yield 15.0 g (50.4%) of (R)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA) as a white solid. Mp: 278-280° C.

EXAMPLE 2

Preparation of GS-7171 (III)

Scheme 1





IV
GS-7340

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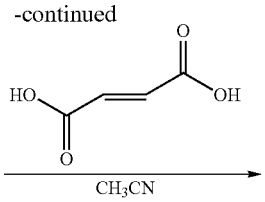
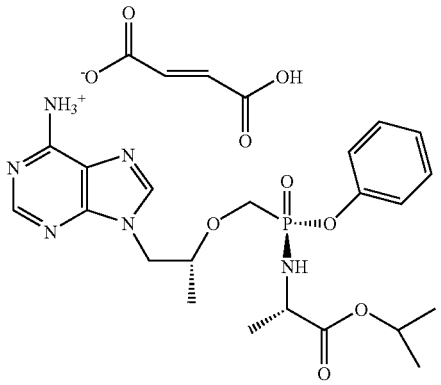




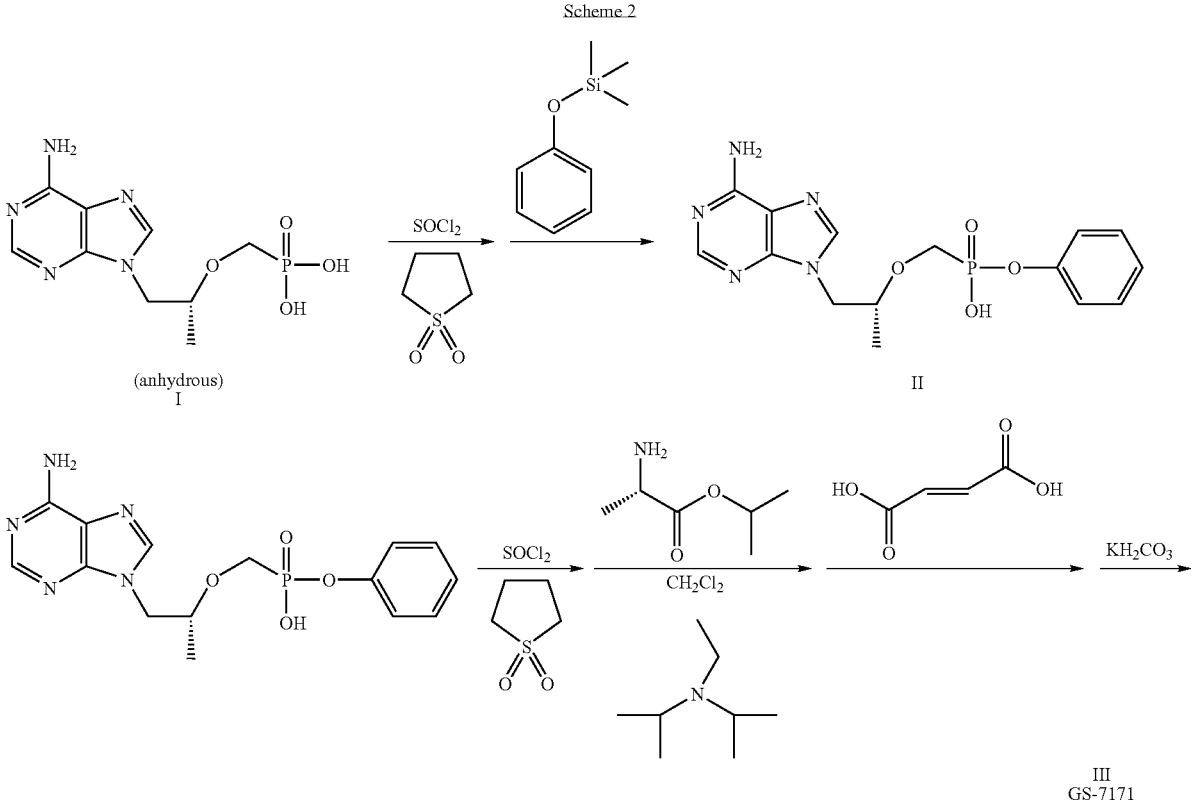
V
GS-7340-02

A glass-lined reactor was charged with anhydrous PMPA, (I) (14.6 kg, 50.8 mol), phenol (9.6 kg, 102 mol), and 1-methyl-2-pyrrolidinone (39 kg). The mixture was heated to 85° C. and-triethylamine (6.3 kg, 62.3 mol) added. A solution of 1,3-dicyclohexylcarbodiimide (17.1 kg, 82.9 mol) in 1-methyl-2-pyrrolidinone (1.6 kg) was then added over 6 hours at 100° C. Heating was continued for 16 hours. The reaction was cooled to 45° C., water (29 kg) added, and cooled to 25° C. Solids were removed from the reaction by filtration and rinsed with water (15.3 kg). The combined filtrate and rinse was concentrated to a tan slurry under reduced pressure, water (24.6 kg) added, and adjusted to pH=11 with NaOH (25% in water). Fines were removed by filtration through diatomaceous earth (2 kg) followed by a water (4.4 kg) rinse. The combined filtrate and rinse was extracted with ethyl acetate (28 kg). The aqueous solution was adjusted to pH=3.1 with HCl (37% in water) (4 kg). Crude II was isolated by filtration and washed with methanol (12.7 kg). The crude II wet cake was slurried in methanol (58 kg). Solids were isolated by filtration, washed with methanol (8.5 kg), and dried under reduced pressure to yield 9.33 kg II as a white powder: ^{1}H NMR (D_2O) δ 1.2 (d, 3H), 3.45 (q, 2H), 3.7 (q, 2H), 4 (m, 2H), 4.2 (q, 2H) 4.35 (dd, 2H), 6.6 (d, 2H), 7 (t, 1H), 7.15 (t, 2H), 8.15 (s, 1H), 8.2 (s, 1H); ^{31}P NMR (D_2O) δ 15.0 (decoupled).

GS-7171 (III). (Scheme 1) A glass-lined reactor was charged with monophenyl PMPA, (II), (9.12 kg, 25.1 mol) and acetonitrile (30.7 kg). Thionyl chloride (6.57 kg, 56.7 mol) was added below 50° C. The mixture was heated at 75° C. until solids dissolved. Reaction temperature was increased to 80° C. and volatiles (11.4 kg) collected by atmospheric distillation under nitrogen. The pot residue was cooled to 25° C., dichloromethane (41 kg) added, and cooled to −29° C. A solution of (L)-alanine isopropyl ester (7.1 kg, 54.4 mol) in dichloromethane (36 kg) was added over 60 minutes at −18° C. followed by triethylamine (7.66 kg, 75.7 mol) over 30 minutes at −18 to −11° C. The reaction mixture was warmed to room temperature and washed five times with sodium dihydrogenphosphate solution (10% in water, 15.7 kg each wash). The organic solution was dried with anhydrous sodium sulfate (18.2 kg), filtered, rinsed with dichloromethane (28 kg), and concentrated to an oil under reduced pressure. Acetone (20 kg) was charged to the oil and the mixture concentrated under reduced pressure. Acetone (18.8 kg) was charged to the resulting oil. Half the product solution was purified by chromatography over a 38×38 cm bed of 22 kg silica gel 60, 230 to 400 mesh. The column was eluted with 480 kg acetone. The purification was repeated on the second half of the oil using fresh silica gel and acetone. Clean product bearing fractions were concentrated under reduced pressure to an oil. Acetonitrile (19.6 kg) was charged to the oil and the mixture concentrated under reduced pressure. Acetonitrile (66.4 kg) was charged and the solution chilled to 0 to −5° C. for 16 hours. Solids were removed by filtration and the filtrate concentrated under reduced pressure to 5.6 kg III as a dark oil: ^{1}H NMR ($CDCl_3$) δ 1.1 (m 12H), 3.7 (m, 1H), 4.0 (m, 5H), 4.2 (m, 1H), 5.0 (m, 1H), 6.2 (s, 2H), 7.05 (m, 5H), 8.0 (s, 1H), 8.25 (d, 1H); ^{31}P NMR ($CDCl_3$) δ 21.0, 22.5 (decoupled).

Alternate Method for GS-7171(III)

Scheme 2



Monophenyl PMPA (II). A round-bottom flask with reflux condenser and nitrogen inlet was placed in a 70° C. oil bath. The flask was charged with anhydrous PMPA (I) (19.2 g, 67 mmol), N,N-dimethylformamide (0.29 g, 3.3 mmol), and tetramethylene sulfone (40 mL). Thionyl chloride (14.2 g, 119 mmol) was added over 4 hours. Heating was increased to 100° C. over the same time. A homogeneous solution resulted. Phenoxytrimethylsilane (11.7 g, 70 mmol) was added to the solution over 5 minutes. Heating in the 100° C. oil bath continued for two hours more. The reaction was poured into rapidly stirring acetone (400 mL) with cooling at 0° C. Solids were isolated by filtration, dried under reduced pressure, and dissolved in methanol (75 mL). The solution pH was adjusted to 3.0 with potassium hydroxide solution (45% aq.) with cooling in ice/water. The resulting solids were isolated by filtration, rinsed with methanol, and dried under reduced pressure to 20.4 g II (Scheme 2) as a white powder.

GS-7171 (III). Monophenyl PMPA (II) (3 g, 8.3 mmol), tetramethylene sulfone (5 mL), and N,N-dimethylformamide (1 drop) were combined in a round bottom flask in a 40° C. oil bath. Thionyl chloride (1.96 g, 16.5 mmol) was added. After 20 minutes the clear solution was removed from heat, diluted with dichloromethane (10 ml), and added to a solution of (L)-alanine isopropyl ester (5 g, 33 mmol) and diisopropylethylamine (5.33 g, 41 mmol) in dichloromethane (20 mL) at −10° C. The reaction mixture was warmed to room temperature and washed three times with sodium dihydrogenphosphate solution (10% aq., 10 mL each wash). The organic solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to a oil. The oil was combined with fumaric acid (0.77 g, 6.6 mmol) and acetonitrile (40 mL) and heated to reflux to give a homogeneous solution. The solution was cooled in an ice bath and solids isolated by filtration. The solid GS-7171 fumarate salt was dried under reduced pressure to 3.7 g. The salt (3.16 g, 5.3 mmol) was suspended in dichloromethane (30 mL) and stirred with potassium carbonate solution (5 mL, 2.5 M in water) until the solid dissolved. The organic layer was isolated, then washed with water (5 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 2.4 g III as a tan foam.

EXAMPLE 3

Diastereomer Separation by Batch Elution Chromatography

The diastereomers of GS-7171 (III) were resolved by batch elution chromatography using a commercially available Chiralpak AS, 20 μm, 21×250 mm semi-preparative HPLC column with a Chiralpak AS, 20 μm, 21×50 mm guard column. Chiralpak® AS is a proprietary packing material manufactured by Diacel and sold in North America by Chiral Technologies, Inc. (U.S. Pat. Nos. 5,202,433, RE 35,919, 5,434,298, 5,434,299 and 5,498,752). Chiralpak AS is a chiral stationary phase (CSP) comprised of amylosetris[(S)-α-methylbenzyl carbamate] coated onto a silica gel support.

The GS-7171 diastereomeric mixture was dissolved in mobile phase, and approximately 1 g aliquots of GS-7171 were pumped onto the chromatographic system. The undesired diastereomer, designated GS-7339, was the first major broad (approx. 15 min. duration) peak to elute from the column. When the GS-7339 peak had finished eluting, the mobile phase was immediately switched to 100% methyl alcohol, which caused the desired diastereomer, designated GS-7340 (IV), to elute as a sharp peak from the column with the methyl alcohol solvent front. The methyl alcohol was used to reduce the over-all cycle time. After the first couple of injections, both diastereomers were collected as a single large fractions containing one of the purified diastereomers (>99.0% single diastereomer). The mobile phase solvents were removed in vacuo to yield the purified diastereomer as a friable foam.

About 95% of the starting GS-7171 mass was recovered in the two diastereomer fractions. The GS-7340 fraction comprised about 50% of the total recovered mass.

The chromatographic conditions were as follows:

Mobile Phase (Initial): GS-7171-Acetonitrile: Isopropyl Alcohol (90:10)

(Final): 100% Methyl Alcohol

Flow: 10 mL/minute

Run Time: About 45 minute

Detection: UV at 275 nm

Temperature: Ambient

Elution Profile: GS-7339 (diastereomer B)

:GS-7340 (diastereomer A; (IV))

Diastereomer Separation of GS-7171 by SMB Chromatography

For a general description of simulated moving bed (SMB) chromatography, see Strube et al., "Organic Process Research and Development" 2:305-319 (1998).

GS-7340 (IV). GS-7171 (III), 2.8 kg, was purified by simulated moving bed chromatography over 10 cm by 5 cm beds of packing (Chiral Technologies Inc., 20 micron Chiralpak AS coated on silica gel) (1.2 kg). The columns were eluted with 30% methanol in acetonitrile. Product bearing fractions were concentrated to a solution of IV in acetonitrile (2.48 kg). The solution solidified to a crystalline mass wet with acetonitrile on standing. The crystalline mass was dried under reduced pressure to a tan crystalline powder, 1.301 kg IV, 98.7% diastereomeric purity: mp 117-120° C.; ^{1}H NMR ($CDCl_3$) δ 1.15 (m 12H), 3.7 (t, 1H), 4.0 (m, 5H), 4.2 (dd, 1H), 5.0 (m, 1H), 6.05 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.2 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 21.0 (decoupled).

Diastereomer Separation by C18 RP-HPLC

GS-7171 (III) was chromatographed by reverse phase HPLC to separate the diastereomers using the following summary protocol.

Chromatographic column: Phenomenex Luna™ C18(2), 5 μm, 100 Å pore size, (Phenomenex, Torrance, Calif.), or equivalent

Guard column: Pellicular C18 (Alltech, Deerfield, Ill.), or equivalent

Mobile Phase: A—0.02% (85%) H_3PO_4 in water: acetonitrile (95:5)

B—0.02% (85%) H_3PO_4 in water: acetonitrile (50:50)

Mobile Phase Gradient:

Time	% Mobile Phase A	% Mobile Phase B
0	100	0
5	100	0
7	70	30
32	70	30
40	0	100
50	0	100

Run Time: 50 minutes

Equilibration Delay: 10 min at 100% mobile phase A

Flow Rate: 1.2 mL/min

Temperature: Ambient

Detection: UV at 260 nm

Sample Solution: 20 mM sodium phosphate buffer, pH 6

Retention Times: GS-7339, about 25 minutes

GS-7340, about 27 minutes

Diastereomer Separation by Crystallization

GS-7340 (IV). A solution of GS-7171 (III) in acetonitrile was concentrated to an amber foam (14.9 g) under reduced pressure. The foam was dissolved in acetonitrile (20 mL) and seeded with a crystal of IV. The mixture was stirred overnight, cooled to 5° C., and solids isolated by filtration. The solids were dried to 2.3 g IV as white crystals, 98% diastereomeric purity (^{31}P NMR): ^{1}H NMR ($CDCl_3$) δ 1.15 (m 12H), 3.7 (t, 1H), 3.95 (m, 2H), 4.05 (m, 2H), 4.2 (m, 2H), 5.0 (m, 1H), 6.4 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.2 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 19.5 (decoupled). X-ray crystal analysis of a single crystal selected from this product yielded the following data:

Crystal Color, Habit	colorless, column
Crystal Dimensions	0.25 × 0.12 × 0.08 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 8.352(1) Å b = 15.574(2) Å c = 18.253(2) Å V = 2374.2(5) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.333 g/cm^3
F_{000}	1008.00
μ(MoKα)	1.60 cm^{-1}

EXAMPLE 4

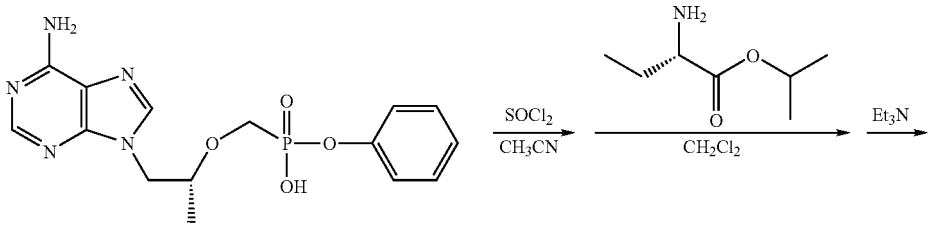
Preparation of Fumarate Salt of GS-7340

GS-7340-02 (V). (Scheme 1) A glass-lined reactor was charged with GS-7340 (IV), (1.294 kg, 2.71 mol), fumaric acid (284 g, 2.44 mol), and acetonitrile (24.6 kg). The mixture was heated to reflux to dissolve the solids, filtered while hot and cooled to 5° C. for 16 hours. The product was isolated by filtration, rinsed with acetonitrile (9.2 kg), and dried to 1329 g (V) as a white powder: mp 119.7-121.1° C.; $[\alpha]_D^{20}$ −41.7° (c 1.0, acetic acid).

EXAMPLE 5

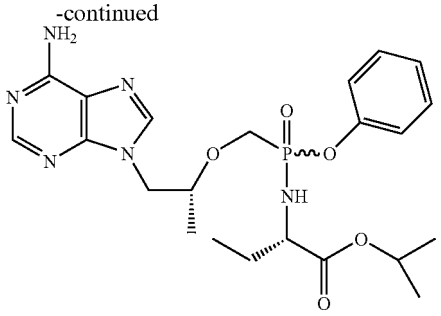
Preparation of GS-7120 (VI)

Scheme 3



II

-continued



VI
GS-7120

A 5 L round bottom flask was charged with monophenyl PMPA, (II), (200 g, 0.55 mol) and acetonitrile (0.629 kg); Thionyl chloride (0.144 kg, 1.21 mol) was added below 27° C. The mixture was heated at 70° C. until solids dissolved. Volatiles (0.45 L) were removed by atmospheric distillation under nitrogen. The pot residue was cooled to 25° C., dichloromethane (1.6 kg) was added and the mixture was cooled to −20° C. A solution of (L)-α aminobutyric acid ethyl ester (0.144 kg, 1.1 mol) in dichloromethane (1.33 kg) was added over 18 minutes at −20 to −10° C. followed by triethylamine (0.17 kg, 1.65 mol) over 15 minutes at −8 to −15° C. The reaction mixture was warmed to room temperature and washed four times with sodium dihydrogenphosphate solution (10% aq., 0.3 L each wash). The organic solution was dried with anhydrous sodium sulfate (0.5 kg) and filtered. The solids were rinsed with dichloromethane (0.6 kg) and the combined filtrate and rinse was concentrated to an oil under reduced pressure. The oil was purified by chromatography over a 15×13 cm bed of 1.2 kg silica gel 60, 230 to 400 mesh. The column was eluted with a gradient of dichloromethane and methanol. Product bearing fractions were concentrated under reduced pressure to afford 211 g VI (Scheme 3) as a tan foam.

EXAMPLE 5a

Diastereomer Separation of GS-7120 by Batch Elution Chromatography

The diastereomeric mixture was purified using the conditions described for GS-7171 in Example 3A except for the following:

Mobile Phase (Initial): GS-7120-Acetonitrile: Isopropyl Alcohol (98:2)

(Final): 100% Methyl Alcohol

Elution Profile: GS-7341 (diastereomer B)

:GS-7342 (diastereomer A)

EXAMPLE 6

Diastereomer Separation of GS-7120 by Crystallization

A 1 L round bottom flask was charged with monophenyl PMPA, (II), (50 g, 0.137 mol) and acetonitrile (0.2 L). Thionyl chloride (0.036 kg, 0.303 mol) was added with a 10° C. exotherm. The mixture was heated to reflux until solids dissolved. Volatiles (0.1 L) were removed by atmospheric distillation under nitrogen. The pot residue was cooled to 25° C., dichloromethane (0.2 kg) was added, and the mixture was cooled to −20° C. A solution of (L)-α aminobutyric acid ethyl ester (0.036 kg, 0.275 mol) in dichloromethane (0.67 kg) was added over 30 minutes at −20 to −8° C. followed by triethylamine (0.042 kg, 0.41 mol) over 10 minutes at up to −6° C. The reaction mixture was warmed to room temperature and washed four times with sodium dihydrogenphosphate solution (10% aq., 0.075 L each wash). The organic solution was dried with anhydrous sodium sulfate (0.1 kg) and filtered. The solids were rinsed with ethyl acetate (0.25 L, and the combined filtrate and rinse was concentrated to an oil under reduced pressure. The oil was diluted with ethyl acetate (0.25 L), seeded, stirred overnight, and chilled to −15° C. The solids were isolated by filtration and dried under reduced pressure to afford 17.7 g of GS-7342 (Table 5) as a tan powder: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.3 (m, 6H), 1.7, (m, 2H), 3.7 (m, 2H), 4.1(m, 6H), 4.4 (dd, 1H), 5.8 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.4 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 21 (decoupled).

EXAMPLE 7

Diastereomer Separation of GS-7097

The diastereomeric mixture was purified using the conditions described for GS-7171 (Example 3A) except for the following:

Mobile Phase (Initial): GS-7120-Acetonitrile: Isopropyl Alcohol (95:5)

(Final): 100% Methyl Alcohol

Elution Profile: GS-7115 (diastereomer B)

:GS-7114 (diastereomer A)

EXAMPLE 8

Alternative Procedure for Preparation of GS-7097

GS-7097: Phenyl PMPA, Ethyl L-Alanyl Amidate. Phenyl PMPA (15.0 g, 41.3 mmol), L-alanine ethyl ester hydrochloride (12.6 g, 83 mmol) and triethylamine (11.5 mL, 83 mmol) were slurried together in 500 mL pyridine under dry N_2. This

suspension was combined with a solution of triphenylphosphine (37.9 g, 145 mmol), Aldrithiol 2 (2,2'-dipyridyl disulfide) (31.8 g, 145 mmol), and 120 mL pyridine. The mixture was heated at an internal temperature of 57° C. for 15 hours. The complete reaction was concentrated under vacuum to a yellow paste, 100 g. The paste was purified by column chromatography over a 25×11 cm bed of 1.1 kg silica gel 60, 230 to 400 mesh. The column was eluted with 8 liters of 2% methanol in dichloromethane followed by a linear gradient over a course of 26 liters eluent up to a final composition of 13% methanol. Clean product bearing fractions were concentrated to yield 12.4 g crude (5), 65% theory. This material was contaminated with about 15% (weight) triethylamine hydrochloride by ^{1}H NMR. The contamination was removed by dissolving the product in 350 mL ethyl acetate, extracting with 20 mL water, drying the organic solution over anhydrous sodium sulfate, and concentrating to yield 11.1 g pure GS-7097 as a white solid, 58% yield. The process also is employed to synthesize the diastereomeric mixture of GS-7003a and GS-7003b (the phenylalanyl amidate) and the mixture GS-7119 and GS-7335 (the glycyl amidate). These diastereomers are separated using a batch elution procedure such as shown in Example 3A, 6 and 7.

EXAMPLE 9

In Vitro Studies of Prodrug Diastereomers

The in vitro anti-HIV-1 activity and cytotoxicity in MT-2 cells and stability in human plasma and MT-2 cell extracts of GS-7340 (freebase) and tenofovir disoproxil fumarate (TDF), are shown in Table 1. GS-7340 shows a 10-fold increase in antiviral activity relative to TDF and a 200-fold increase in plasma stability. This greater plasma stability is expected to result in higher circulating levels of GS-7340 than TDF after oral administration.

TABLE 1

In Vitro Activity and Stability

	HIV-1		Stability T ½ (min)		
	Activity $IC_{50\ \mu M}$	Cytotoxicity $CC_{50\ \mu M}$	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0.005	>40	90.0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	—	—	—

In order to estimate the relative intracellular PMPA resulting from the intracellular metabolism of TDF as compared to that from GS-7340, both prodrugs and PMPA were radiolabeled and spiked into intact human whole blood at equimolar concentrations. After 1 hour, plasma, red blood cells (RBCs) and peripheral blood mononuclear cells (PBMCs) were isolated and analyzed by HPLC with radiometric detection. The results are shown in Table 2.

After 1 hour, GS-7340 results in 10× and 30× the total intracellular concentration of PMPA species in PBMCs as compared to TDF and PMPA, respectively. In plasma after 1 hour, 84% of the radioactivity is due to intact GS-7340, whereas no TDF is detected at 1 hour. Since no intact TDF is detected in plasma, the 10× difference at 1 hour between TDF and GS-7340 is the minimum difference expected in vivo. The HPLC chromatogram for all three compounds in PBMCs is shown in FIG. **1**.

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

		Total C-14 Recovered,	Metabolites (% of Total Peak Area)					
Compound	Matrix	µg-eq	PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

Met. X and Met Y (metabolites X and Y) are shown in Table 5. Lower case "p" designates phosphorylation. These results were obtained after 1 hour in human blood. With increasing time, the in vitro differences are expected to increase, since 84% of GS-7340 is still intact in plasma after one hour. Because intact GS-7340 is present in plasma after oral administration, the relative clinical efficacy should be related to the IC_{50} values seen in vitro.

in Table 3 below, IC_{50} values of tenofovir, TDF, GS-7340, several nucleosides and the protease inhibitor nelfinivir are listed. As shown, nelfinavir and GS-7340 are 2-3 orders of magnitude more potent than all other nucleotides or nucleosides.

TABLE 3

In Vitro Anti-HIV-1 Activities of Antiretroviral Compounds

Compound	IC_{50} (μM)
Adefovir (PMEA)	13.4 ± 4.2[1]
Tenofovir (PMPA)	6.3 ± 3.3[1]
AZT	0.17 ± 0.08[1]
3TC	1.8 ± 0.25[1]
d4T	8 ± 2.5[1]
Nelfinavir	0.006 ± 0.002[1]
TDF	0.05
GS 7340	0.005

[1]A. S. Mulato and J. M. Cherrington, Antiviral Research 36, 91 (1997)

Additional studies of the in vitro cell culture anti-HIV-1 activity and CC_{50} of separated diastereomers of this invention were conducted and the results tabulated below.

TABLE 4

Effect of Diastereomer

Compound	Diastereomer residue	IC_{50} (μM)	Fold change	A/B activity	CC_{50} (μM)
PMPA	—	5	1×	—	6000
Ala-methylester	Mixture 1:1	0.025	200×	20×	80
GS-6957a	A	0.0075	670×		
GS-6957b		0.15	33×		
Phe-methylester	Mixture 1:1	0.03	170×	10×	60
GS-7003a	A	0.01	500×		
GS-7003b	B	0.1	50×		
Gly-ethylester	Mixture 1:1	0.5	10×	20×	
GS-7119	A	0.05	100×		>100
GS-7335	B	1.0	5×		
Ala-isopropyl	Mixture 1:1	0.01	500×	12×	
GS-7340	A	0.005	1,000×		40
GS-7339	B	0.06	83×		>100
ABA-ethyl	Mixture 1:1	0.008	625×	7.5×	>100
GS-7342	A	0.004	1,250×		
GS-7341	B	0.03	170×		
Ala-ethyl	Mixture 1:1	0.02	250×	10×	60
GS-7114	A	0.005	1,000×		
GS-7115	B	0.05	100×		

Assay reference: Arimilli, M N, et al., (1997) Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs. Antiviral Chemistry and Chemotherapy 8(6):557-564.

"Phe-methylester" is the methylphenylalaninyl monoamidate, phenyl monoester of tenofovir; "gly-methylester" is the methylglycyl monoamidate, phenyl monoester of tenofovir.

In each instance above, isomer A is believed to have the same absolute stereochemistry as GS-7340 (S), and isomer B is believed to have the same absolute stereochemistry that of GS-7339.

The in vitro metabolism and stability of separated diastereomers were determined in PLCE, MT-2 extract and human plasma. A biological sample listed below, 80 μL, was transferred into a screw-capped centrifuge tube and incubated at 37° C. for 5 min. A solution containing 0.2 mg/mL of the test compound in a suitable buffer, 20 μL, was added to the biological sample and mixed. The reaction mixture, 20 μL, was immediately sampled and mixed with 60 μL of methanol containing 0.015 mg/mL of 2-hydroxymethylnaphthalene as an internal standard for HPLC analysis. The sample was taken as the time-zero sample. Then, at specific time points, the reaction mixture, 20 μL, was sampled and mixed with 60 μL of methanol containing the internal standard. The mixture thus obtained was centrifuged at 15,000 G for 5 min and the supernatant was analyzed with HPLC under the conditions described below.

The biological samples evaluated are as follows.

(1) PLCE (porcine liver carboxyesterase from Sigma, 160 u/mg protein, 21 mg protein/mL) diluted 20 fold with PBS (phosphated-buffered saline).

(2) MT-2 cell extract was prepared from MT-2 cells according to the published procedure [A. Pompon, I. Lefebvre, J.-L. Imbach, S. Kahn, and D. Farquhar, "Antiviral Chemistry & Chemotherapy", 5:91-98 (1994)] except for using HEPES buffer described below as the medium.

(3) Human plasma (pooled normal human plasma from George King Biomedical Systems, Inc.)

The buffer systems used in the studies are as follows.

In the study for PLCE, the test compound was dissolved in PBS. PBS (phosphate-buffered saline, Sigma) contains 0.01 M phosphate, 0.0027 M potassium chloride, and 0.137 M sodium chloride. pH 7.4 at 37° C.

In the study for MT-2 cell extracts, the test compound was dissolved in HEPES buffer. HEPES buffer contains 0.010 M HEPES, 0.05 M potassium chloride, 0.005 M magnesium chloride, and 0.005 M dl-dithiothreitol. pH 7.4 at 37° C. In the study for human plasma, the test compound was dissolved in TBS. TBS (tris-buffered saline, Sigma) contains 0.05 M Tris, 0.0027 M potassium chloride, and 0.138 M sodium chloride. pH 7.5 at 37° C.

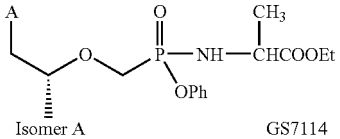
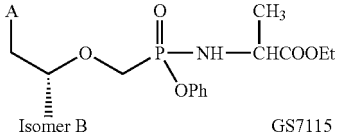
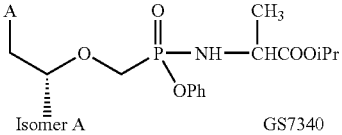
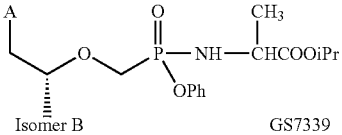
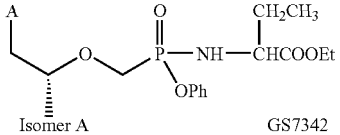
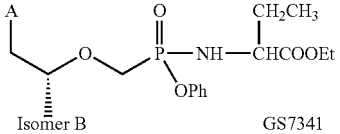
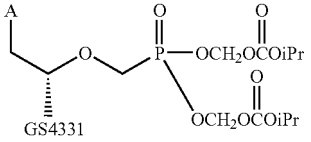
The HPLC analysis was carried out under the following conditions.

Column: Zorbax Rx-C8, 4.6×250 mm, 5μ (MAC-MOD Analytical, Inc. Chadds Ford, Pa.)
Detection: UV at 260 nm
Flow Rate: 1.0 mL/min
Run Time: 30 min
Injection Volume: 20 μL
Column Temperature: Ambient temperature
Mobile Phase A: 50 mM potassium phosphate (pH 6.0)/CH_3CN=95/5 (v/v)
Mobile Phase B: 50 mM Potassium phosphate (pH 6.0)/CH_3CN=50/50 (v/v)
Gradient Run: 0 min 100% Mobile Phase A
25 min 100% Mobile Phase B
30 min 100% Mobile Phase B

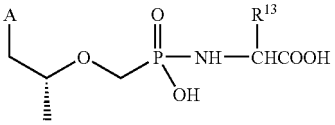
The results are shown below in Table 5 (also including selected IC_{50} data from Table 4).

TABLE 5

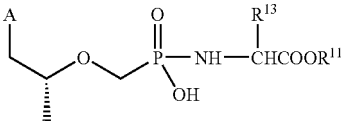
In Vitro Metabolism of Isomers A and B of PMPA monoamidate at 37° C.

No.	PMPA monoamidate structure	HIV IC_{50} (μM)	PLCE hydrolysis rate and product	MT-2 extract hydrolysis rate and product	Human Plasma Stability (HP)
1	 Isomer A GS7114	0.005	t½ = 2.9 min Met. X & PMPA	t½ = 2.9 min Met. X & PMPA	t½= 148 min Met. Y
2	 Isomer B GS7115	0.05	t½ = 8.0 min Met. X & PMPA	t½ = 150.6 min Met. X & PMPA	t½ = 495 min Met. Y
3	 Isomer A GS7340	0.005	t½ = 3.3 min Met. X & PMPA	t½ = 28.3 min Met. X & PMPA	t½ = 90.0 min Met. Y
4	 Isomer B GS7339	0.06	t½ = 10.1 min Met. X & PMPA	t½ > 1000 min	t½ = 231 min Met. Y
5	 Isomer A GS7342	0.004	t½ = 3.9 min Met. X	t½ = 49.2 min Met. X & PMPA	t½ = 103 min Met. Y
6	 Isomer B GS7341	0.03	t½ = 11.3 min Met. X	t½ > 1000 min	t½ = 257 min Met. Y
7	 GS4331	0.05	t½ < 0.14 min MonoPOC PMPA	t½ = 70.7 min monoPOC PMPA	t½ = 0.41 min monoPOC PMPA

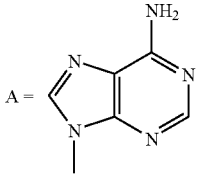
Met. X:



Met. Y:



A =



EXAMPLE 10

Plasma and PBMC Exposures Following Oral Administration Of Prodrug Diastereomers to Beagle Dogs

The pharmacokinetics of GS 7340 were studied in dogs after oral administration of a 10 mg-eq/kg dose.

Formulations. The prodrugs were formulated as solutions in 50 mM citric acid within 0.5 hour prior to dose. All compounds used in the studies were synthesized by Gilead Sciences. The following lots were used:

GSI	Amidate Amino acid	AA Ester	Diastereoisomer	Lot Number
GS-7340-2	Alanine	i-Propyl	Isomer A	1504-187-19
GS-7339	Alanine	i-Propyl	Isomer B	1509-185-31
GS7114	Alanine	Ethyl	Isomer A	1509-181-26
GS7115	Alanine	Ethyl	Isomer B	1509-181-22
GS7119	Glycine	Ethyl	Isomer A	1428-163-28
GS7342	α-Aminobutyric Acid	Ethyl	Isomer A	1509-191-12
GS7341	α-Aminobutyric Acid	Ethyl	Isomer B	1509-191-7

Dose Administration and Sample Collection. The in-life phase of this study was conducted in accordance with the recommendations of the "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health publication 86-23) and was approved by an Institutional Animal Care and Use Committee. Fasted male beagle dogs (10±2 kg) were used for the studies. Each drug was administered as a single dose by oral gavage (1.5-2 ml/kg). The dose was 10 mg-equivalent of PMPA/kg. For PBMCs, blood samples were collected at 0 (pre-dose), 2, 8, and 24 h post-dose. For plasma, blood samples were collected at 0 (pre-dose), 5, 15, and 30 min, and 1, 2, 3, 4, 6, 8, 12 and 24 h post-dose. Blood (1.0 ml) was processed immediately for plasma by centrifugation at 2,000 rpm for 10 min. Plasma samples were frozen and maintained at 70° C. until analyzed.

Peripheral Blood Mononuclear Cell (PBMC) preparation. Whole blood (8 ml) drawn at specified time points was mixed in equal proportion with phosphate buffered saline (PBS), layered onto 15 ml of Ficoll-Paque solution (Pharmacia Biotech,) and centrifuged at 400×g for 40 min. PBMC layer was removed and washed once with PBS. Formed PMBC pellet was reconstituted in 0.5 ml of PBS, cells were resuspended, counted using hemocytometer and maintained at 70° C. until analyzed. The number of cells multiplied by the mean single-cell volume was used in calculation of intracellular concentrations. A reported value of 200 femtoliters/cell was used as the resting PBMC volume (B. L. Robins, R. V. Srinivas, C. Kim, N. Bischofberger, and A. Fridland, Antimicrob. Agents Chemother. 42, 612 (1998).

Determination of PMPA and Prodrugs in plasma and PBMCs. The concentration of PMPA in dog plasma samples was determined by derivatizing PMPA with chloroacetaldehyde to yield a highly fluorescent N^1, N^6-ethenoadenine derivative (L. Naesens, J. Balzarini, and E. De Clercq, Clin. Chem. 38, 480 (1992). Briefly, plasma (100 µl) was mixed with 200 µl acetonitrile to precipitateprotein. Samples were then evaporated to dryness under reduced pressure at room temperature. Dried samples were reconstituted in 200 µl derivatization cocktail (0.34% chloroacetaldehyde in 100 mM sodium acetate, pH 4.5), vortexed, and centrifuged. Supernatant was then transferred to a clean screw-cap tube and incubated at 95° C. for 40 min. Derivatized samples were then evaporated to dryness and reconstituted in 100 µl of water for HPLC analysis.

Before intracellular PMPA could be determined by HPLC, the large amounts of adenine related ribonucleotides present in the PBMC extracts had to be removed by selective oxidation. We used a modified procedure of Tanaka et al (K. Tanaka, A. Yoshioka, S. Tanaka, and Y. Wataya, Anal. Biochem., 139, 35 (1984). Briefly, PBMC samples were mixed 1:2 with methanol and evaporated to dryness under reduced pressure. The dried samples were derivatized as described in the plasma assay. The derivatized samples were mixed with 20 µL of 1M rhamnose and 30 µL of 0.1M sodium periodate and incubated at 37° C. for 5 min. Following incubation, 40 µL of 4M methylamine and 20 µL of 0.5M inosine were added. After incubation at 37° C. for 30 min, samples were evaporated to dryness under reduced pressure and reconstituted in water for HPLC analysis.

No intact prodrug was detected in any PBMC samples. For plasma samples potentially containing intact prodrugs, experiments were performed to verify that no further conversion to PMPA occurred during derivatization. Prodrug standards were added to drug-free plasma and derivatized as described. There were no detectable levels of PMPA present in any of the plasma samples, and the projected % of conversion was less than 1%.

The HPLC system was comprised of a P4000 solvent delivery system with AS3000 autoinjector and F2000 fluorescence detector (Thermo Separation, San Jose, Calif.). The column was an Inertsil ODS-2 column (4.6×150 mm). The mobile phases used were: A, 5% acetonitrile in 25 mM potassium phosphate buffer with 5 mM tetrabutyl ammonium bromide (TBABr), pH 6.0; B, 60% acetonitrile in 25 mM potassium phosphate buffer with 5 mM TBABr, pH 6.0. The flow rate was 2 ml/min and the column temperature was maintained at 35° C. by a column oven. The gradient profile was 90% A/10% B for 10 min for PMPA and 65% A/35% B for 10 min for the prodrug. Detection was by fluorescence with excitation at 236 nm and emission at 420 nm, and the injection volume was 10 µl. Data was acquired and stored by a laboratory data acquisition system (PeakPro, Beckman, Allendale, N.J.).

Pharmacokinetic Calculations. PMPA and prodrug exposures were expressed as areas under concentration curves in plasma or PBMC from zero to 24 hours (AUC). The AUC values were calculated using the trapezoidal rule.

Plasma and PBMC Concentrations. The results of this study is shown in FIGS. **2** and **3**. FIG. **2** shows the time course of GS 7340-2 metabolism summary of plasma and PBMC exposures following oral administration of pure diastereoisomers of the PMPA prodrugs.

The bar graph in FIG. **2** shows the AUC (0-24 h) for tenofovir in dog PBMCs and plasma after administration of PMPA s.c., TDF and amidate ester prodrugs. All of the amidate prodrugs exhibited increases in PBMC exposure. For example, GS 7340 results in a ~21-fold increase in PBMC exposure as compared to PMPA s.c. and TDF; and a 6.25-fold and 1.29-fold decrease in plasma exposure, respectively.

These data establish in vivo that GS 7340 can be delivered orally, minimizes systemic exposure to PMPA and greatly enhances the intracellular concentration of PMPA in the cells primarily responsible for HIV replication.

TABLE 6

PMPA Exposure in PBMC and Plasma from Oral Prodrugs of PMPA in Dogs

		PMPA AUC in Plasma			PMPA AUC in PBMC			Prodrug	PBMC/Plasma
GS#	Moiety	Mean	StDev	N	Mean	StDev	N	in Plasma	Exposure Ratio
GS-7114	Mono-Ala-Et-A	5.8	0.9	2	706	331	5	YES	122
GS-7115	Mono-Ala-Et-B	6.6	1.5	2	284	94	5	YES	43
GS-7340-2	Mono-Ala-iPr-A	5.0	1.1	5	805	222	5	YES	161
GS-7339	Mono-Ala-iPr-A	6.4	1.3	2	200	57	5	YES	31
GS-7119	Mono-Gly-Et-A	6.11	1.86	2	530	304	5	YES	87
GS-7342	Mono-ABA-Et-A	4.6	1.2	2	1060	511	5	YES	230
GS7341	Mono-ABA-Et-B	5.8	1.4	2	199	86	5	YES	34

EXAMPLE 11

Biodistribution of GS-7340

As part of the preclinical characterization of GS-7340, its biodistribution in dogs was determined. The tissue distribution of GS-7340 (isopropyl alaninyl monoamidate, phenyl monoester of tenofovir) was examined following oral administration to beagle dogs. Two male animals were dosed orally with ^{14}C=GS-7340 (8.85 mg-equiv. of PMPA/kg, 33.2 μCi/kg; the 8-carbon of adenine is labeled) in an aqueous solution (50 mM citric acid, pH 2.2). Plasma and peripheral blood mononuclear cells (PBMCs) were obtained over the 24-hr period. Urine and feces were cage collected over 24 hr. At 24 h after the dose, the animals were sacrificed and tissues removed for analysis. Total radioactivity in tissues was determined by oxidation and liquid scintillation counting.

The biodistribution of PMPA after 24 hours after a single oral dose of radiolabelled GS 7340 is shown in Table 4 along with the data from a previous study with TDF (GS-4331). In the case of TDF, the prodrug concentration in the plasma is below the level of assay detection, and the main species observed in plasma is the parent drug. Levels of PMPA in the lymphatic tissues, bone marrow, and skeletal muscle are increased 10-fold after administration of GS-7340.

Accumulation in lymphatic tissues is consistent with the data observed from the PBMC analyses, since these tissues are composed primarily of lymphocytes. Likewise, accumulation in bone marrow is probably due to the high percentage of lymphocytes (70%) in this tissue.

TABLE 7

Excretion and Tissue Distribution of Radiolabelled GS-7340 in Dogs (Mean, N = 2) Following an Oral Dose at 10 mg-eq. PMPA/kg.

	GS-4331		GS-7340		Tissue Conc.
Tissue/Fluid	% Dose	Conc. (ug-eq/g)	% Dose	Conc. (ug-eq/g)	Ratio of GS 7340 to GS-4331
Liver	12.40	38.30	16.45	52.94	1.4
Kidney	4.58	87.90	3.78	80.21	0.9
Lungs	0.03	0.53	0.34	4.33	8.2
Iliac Lymph Nodes	0.00	0.51	0.01	5.42	10.6
Axillary Lymph Nodes	0.00	0.37	0.01	5.54	14.8
Inguinal Lymph Nodes	0.00	0.28	0.00	4.12	15.0
Mesenteric Lymph Nodes	0.00	1.20	0.04	6.88	5.7
Thyroid Gland	0.00	0.30	0.00	4.78	15.8
Pituitary Gland	0.00	0.23	0.00	1.80	7.8
Salivary Gland (L + R)	0.00	0.45	0.03	5.54	12.3
Adrenal Gland	0.00	1.90	0.00	3.47	1.8
Spleen	0.00	0.63	0.17	8.13	12.8
Pancreas	0.00	0.57	0.01	3.51	6.2
Prostate	0.00	0.23	0.00	2.14	9.1
Testes (L + R)	0.02	1.95	0.02	2.01	1.0
Skeletal Muscle	0.00	0.11	0.01	1.12	10.1
Heart	0.03	0.46	0.15	1.97	4.3
Femoral Bone	0.00	0.08	0.00	0.28	3.5
Bone Marrow	0.00	0.20	0.00	2.05	10.2
Skin	0.00	0.13	0.00	0.95	7.2
Abdominal fat	0.00	0.16	0.00	0.90	5.8
Eye (L + R)	0.00	0.06	0.00	0.23	3.7
Brain	0.00	<LOD	0.00	<LOD	n.d.
Cerebrospinal Fluid	0.00	<LOD	0.00	0.00	n.d.
Spinal Cord	0.00	<LOD	0.00	0.04	n.d.
Stomach	0.11	1.92	0.26	2.68	1.4
Jejunum	1.34	3.01	0.79	4.16	1.4
Duodenum	0.49	4.96	0.44	8.77	1.8
Ileum	0.01	0.50	0.16	4.61	9.2
Large Intestine	1.63	5.97	2.65	47.20	7.9
Gall bladder	0.00	3.58	0.04	25.02	7.0

TABLE 7-continued

Excretion and Tissue Distribution of Radiolabelled GS-7340 in Dogs (Mean, N = 2) Following an Oral Dose at 10 mg-eq. PMPA/kg.

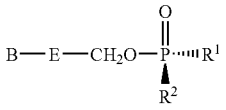
	GS-4331		GS-7340		Tissue Conc.
Tissue/Fluid	% Dose	Conc. (ug-eq/g)	% Dose	Conc. (ug-eq/g)	Ratio of GS 7340 to GS-4331
Bile	0.00	9.63	0.22	40.48	4.2
Feces	40.96	n.d.	0.19	n.d.	n.a.
Total GI Tract Contents	5.61	n.d.	21.64	n.d.	n.a.
Urine	23.72	n.d.	14.73	n.d.	n.a.
Plasma at 24 h	0.00	0.20	0.00	0.20	1.0
Plasma at 0.25 h	n.a.	3.68	n.a.	3.48	0.9
PBMC*	0.00	n.d.	0.00	63.20	n.d.
Whole Blood	0.00	0.85	0.16	0.20	0.2
Total Recovery	81.10		68.96		

Calculated using typical recovery of 15×10^6 cells total, and mean PBMC volume of 0.2 picoliters/cell
n.s. = no sample,
n.a. = not applicable,
n.d. = not determined.

The invention claimed is:

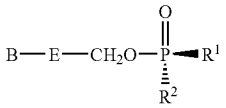
1. A diastereomerically enriched compound having the structure (3)

(3)



which contains less than 40% by weight of the diastereomer (4)

(4)



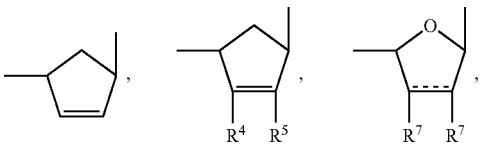
wherein

R^1 is an oxyester which is hydrolyzable in vivo, or hydroxyl;

B is a heterocyclic base;

R^2 is hydroxyl, or the residue of an amino acid bonded to the P atom through an amino group of the amino acid and having each carboxy substituent of the amino acid optionally esterified, but not both of R^1 and R^2 are hydroxyl;

E is $—(CH_2)_2—$, $—CH(CH_3)CH_2—$, $—CH(CH_2F)CH_2—$, $—CH(CH_2OH)CH_2—$, $—CH(CH{=}CH_2)CH_2—$, $—CH(C{\equiv}CH)CH_2—$, $—CH(CH_2N_3)CH_2—$,



$—CH(R^6)OCH(R^6)—$, $—CH(R^9)CH_2O—$ or $—CH(R^8)O—$, wherein the right hand bond is linked to the heterocyclic base;

the broken line represents an optional double bond;

R^4 and R^5 are independently hydrogen, hydroxy, halo, amino or a substituent having 1-5 carbon atoms selected from acyloxy, alkyoxy, alkylthio, alkylamino and dialkylamino;

R^6 and $R^{6'}$ are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_2-C_7 alkanoyl;

R^7 is independently H, C_1-C_6 alkyl, or are taken together to form —O— or $—CH_2—$;

R^8 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl or C_1-C_6 haloalkyl; and

R^9 is H, hydroxymethyl or acyloxymethyl;

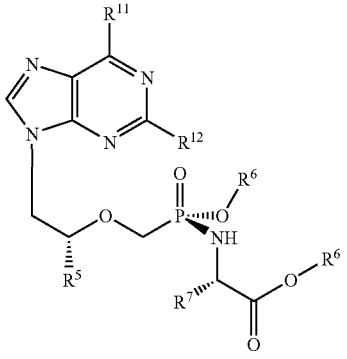
and their salts, free base, and solvates.

2. The compound of claim **1** containing less than 20% by weight of the diastereomer (4).

3. The compound of claim **1** containing less than 5% by weight of the diastereomer (4).

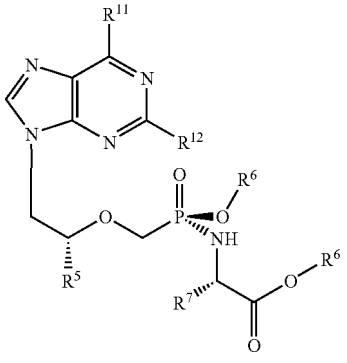
4. A diastereomerically enriched compound having the structure (5a)

(5a)



which contains less than 40% by weight of diastereomer (5b)

(5b)



wherein

R^5 is methyl or hydrogen;

R^6 independently is H, alkyl, alkenyl, alkynyl, aryl or arylalkyl, or R^6 independently is alkyl, alkenyl, alkynyl, aryl or arylalkyl which is substituted with from 1 to 3 substituents selected from alkylamino, alkylaminoalkyl, dialkylaminoalkyl, dialkylamino, hydroxyl, oxo, halo, amino, alkylthio, alkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylalkoxyalkyl, haloalkyl, nitro, nitroalkyl, azido, azidoalkyl, alkylacyl, alkylacylalkyl, carboxyl, or alkylacylamino;

R^7 is the side chain of any naturally-occurring or pharmaceutically acceptable amino acid and which, if the side chain comprises carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group;

R^{11} is amino, alkylamino, oxo, or dialkylamino; and

R^{12} is amino or H;

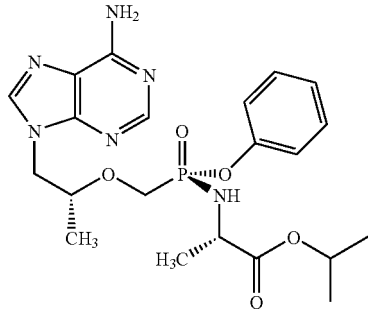
and its salts, tautomers, free base and solvates.

5. The compound of claim **4** containing less than 20% by weight of the diastereomer (5b).

6. The compound of claim **4** containing less than 5% by weight of the diastereomer (5b).

7. A diastereomerically enriched compound of structure (6)

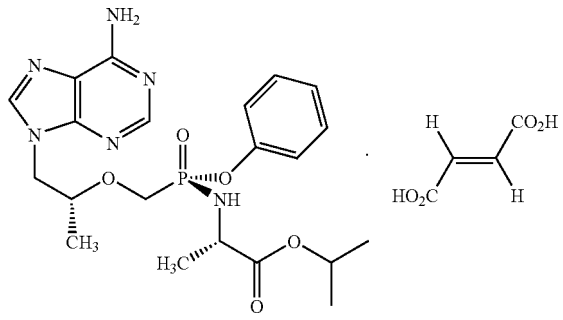
(6)



and its salts, tautomers, free base and solvates.

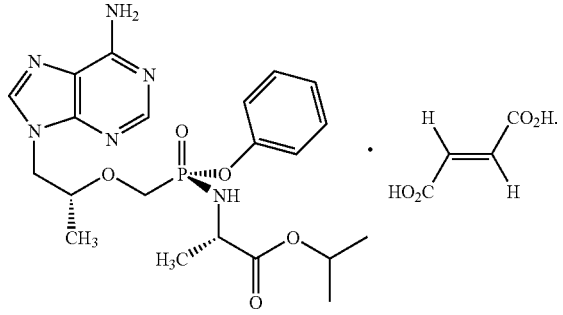
8. A diastereomerically enriched compound of structure (7)

(7)



which contains less than 40% of diastereomer (7a)

(7a)



9. The compound of claim **8** containing less than 20% by weight of the diastereomer (7a).

10. The compound of claim **8** containing less than 5% by weight of the diastereomer (7a).

11. A composition comprising a compound of any of claims **1-8** or **2-10** and a pharmaceutically effective excipient.

12. The composition of claim **11** wherein the excipient is a gel.

13. The composition of claim **11** which is suitable for topical administration.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,390,791 B2
APPLICATION NO. : 10/798692
DATED : June 24, 2008
INVENTOR(S) : Mark W. Becker et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

ON THE TITLE PAGE [56] REFERENCES CITED:

Foreign Patent Documents, "WO 0208241 A2*" should read --WO 02/08241 A2*--.

COLUMN 3:

Line 17, "alkyoxy" should read --alkyloxy--.

COLUMN 5:

Line 8, "Dogs" should read --dogs--.

COLUMN 8:

Line 19, "possess" should read --possesses--.

COLUMN 10:

Line 10, "therefore." should read --therefor.--.

COLUMN 11:

Line 16, "R_{22};" should read --R^{22};--.

COLUMN 12:

Line 48, "1-dezazadenyl," should read --l-dezaadenyl,--.

COLUMN 13:

Line 4, "C_6-C_1" should read --C_6-C_{15}--.

Signed and Sealed this
Nineteenth Day of March, 2013

Teresa Stanek Rea

Teresa Stanek Rea
Acting Director of the United States Patent and Trademark Office

COLUMN 21:

Line 61, “a oil.” should read --an oil.--.

COLUMN 23:

Line 8, “minute” should read --minutes--.

COLUMN 29:

Line 1, “Met Y” should read --Met. Y--;
Line 10, “in Table 3” should read --In Table 3--;
Line 11, “nelfinivir” should read --nelfinavir--; and
Line 59, “Arimilli, M N,” should read --Arimilli, MN,--.

COLUMN 30:

Line 3, “that of” should read --as that of--; and
Line 51, “Rx-C8,” should read --Rx-C_8,--.

COLUMN 33:

Line 63, “precipitateprotein.” should read --precipitate protein.--.

COLUMN 34:

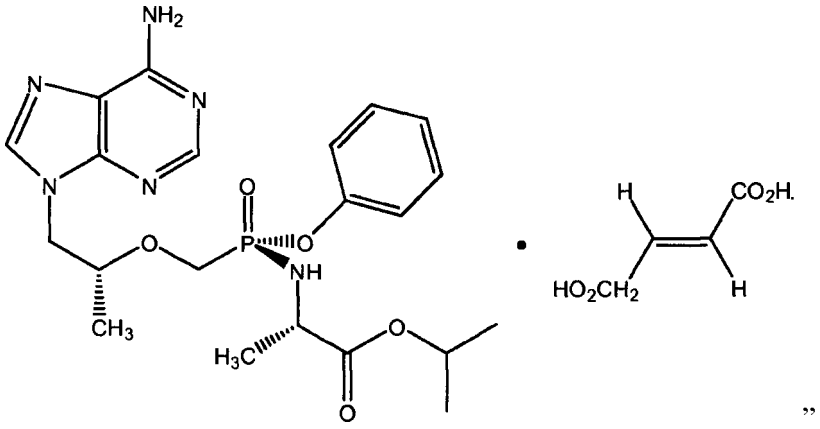
Line 53, “is shown” should read --are shown--.

COLUMN 37:

Line 66, “alkyoxy” should read --alkyloxy--.

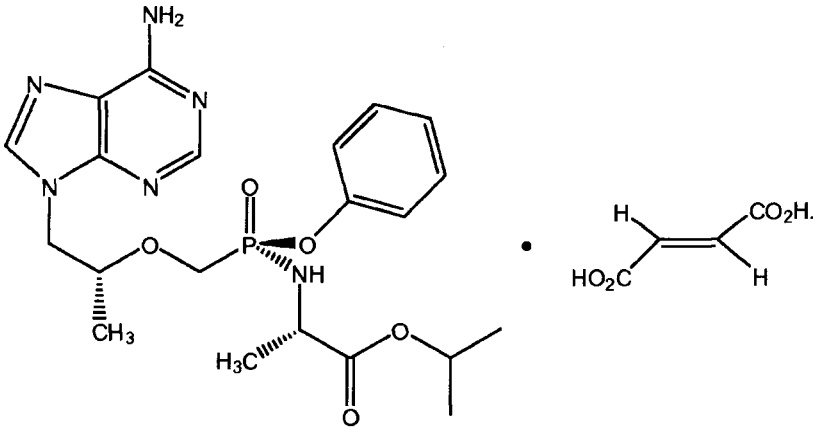
COLUMN 40:

Lines 21-32,



“ ”

should read



--; and

Line 39, "claims 1-8 or 2-10" should read --claims 1-10--.

Exhibit B

US007803788B2

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

(10) **Patent No.: US 7,803,788 B2**
(45) **Date of Patent: Sep. 28, 2010**

(54) **PRODRUGS OF PHOSPHONATE NUCOLEOTIDE ANALOGUES**

(75) Inventors: **Mark W. Becker**, Redwood City, CA (US); **Harlan H. Chapman**, La Honda, CA (US); **Tomas Cihlar**, Foster City, CA (US); **Eugene J. Eisenberg**, San Carlos, CA (US); **Gong-Xin He**, Cupertino, CA (US); **Michael R. Kernan**, Pacifica, CA (US); **William A. Lee**, Los Altos, CA (US); **Ernest J. Prisbe**, Los Altos, CA (US); **John C. Rohloff**, Boulder, CO (US); **Mark L. Sparacino**, Morgan Hill, CA (US)

(73) Assignee: **Gilead Sciences, Inc.**, Foster City, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 197 days.

(21) Appl. No.: **12/110,829**

(22) Filed: **Apr. 28, 2008**

(65) **Prior Publication Data**

US 2008/0227754 A1 Sep. 18, 2008

Related U.S. Application Data

(63) Continuation of application No. 10/798,692, filed on Mar. 11, 2004, now Pat. No. 7,390,791, which is a continuation of application No. 10/354,207, filed on Jan. 28, 2003, now abandoned, which is a continuation of application No. 09/909,560, filed on Jul. 20, 2001, now abandoned.

(60) Provisional application No. 60/220,021, filed on Jul. 21, 2000.

(51) **Int. Cl.**
A61K 31/675 (2006.01)
A61P 31/12 (2006.01)

(52) **U.S. Cl.** **514/81**; 514/7; 514/85; 435/4; 435/9.1

(58) **Field of Classification Search** 435/4, 435/9.1; 514/7, 81, 85

See application file for complete search history.

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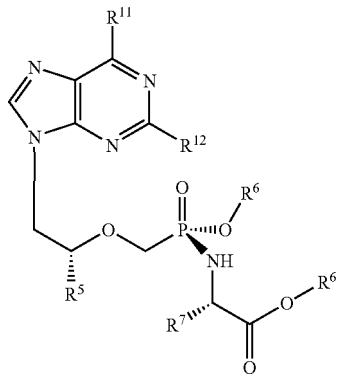
(Continued)

Primary Examiner—Jon P Weber
Assistant Examiner—Kailash C Srivastava
(74) *Attorney, Agent, or Firm*—Allan N. Kutzenco

(57) **ABSTRACT**

A novel method has led to the identification of novel mixed ester-amidates of PMPA for retroviral or hepadnaviral therapy, including compounds of structure (5a)

(5a)



having substituent groups as defined herein. Compositions of these novel compounds in pharmaceutically acceptable excipients and their use in therapy and prophylaxis are provided.

10 Claims, 3 Drawing Sheets

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Figure 1. HPLC/C-14 Traces of PBMC Extracts from Human Blood Incubated for 1 h at 37°C with TDF, GS-7340 or PMPA.

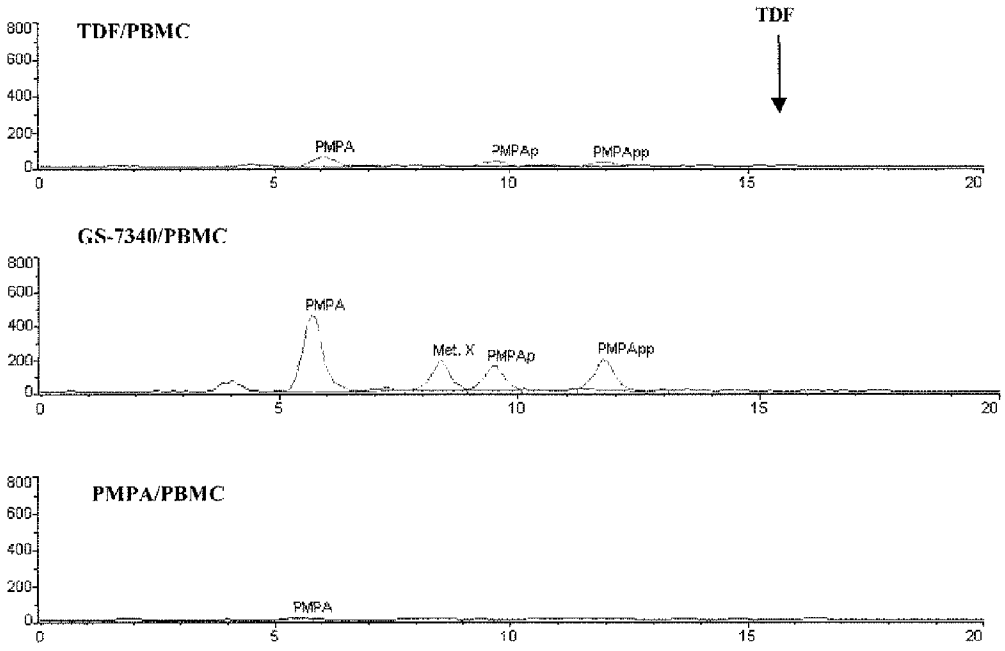


Figure 2. PMPA and Prodrug Concentration in Plasma and PBMCs Following Oral Administration of GS 7340-2 to Dogs at 10 mg-eq/kg.

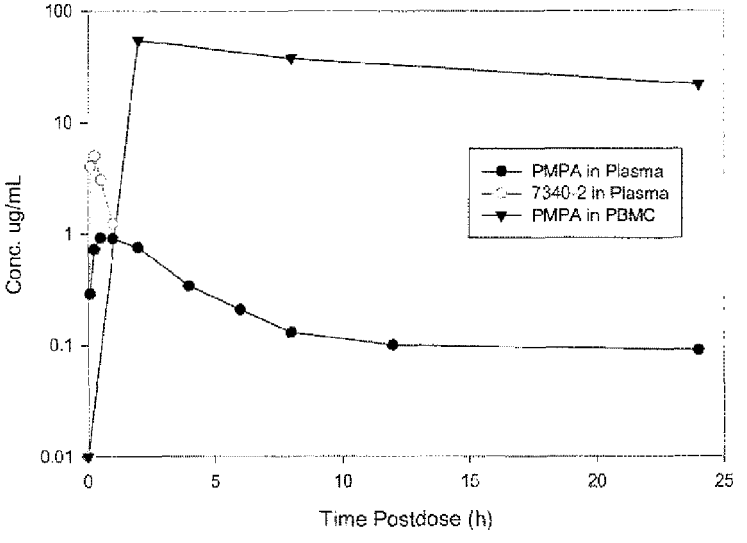
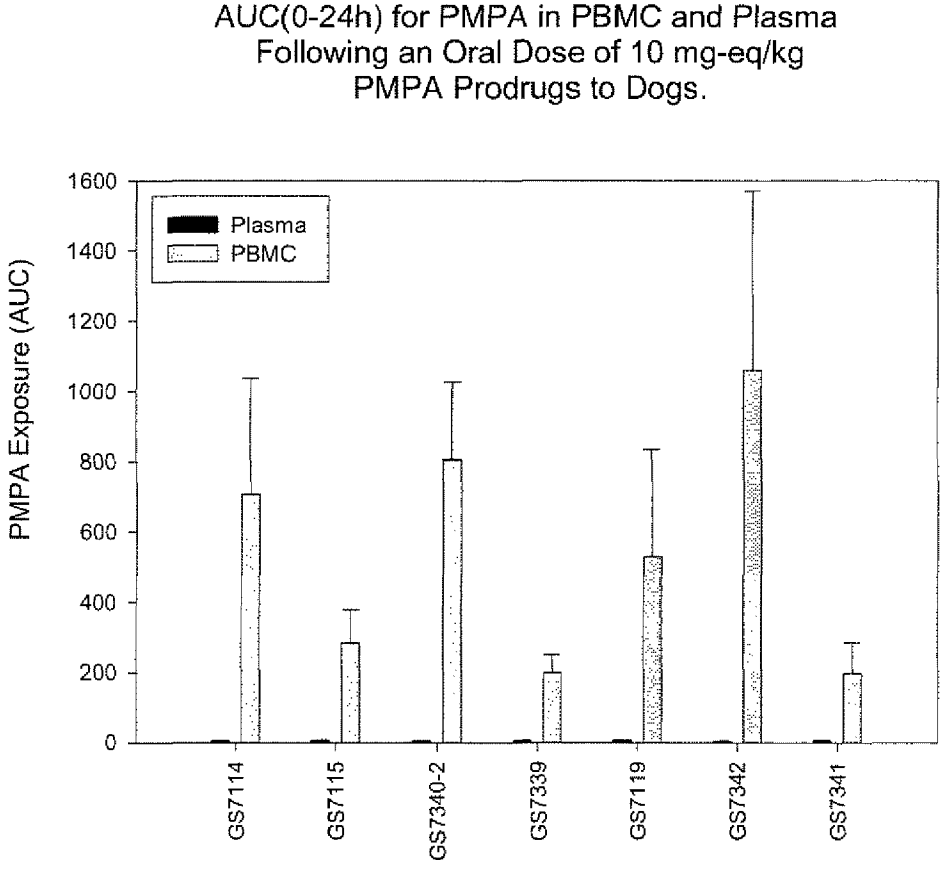


Figure 3. Depicts Tenofovir Exposure in PBMCs and Plasma Upon Administration of 10 mg-eq/kg in dogs



PRODRUGS OF PHOSPHONATE NUCOLEOTIDE ANALOGUES

This non-provisional application is a continuation application of application Ser. No. 10/798,692, filed Mar. 11, 2004 now U.S. Pat. No. 7,390,791, which is a continuation of application Ser. No. 10/354,207, filed Jan. 28, 2003, now abandoned, which is a continuation application of application Ser. No. 09/909,560, filed Jul. 20, 2001, now abandoned, which is a regular utility application of provisional application 60/220,021, filed Jul. 21, 2000, now abandoned, all of which are incorporated herein by reference.

This application relates to prodrugs of methoxyphosphonate nucleotide analogues. In particular it relates to improved methods for making and identifying such prodrugs.

Many methoxyphosphonate nucleotide analogues are known. In general, such compounds have the structure A-$OCH_2P(O)(OR)_2$ where A is the residue of a nucleoside analogue and R independently is hydrogen or various protecting or prodrug functionalities. See U.S. Pat. Nos. 5,663,159, 5,977,061 and 5,798,340, Oliyai et al, "Pharmaceutical Research" 16(11):1687-1693 (1999), Stella et al., "J. Med. Chem." 23(12):1275-1282 (1980), Aarons, L., Boddy, A. and Petrak, K. (1989) *Novel Drug Delivery and Its Therapeutic Application* (Prescott, L. F. and Nimmo, W. S., ed.), pp. 121-126; Bundgaard, H. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 70-74 and 79-92; Banerjee, P. K. and Amidon, G. L. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 118-121; Notari, R. E. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 135-156; Stella, V. J. and Himmelstein, K. J. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 177-198; Jones, G. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 199-241; Connors, T. A. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 291-316. All literature and patent citations herein are expressly incorporated by reference.

SUMMARY OF THE INVENTION

Prodrugs of methoxyphosphonate nucleotide analogues intended for antiviral or antitumor therapy, while known, traditionally have been selected for their systemic effect. For example, such prodrugs have been selected for enhanced bioavailability, i.e., ability to be absorbed from the gastrointestinal tract and converted rapidly to parent drug to ensure that the parent drug is available to all tissues. However, applicants now have found that it is possible to select prodrugs that become enriched at therapeutic sites, as illustrated by the studies described herein where the analogues are enriched at localized focal sites of HIV infection. The objective of this invention is, among other advantages, to produce less toxicity to bystander tissues and greater potency of the parental drug in tissues which are the targets of therapy with the parent methoxyphosphonate nucleotide analogue.

Accordingly, pursuant to these observations, a screening method is provided for identifying a methoxyphosphonate nucleotide analogue prodrug conferring enhanced activity in a target tissue comprising:

(a) providing at least one of said prodrugs;

(b) selecting at least one therapeutic target tissue and at least one non-target tissue;

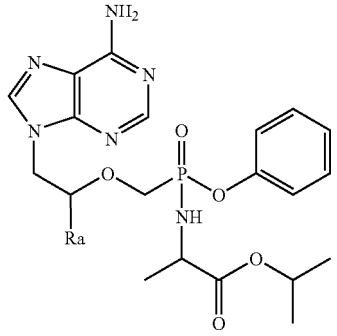
(c) administering the prodrug to the target tissue and to said at least one non-target tissue; and

(d) determining the relative antiviral activity conferred by the prodrug in the tissues in step (c).

In preferred embodiments, the target tissue are sites where HIV is actively replicated and/or which serve as an HIV reservoir, and the non-target tissue is an intact animal. Unexpectedly, we found that selecting lymphoid tissue as the target tissue for the practice of this method for HIV led to identification of prodrugs that enhance the delivery of active drug to such tissues.

A preferred compound of this invention, which has been identified by this method has the structure (1),

(1)

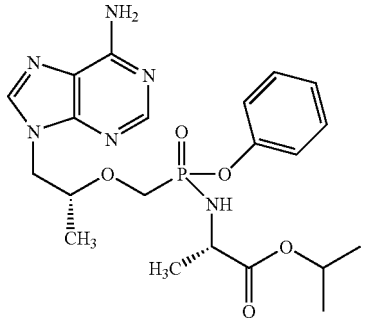


where Ra is H or methyl,

and chirally enriched compositions thereof, salts, their free base and solvates thereof.

A preferred compound of this invention has the structure (2)

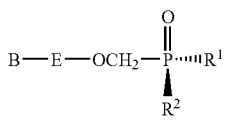
(2)



and its enriched diasteromers, salts, free base and solvates.

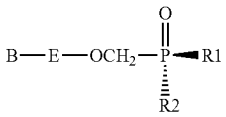
In addition, we unexpectedly found that the chirality of substituents on the phosphorous atom and/or the amidate substituent are influential in the enrichment observed in the practice of this invention. Thus, in another embodiment of this invention, we provide diastereomerically enriched compounds of this invention having the structure (3)

(3)



which are substantially free of the diastereomer (4)

(4)



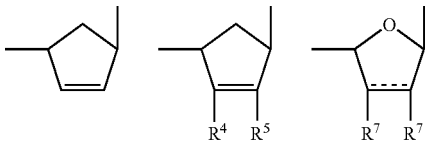
wherein

R^1 is an oxyester which is hydrolyzable in vivo, or hydroxyl;

B is a heterocyclic base;

R^2 is hydroxyl, or the residue of an amino acid bonded to the P atom through an amino group of the amino acid and having each carboxy substituent of the amino acid optionally esterified, but not both of R^1 and R^2 are hydroxyl;

E is $—(CH_2)_2—$, $—CH(CH_3)CH_2—$, $—CH(CH_2F)CH_2—$, $—CH(CH_2OH)CH_2—$, $—CH(CH═CH_2)CH_2—$, $—CH(C═CH)CH_2—$, $—CH(CH_2N_3)CH_2—$,



$—CH(R^6)OCH(R^{6'})—$, $—CH(R^9)CH_2O—$ or $—CH(R^8)O—$, wherein the right hand bond is linked to the heterocyclic base;

the broken line represents an optional double bond;

R^4 and R^5 are independently hydrogen, hydroxy, halo, amino or a substituent having 1-5 carbon atoms selected from acyloxy, alkyoxy, alkylthio, alkylamino and dialkylamino;

R^6 and $R^{6'}$ are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_2-C_7 alkanoyl;

R^7 is independently H, C_1-C_6 alkyl, or are taken together to form —O— or $—CH_2—$;

R^8 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl or C_1-C_6 haloalkyl; and

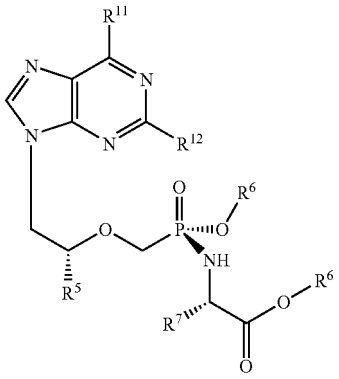
R^9 is H, hydroxymethyl or acyloxymethyl;

and their salts, free base, and solvates.

The diastereomers of structure (3) are designated the (S) isomers at the phosphorus chiral center.

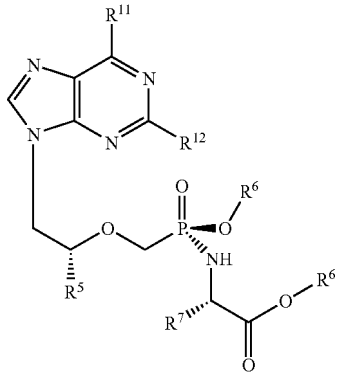
Preferred embodiments of this invention are the diastereomerically enriched compounds having the structure (5a)

(5a)



which is substantially free of diastereomer (5b)

(5b)



wherein

R^5 is methyl or hydrogen;

R^6 independently is H, alkyl, alkenyl, alkynyl, aryl or arylalkyl, or R^6 independently is alkyl, alkenyl, alkynyl, aryl or arylalkyl which is substituted with from 1 to 3 substituents selected from alkylamino, alkylaminoalkyl, dialkylaminoalkyl, dialkylamino, hydroxyl, oxo, halo, amino, alkylthio, alkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylalkoxyalkyl, haloalkyl, nitro, nitroalkyl, azido, azidoalkyl, alkylacyl, alkylacylalkyl, carboxyl, or alkylacylamino;

R^7 is the side chain of any naturally-occurring or pharmaceutically acceptable amino acid and which, if the side chain comprises carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group;

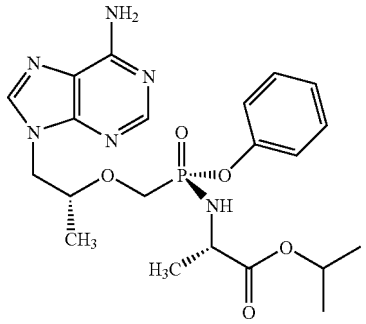
R^{11} is amino, alkylamino, oxo, or dialkylamino; and

R^{12} is amino or H;

and its salts, tautomers, free base and solvates.

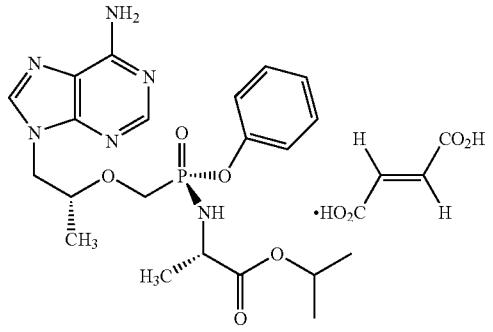
A preferred embodiment of this invention is the compound of structure (6), 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine, also designated herein GS-7340

(6)



Another preferred embodiment of this invention is the fumarate salt of structure (5) (structure (7)), 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine fumarate (1:1), also designated herein GS-7340-2

(7)



The compounds of structures (1)-(7) optionally are formulated into compositions containing pharmaceutically acceptable excipients. Such compositions are used in effective doses in the therapy or prophylaxis of viral (particularly HIV or hepadnaviral) infections.

In a further embodiment, a method is provided for the facile manufacture of 9-[2-(phosphonomethoxy)propyl]adenine (hereinafter "PMPA" or 9-[2-(phosphonomethoxy)ethyl]adenine (hereinafter "PMEA") using magnesium alkoxide, which comprises combining 9-(2-hydroxypropyl)adenine or 9-(2-hydroxyethyl)adenine, protected p-toluenesulfonyloxymethylphosphonate and magnesium alkoxide, and recovering PMPA or PMEA, respectively.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows HPLC/C-14 traces of PBMC extracts from human blood incubated for 1 h at 37° C. with TDF, GS-7340 and PMPA.

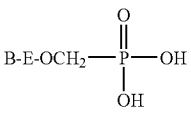
FIG. **2** shows PMPA and Prodrug concentration in plasma and PBMCs following oral administration of GS 7340-2 to Dogs at 10 mg-eq/kg.

FIG. **3** depicts Tenofovir exposure in PBMCs and plasma upon administration of 10 mg-eq/kg in dogs.

DETAILED DESCRIPTION OF THE INVENTION

The methoxyphosphonate nucleotide analogue parent drugs for use in this screening method are compounds having the structure A-$OCH_2P(O)(OH)_2$ wherein A is the residue of a nucleoside analogue. These compounds are known

(7a)



per se and are not part of this invention. More particularly, the parent compounds comprise a heterocyclic base B and an aglycon E, in general having the structure wherein the group B is defined below and group E is defined above. Examples are described in U.S. Pat. Nos. 4,659,825, 4,808,716, 4,724,233, 5,142,051, 5,130,427, 5,650,510, 5,663,159, 5,302,585, 5,476,938, 5,696,263, 5,744,600, 5,688,778, 5,386,030, 5,733,896, 5,352,786, and 5,798,340, and EP 821,690 and 654,037.

The prodrugs for use in the screening method of this invention are covalently modified analogues of the parent methoxyphosphonate nucleotide analogues described in the preceding paragraph. In general, the phosphorus atom of the parent drug is the preferred site for prodrug modification, but other sites are found on the heterocyclic base B or the aglycon E. Many such prodrugs are already known. Primarily, they are esters or amidates of the phosphorus atom, but also include substitutions on the base and aglycon. None of these modifications per se is part of this invention and none are to be considered limiting on the scope of the invention herein.

The phosphorus atom of the methoxyphosphonate nucleotide analogues contains two valences for covalent modification such as amidation or esterification (unless one phosphoryl hydroxyl is esterified to an aglycon E hydroxyl substituent, whereupon only one phosphorus valence is free for substitution). The esters typically are aryloxy. The amidates ordinarily are naturally occurring monoamino acids having free carboxyl group(s) esterified with an alkyl or aryl group, usually phenyl, cycloalkyl, or t-, n- or s-alkyl groups. Suitable prodrugs for use in the screening method of this invention are disclosed for example in U.S. Pat. No. 5,798,340. However, any prodrug which is potentially believed to be capable of being converted in vivo within target tissue cells to the free methoxyphosphonate nucleotide analogue parent drug, e.g., whether by hydrolysis, oxidation, or other covalent transformation resulting from exposure to biological tissues, is suitable for use in the method of this invention. Such prodrugs may not be known at this time but are identified in the future and thus become suitable candidates available for testing in the method of this invention. Since the prodrugs are simply candidates for screening in the methods their structures are not relevant to practicing or enabling the screening method, although of course their structures ultimately are dispositive of whether or not a prodrug will be shown to be selective in the assay.

The pro-moieties bound to the parent drug may be the same or different. However, each prodrug to be used in the screening assay will differ structurally from the other prodrugs to be tested. Distinct, i.e. structurally different, prodrugs generally are selected on the basis of either their stereochemistry or their covalent structure, or these features are varied in combination. Each prodrug tested, however, desirably is structurally and stereochemically substantially pure, else the output of the screening assay will be less useful. It is of course within the scope of this invention to test only a single prodrug in an individual embodiment of the method of this invention, although typically then one would compare the results with prior studies with other prodrugs.

We have found that the stereochemistry of the prodrugs is capable of influencing the enrichment in target tissues. Chiral sites are at the phosphorus atom and are also found in its substituents. For example, amino acid used in preparing amidates may be D or L forms, and the phosphonate esters or the amino acid esters can contain chiral centers as well. Chiral sites also are found on the nucleoside analogue portion of the molecules, but these typically are already dictated by the stereochemistry of the parent drug and will not be varied as part of the screen. For example the R isomer of PMPA is preferred as it is more active than the corresponding S isomer. Typically these diasteromers or enantiomers will be chirally enriched if not pure at each site so that the results of the screen will be more meaningful. As noted, distinctiveness of stereoisomers is conferred by enriching or purifying the stereoisomer (typically this will be a diastereomer rather than an enantiomer in the case of most methoxyphosphonate nucleotide analogues) free of other stereoisomers at the chiral center in question, so that each test compound is substantially homogeneous. By substantially homogeneous or chirally

enriched, we mean that the desired stereoisomer constitutes greater than about 60% by weight of the compound, ordinarily greater than about 80% and preferably greater than about 95%.

Novel Screening Method

Once at least one candidate prodrug has been selected, the remaining steps of the screening method of this invention are used to identify a prodrug possessing the required selectivity for the target tissue. Most conveniently the prodrugs are labeled with a detectable group, e.g. radiolabeled, in order to facilitate detection later in tissues or cells. However, a label is not required since other suitable assays for the prodrug or its metabolites (including the parent drug) can also be employed. These assays could include mass spectrometry, HPLC, bioassays or immunoassays for instance. The assay may detect the prodrug and any one or more of its metabolites, but preferably the assay is conducted to detect only the generation of the parent drug. This is based on the assumption (which may not be warranted in all cases) that the degree and rate of conversion of prodrug to antivirally active parent diphosphate is the same across all tissues tested. Otherwise, one can test for the diphosphate.

The target tissue preferably will be lymphoid tissue when screening for prodrugs useful in the treatment of HIV infection. Lymphoid tissue will be known to the artisan and includes CD4 cells, lymphocytes, lymph nodes, macrophages and macrophage-like cells including monocytes such as peripheral blood monocytic cells (PBMCs) and glial cells. Lymphoid tissue also includes non-lymphoid tissues that are enriched in lymphoid tissues or cells, e.g. lung, skin and spleen. Other targets for other antiviral drugs of course will be the primary sites of replication or latency for the particular virus concerned, e.g., liver for hepatitis and peripheral nerves for HSV. Similarly, target tissues for tumors will in fact be the tumors themselves. These tissues are all well-known to the artisan and would not require undue experimentation to select. When screening for antiviral compounds, target tissue can be infected by the virus.

Non-target tissues or cells also are screened as part of the method herein. Any number or identity of such tissues or cells can be employed in this regard. In general, tissues for which the parent drug is expected to be toxic will be used as non-target tissues. The selection of a non-target tissue is entirely dependent upon the nature of the prodrug and the activity of the parent. For example, non-hepatic tissues would be selected for prodrugs against hepatitis, and untransformed cells of the same tissue as the tumor will suffice for the antitumor-selective prodrug screen.

It should be noted that the method of this invention is distinct from studies typically undertaken to determine oral bioavailability of prodrugs. In oral bioavailability studies, the objective is to identify a prodrug which passes into the systemic circulation substantially converted to parent drug. In the present invention, the objective is to find prodrugs that are not metabolized in the gastrointestinal tract or circulation. Thus, target tissues to be evaluated in the method of this invention generally do not include the small intestines or, if the intestines are included, then the tissues also include additional tissues other than the small intestines.

The target and non-target tissues used in the screening method of this invention typically will be in an intact living animal. Prodrugs containing esters are more desirably tested in dogs, monkeys or other animals than rodents; mice and rat plasma contains high circulating levels of esterases that may produce a misleading result if the desired therapeutic subject is a human or higher mammal.

It is not necessary to practice this method with intact animals. It also is within the scope of this invention to employ perfused organs, in vitro culture of organs (e.g. skin grafts) or cell lines maintained in various forms of cell culture, e.g. roller bottles or zero gravity suspension systems. For example, MT-2 cells can be used as a target tissue for selecting HIV prodrugs. Thus, the term "tissue" shall not be construed to require organized cellular structures, or the structures of tissues as they may be found in nature, although such would be preferred. Rather, the term "tissue" shall be construed to be synonymous with cells of a particular source, origin or differentiation stage.

The target and non-target tissue may in fact be the same tissue, but the tissues will be in different biological status. For example, the method herein could be used to select for prodrugs that confer activity in virally-infected tissue (target tissue) but which remain substantially inactive in virally-uninfected cells (corresponding non-target tissue). The same strategy would be employed to select prophylactic prodrugs, i.e., prodrugs metabolized to antivirally active forms incidental to viral infection but which remain substantially unmetabolized in uninfected cells. Similarly, prodrugs could be screened in transformed cells and the untransformed counterpart tissue. This would be particularly useful in comparative testing to select prodrugs for the treatment of hematological malignancies, e.g. leukemias.

Without being limited by any particular theory of operation, tissue selective prodrugs are thought to be selectively taken up by target cells and/or selectively metabolized within the cell, as compared to other tissues or cells. The unique advantage of the methoxyphosphonate prodrugs herein is that their metabolism to the dianion at physiological pH ensures that they will be unable to diffuse back out of the cell. They therefore remain effective for lengthy periods of time and are maintained at elevated intracellular concentrations, thereby exhibiting increased potency. The mechanisms for enhanced activity in the target tissue are believed to include enhanced uptake by the target cells, enhanced intracellular retention, or both mechanisms working together. However, the manner in which selectivity or enhanced delivery occurs in the target tissue is not important. It also is not important that all of the metabolic conversion of the prodrug to the parent compound occurs within the target tissue. Only the final drug activity-conferring conversion need occur in the target tissue; metabolism in other tissues may provide intermediates finally converted to antiviral forms in the target tissue.

The degree of selectivity or enhanced delivery that is desired will vary with the parent compound and the manner in which it is measured (% dose distribution or parent drug concentration). In general, if the parent drug already possess a generous therapeutic window, a low degree of selectivity may be sufficient for the desired prodrug. On the other hand, toxic compounds may require more extensive screening to identify selective prodrugs. The relative expense of the method of this invention can be reduced by screening only in the target tissue and tissues against which the parent compound is known to be relatively toxic e.g. for PMEA, which is nephrotoxic at higher doses, the primary focus will be on kidney and lymphoid tissues.

The step of determining the relative antiviral activity of a prodrug in the selected tissues ordinarily is accomplished by assaying target and non-target tissues for the relative presence or activity of a metabolite of the prodrug, which metabolite is known to have, or is converted to, a metabolite having antiviral or antitumor activity. Thus, typically one would deter-

mine the relative amount of the parent drug in the tissues over substantially the same time course in order to identify prodrugs that are preferentially metabolized in the target tissue to an antivirally or antitumor active metabolite or precursor thereof which in the target tissue ultimately produces the active metabolite. In the case of antiviral compounds, the active metabolite is the diphosphate of the phosphonate parent compounds. It is this metabolite that is incorporated into the viral nucleic acid, thereby truncating the elongating nucleic acid strand and halting viral replication. Metabolites of the prodrug can be anabolic metabolites, catabolic metabolites, or the product of anabolism and catabolism together. The manner in which the metabolite is produced is not important in the practice of the method of this invention.

The method of this invention is not limited to assaying a metabolite which per se possesses antiviral or antitumor activity. Instead, one can assay inactive precursors of the active metabolites. Precursors of the antivirally active diphosphate metabolite include the monophosphate of the parent drug, monophosphates of other metabolites of the parent drug (e.g., an intermediate modification of a substituent on the heterocyclic base), the parent itself and metabolites generated by the cell in converting the prodrug to the parent prior to phosphorylation. The precursor structures may vary considerably as they are the result of cellular metabolism. However, this information is already known or could be readily determined by one skilled in the art.

If the prodrug being assayed does not exhibit antitumor or antiviral activity per se then adjustments to the raw assay results may be required. For example, if the intracellular processing of the inactive metabolite to an active metabolite occurs at different rates among the tissues being tested, the raw assay results with the inactive metabolite would need to be adjusted to take account of the differences among the cell types because the relevant parameter is the generation of activity in the target tissue, not accumulation of inactive metabolites. However, determining the proper adjustments would be within the ordinary skill. Thus, when step (d) of the method herein calls for determining the activity, activity can be either measured directly or extrapolated. It does not mean that the method herein is limited to only assaying intermediates that are active per se. For instance, the absence or decline of the prodrug in the test tissues also could be assayed. Step (d) only requires assessment of the activity conferred by the prodrug as it interacts with the tissue concerned, and this may be based on extrapolation or other indirect measurement.

Step (d) of the method of this invention calls for determining the "relative" activity of the prodrug. It will be understood that this does not require that each and every assay or series of assays necessarily must also contain runs with the selected non-target tissue. On the contrary, it is within the scope of this invention to employ historical controls of the non-target tissue or tissues, or algorithms representing results to be expected from such non-target tissues, in order to provide the benchmark non-target activity.

The results obtained in step (d) are then used optimally to select or identify a prodrug which produces greater antiviral activity in the target tissue than in the non-target tissue. It is this prodrug that is selected for further development.

It will be appreciated that some preassessment of prodrug candidates can be undertaken before the practice of the method of this invention. For example, the prodrug will need to be capable of passing largely unmetabolized through the gastrointestinal tract, it will need to be substantially stable in blood, and it should be able to permeate cells at least to some degree. In most cases it also will need to complete a first pass of the hepatic circulation without substantial metabolism. Such prestudies are optional, and are well-known to those skilled in the art.

The same reasoning as is described above for antiviral activity is applicable to antitumor prodrugs of methoxyphosphonate nucleotide analogues as well. These include, for example, prodrugs of PMEG, the guanyl analogue of PMEA. In this case, cytotoxic phosphonates such as PMEG are worthwhile candidates to pursue as their cytotoxicity in fact confers their antitumor activity.

A compound identified by this novel screening method then can be entered into a traditional preclinical or clinical program to confirm that the desired objectives have been met. Typically, a prodrug is considered to be selective if the activity or concentration of parent drug in the target tissue (% dose distribution) is greater than 2×, and preferably 5×, that of the parent compound in non-target tissue. Alternatively, a prodrug candidate can be compared against a benchmark prodrug. In this case, selectivity is relative rather than absolute. Selective prodrugs will be those resulting in greater than about 10× concentration or activity in the target tissue as compared with the prototype, although the degree of selectivity is a matter of discretion.

Novel Method for Preparation of Starting Materials or Intermediates

Also included herein is an improved method for manufacture of preferred starting materials (parent drugs) of this invention, PMEA and (R)-PMPA. Typically, this method comprises reacting 9-(2-hydroxypropyl)adenine (HPA) or 9-(2-hydroxyethyl)adenine (HEA) with a magnesium alkoxide, thereafter adding the protected aglycon synthon p-toluene-sulfonyloxymethylphosphonate (tosylate) to the reaction mixture, and recovering PMPA or PMEA, respectively.

Preferably, HPA is the enriched or isolated R enantiomer. If a chiral HPA mixture is used, R-PMPA can be isolated from the chiral PMPA mixture after the synthesis is completed.

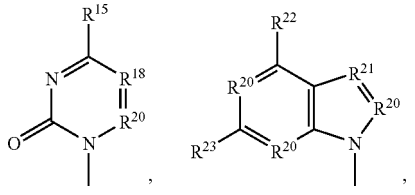
Typically the tosylate is protected by lower alkyl groups, but other suitable groups will be apparent to the artisan. It may be convenient to employ the tosylate presubstituted with the prodrug phosphonate substituents which are capable of acting as protecting groups in the tosylation reaction, thereby allowing one to bypass the deprotection step and directly recover prodrug or an intermediate therefore.

The alkyl group of the magnesium alkoxide is not critical and can be any C_1-C_6 branched or normal alkyl, but is preferably t-butyl (for PMPA) or isopropyl (for PMEA). The reaction conditions also are not critical, but preferably comprise heating the reaction mixture at about 70-75° C. with stirring or other moderate agitation.

If there is no interest in retaining the phosphonate substituents, the product is deprotected (usually with bromotrimethylsilane where the tosylate protecting group is alkyl), and the product then recovered by crystallization or other conventional method as will be apparent to the artisan.

Heterocyclic Base

In the compounds of this invention depicted in structures (3) and (4), the heterocyclic base B is selected from the structures



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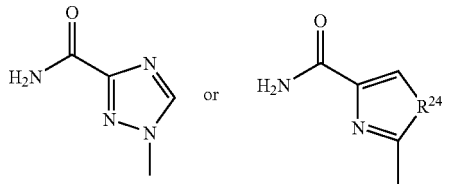


wherein

R^{15} is H, OH, F, Cl, Br, I, OR^{16}, SH, SR^{16}, NH_2, or NHR^{17};

R^{16} is C_1-C_6 alkyl or C_2-C_6 alkenyl including —CH_3, —CH_2CH_3, —$CH_2C{\equiv}CH$, —$CH_2CH{=}CH_2$ and —C_3H_7;

R^{17} is C_1-C_6 alkyl or C_2-C_6 alkenyl including —CH_3, CH_2CH_3, —$CH_2C{\equiv}CH$, —$CH_2CH{=}CH_2$, and —C_3H_7;

R^{18} is N, CF, CCl, CBr, CI, CR^{19}, CSR^{19}, or COR^{19};

R^{19} is H, C_1-C_9 alkyl C_2-C_9 alkenyl, C_2-C_9 alkynyl, C_1-C_9 alkyl-C_1-C_9 alkoxy, or C_7-C_9 aryl-alkyl unsubstituted or substituted by OH, F, Cl, Br or I, R^{19} therefore including —CH_3, —CH_2CH_3, —$CHCH_2$, —CHCHBr, —CH_2CH_2Cl, —CH_2CH_2F, —CH_2CCH, —CH_2CHCH_2, —C_3H_7, —CH_2OH, —CH_2OCH_3, —$CH_2OC_2H_5$, —CH_2OCCH, —$CH_2OCH_2CHCH_2$, —$CH_2C_3H_7$, —CH_2CH_2OH, —$CH_2CH_2OCH_3$, —$CH_2CH_2OC_2H_5$, —CH_2CH_2OCCH, —$CH_2CH_2OCH_2CHCH_2$, and —$CH_2CH_2OC_3H_7$;

R^{20} is N or CH;

R^{21} is N, CH, CCN, CCF_3, CC≡CH or $CC(O)NH_2$;

R^{22} is H, OH, NH_2, SH, SCH_3, SCH_2CH_3, $SCH_2C{\equiv}CH$, $SCH_2CH{-}CH_2$, SC_3H_7, $NH(CH_3)$, $N(CH_3)_2$, $NH(CH_2CH_3)$, $N(CH_2CH_3)_2$, $NH(CH_2C{\equiv}CH)$, $NH(CH_2CHCH_2)$, $NH(C_3H_7)$, halogen (F, Cl, Br or I) or X wherein X is $—(CH_2)_m(O)_n(CH_2)_mN(R^{10})_2$ wherein each m is independently 0-2, n is 0-1, and

R^{10} independently is H,

C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_6-C_{15} arylalkynyl, C_2-C_{15} alkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroaralkyl, C_5-C_6 aryl, C_2-C_6 heterocycloalkyl,

C_2-C_{15} alkyl, C_3-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_3-C_{15} alkynyl, C_7-C_{15} arylalkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroalkyl or C_3-C_6 heterocycloalkyl wherein methylene in the alkyl moiety not adjacent to N^6 has been replaced by —O—,

optionally both R^{10} are joined together with N to form a saturated or unsaturated C_2-C_5 heterocycle containing one or two N heteroatoms and optionally an additional O or S heteroatom,

or one of the foregoing R^{10} groups which is substituted with 1 to 3 halo, CN or N_3; but optionally at least one R^{10} group is not H;

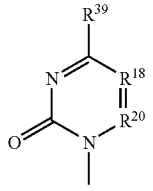
R^{23} is H, OH, F, Cl, Br, I, SCH_3, SCH_2CH_3, $SCH_2C{\equiv}CH$, SCH_2CHCH_2, SC_3H_7, OR^{16}, NH_2, NHR^{17} or R^{22}; and

R^{24} is O, S or Se.

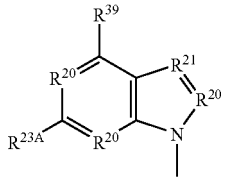
B also includes both protected and unprotected heterocyclic bases, particularly purine and pyrimidine bases. Protecting groups for exocyclic amines and other labile groups are known (Greene et al. "Protective Groups in Organic Synthesis") and include N-benzoyl, isobutyryl, 4,4'-dimethoxytrityl (DMT) and the like. The selection of protecting group will be apparent to the ordinary artisan and will depend upon the nature of the labile group and the chemistry which the protecting group is expected to encounter, e.g. acidic, basic, oxidative, reductive or other conditions. Exemplary protected species are N^4-benzoylcytosine, N^6-benzoyladenine, N^2-isobutyrylguanine and the like.

Protected bases have the formulas Xa.1, XIa.1, XIb.1, XIIa.1 or XIIIa.1

(Xa.1)



(XIa.1)



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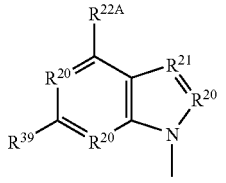
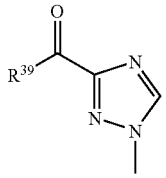
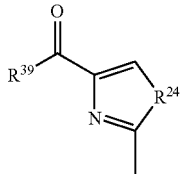


(XIIa.1)



(XIIIa.1)



wherein R^{18}, R^{20}, R^{21}, R^{24} have the meanings previously defined; R^{22A} is R^{39} or R^{22} provided that R^{22} is not NH_2; R^{23A} is R^{39} or R^{23} provided that R^{23} is not NH_2; R^{39} is NHR^{40}, $NHC(O)R^{36}$ or $CR^{41}N(R^{38})_2$ wherein R^{36} is C_1-C_{19} alkyl, C_1-C_{19} alkenyl, C_3-C_{10} aryl, adamantoyl, alkylanyl, or C_3-C_{10} aryl substituted with 1 or 2 atoms or groups selected from halogen, methyl, ethyl, methoxy, ethoxy, hydroxy and cyano; R^{38} is C_1-C_{10} alkyl, or both R^{38} together are 1-morpholino, 1-piperidine or 1-pyrrolidine; R^{40} is C_1-C_{16} alkyl, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, octyl and decanyl; and R^{41} is hydrogen or CH_3.

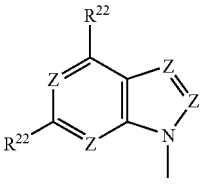
For bases of structures XIa.1 and XIb.1, if R^{39} is present at R^{22A} or R^{23A}, both R^{39} groups on the same base will generally be the same. Exemplary R^{36} are phenyl, phenyl substituted with one of the foregoing R^{36} aryl substituents, —$C_{10}H_{15}$ (where $C_{10}H_{15}$ is 2-adamantoyl), —CH_2—C_6H_5, —C_6H_5, —$CH(CH_3)_2$, —CH_2CH_3, methyl, butyl, t-butyl, heptanyl, nonanyl, undecanyl, or undecenyl.

Specific bases include hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diami-

nopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil and 5-propynyluracil.

Preferably, B is a 9-purinyl residue selected from guanyl, 3-deazaguanyl, 1-deazaguanyl, 8-azaguanyl, 7-deazaguanyl, adenyl, 3-deazaadenyl, 1-dezazadenyl, 8-azaadenyl, 7-deazaadenyl, 2,6-diaminopurinyl, 2-aminopurinyl, 6-chloro-2-aminopurinyl and 6-thio-2-aminopurinyl, or a B' is a 1-pyrimidinyl residue selected from cytosinyl, 5-halocytosinyl, and 5-(C_1-C_3-alkyl)cytosinyl.

Preferred B groups have the formula



wherein

R^{22} independently is halo, oxygen, NH_2, X or H, but optionally at least one R^{22} is X;

X is $—(CH_2)_m(O)_n(CH_2)_mN(R^{10})_2$ wherein m is 0-2, n is 0-1, and

R^{10} independently is H,

C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_6-C_{15} arylalkynyl, C_2-C_{15} alkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroaralkyl, C_5-C_6 aryl, C_2-C_6 heterocycloalkyl,

C_2-C_{15} alkyl, C_3-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_3-C_{15} alkynyl, C_7-C_{15} arylalkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroalkyl or C_3-C_6 heterocycloalkyl wherein methylene in the alkyl moiety not adjacent to N^6 has been replaced by —O—,

optionally both R^{10} are joined together with N to form a saturated or unsaturated C_2-C_5 heterocycle containing one or two N heteroatoms and optionally an additional O or S heteroatom,

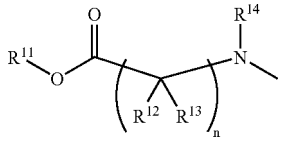
or one of the foregoing R^{10} groups is substituted with 1 to 3 halo, CN or N_3; but optionally at least one R^{10} group is not H; and

Z is N or CH, provided that the heterocyclic nucleus varies from purine by no more than one Z.

E groups represent the aglycons employed in the methoxyphosphonate nucleotide analogues. Preferably, the E group is $—CH(CH_3)CH_2—$ or $—CH_2CH_2—$. Also, it is preferred that the side groups at chiral centers in the aglycon be substantially solely in the (R) configuration (except for hydroxymethyl, which is the enriched (S) enantiomer).

R^1 is an in vivo hydrolyzable oxyester having the structure $—OR^{35}$ or $—OR^6$ wherein R^{35} is defined in column 64, line 49 of U.S. Pat. No. 5,798,340, herein incorporated by reference, and R^6 is defined above. Preferably R^1 is aryloxy, ordinarily unsubstituted or para-substituted (as defined in R^6) phenoxy.

R^2 is an amino acid residue, optionally provided that any carboxy group linked by less than about 5 atoms to the amidate N is esterified. R^2 typically has the structure



(8)

wherein

n is 1 or 2;

R^{11} is R^6 or H; preferably R^6=C_3-C_9 alkyd C_3-C_9 alkyl substituted independently with OH, halogen, O or N; C_3-C_6 aryl; C_3-C_6 aryl which is independently substituted with OH, halogen, O or N; or C_3-C_6 arylalkyl which is independently substituted with OH, halogen, O or N;

R^{12} independently is H or C_1-C_9 alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen; C_3-C_6 aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen; or C_3-C_9 aryl-alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen;

R^{13} independently is C(O)—OR^{11}; amino; amide; guanidinyl; imidazolyl; indolyl; sulfoxide; phosphoryl; C_1-C_3 alkylamino; C_1-C_3 alkyldiamino; C_1-C_6 alkenylamino; hydroxy; thiol; C_1-C_3 alkoxy; C_1-C_3 alkthiol; $(CH_2)_nCOOR^{11}$; C_1-C_6 alkyl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; C_2-C_6 alkenyl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; and C_6-C_{12} aryl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; and

R^{14} is H or C_1-C_9 alkyl or C_1-C_9 alkyl independently substituted with OH, halogen, $COOR^{11}$, O or N; C_3-C_6 aryl; C_3-C_6 aryl which is independently substituted with OH, halogen, $COOR^{11}$, O or N; or C_3-C_6 arylalkyl which is independently substituted with OH, halogen, $COOR^{11}$, O or N.

Preferably, R^{11} is C_1-C_6 alkyl, most preferably isopropyl, R^{13} is the side chain of a naturally occurring amino acid, n=1, R^{12} is H and R^{14} is H. In the compound of structure (2), the invention includes metabolites in which the phenoxy and isopropyl esters have been hydrolyzed to —OH. Similarly, the de-esterified enriched phosphonoamidate metabolites of compounds (5a), 5(b) and (6) are included within the scope of this invention.

Aryl and "O" or "N" substitution are defined in column 16, lines 42-58, of U.S. Pat. No. 5,798,340.

Typically, the amino acids are in the natural or l amino acids. Suitable specific examples are set forth in U.S. Pat. No. 5,798,340, for instance Table 4 and col. 8-10 therein.

Alkyl as used herein, unless stated to the contrary, is a normal, secondary, tertiary or cyclic hydrocarbon. Unless stated to the contrary alkyl is C_1-C_{12}. Examples are $—CH_3$, $—CH_2CH_3$, $—CH_2CH_2CH_3$, $—CH(CH_3)_2$, $—CH_2CH_2CH_2CH_3$), $—CH_2CH(CH_3)_2$, $—CH(CH_3)CH_2CH_3$, $—C(CH_3)_3$, $—CH_2CH_2CH_2CH_2CH_3$, $—CH(CH_3)$

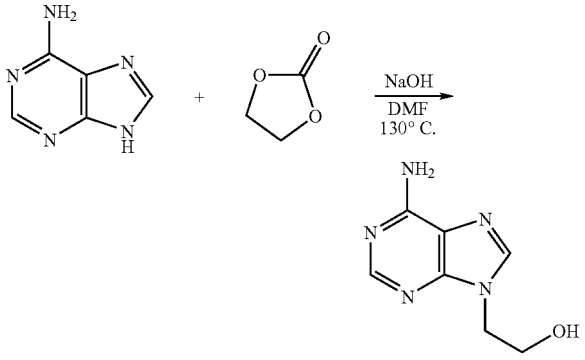
$CH_2CH_2CH_3$, —$CH(CH_2CH_3)_2$, —$C(CH_3)_2CH_2CH_3$), —$CH(CH_3)CH(CH_3)_2$—$CH_2CH_2CH(CH_3)_2$), —$CH_2CH(CH_3)CH_2CH_3$, —$CH_2CH_2CH_2CH_2CH_2CH_3$, —$CH(CH_3)CH_2CH_2CH_2CH_3$, —$CH(CH_2CH_3)(CH_2CH_2CH_3)$, —$C(CH_3)_2CH_2CH_2CH_3$, —$CH(CH_3)CH(CH_3)CH_2CH_3$, —$CH(CH_3)CH_2CH(CH_3)_2$, —$C(CH_3)(CH_2CH_3)_2$, —$CH(CH_2CH_3)CH(CH_3)_2$, —$C(CH_3)_2CH(CH_3)_2$, and —$CH(CH_3)C(CH_3)_3$. Alkenyl and alkynyl are defined in the same fashion, but contain at least one double or triple bond, respectively.

Where enol or keto groups are disclosed, the corresponding tautomers are to be construed as taught as well.

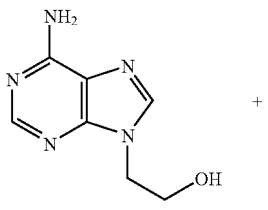
The prodrug compounds of this invention are provided in the form of free base or the various salts enumerated in U.S. Pat. No. 5,798,340, and are formulated with pharmaceutically acceptable excipients or solvating diluents for use as pharmaceutical products also as set forth in U.S. Pat. No. 5,798,340. These prodrugs have the antiviral and utilities already established for the parent drugs (see U.S. Pat. No. 5,798,340 and other citations relating to the methoxyphosphonate nucleotide analogues). It will be understood that the diastereomer of structure (4) at least is useful as an intermediate in the chemical production of the parent drug by hydrolysis in vitro, regardless of its relatively unselective character as revealed in the studies herein.

The invention will be more fully understood by reference to the following examples:

EXAMPLE 1a



Adenine to PMEA using Magnesium Isopropoxide. To a suspension of adenine (16.8 g, 0.124 mol) in DMF (41.9 ml) was added ethylene carbonate (12.1 g, 0.137 mol) and sodium hydroxide (0.100 g, 0.0025 mol). The mixture was heated at 130° C. overnight. The reaction was cooled to below 50° C. and toluene (62.1 ml) was added. The slurry was further cooled to 5° C. for 2 hours, filtered, and rinsed with toluene (2×). The wet solid was dried in vacuo at 65° C. to yield 20.0 g (90%) of 9-(2-hydroxyethyl)adenine as an off-white solid. Mp: 238-240° C.



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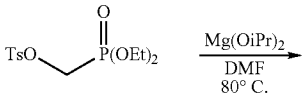
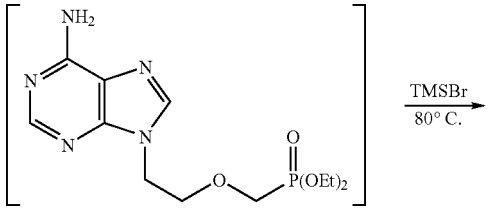
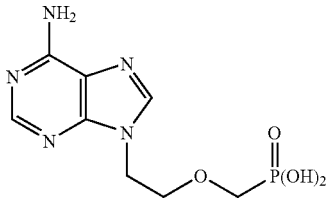
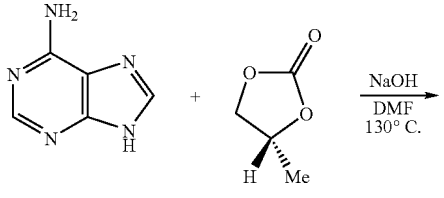






9-(2-Hydroxyethyl)adenine (HEA) (20.0 g, 0.112 mol) was suspended in is DMF (125 ml) and heated to 80° C. Magnesium isopropoxide (11.2 g, 0.0784 mol), or alternatively magnesium t-butoxide, was added to the mixture followed by diethyl p-toluenesulfonyloxymethylphosphonate (66.0 g, 0.162 mol) over one hour. The mixture was stirred at 80° C. for 7 hours. 30 ml of volatiles were removed via vacuum distillation and the reaction was recharged with 30 ml of fresh DMF. After cooling to room temperature, bromotrimethylsilane (69.6 g, 0.450 mol) was added and the mixture heated to 80° C. for 6 hours. The reaction was concentrated to yield a thick gum. The gum was dissolved into 360 ml water, extracted with 120 ml dichloromethane, adjusted to pH 3.2 with sodium hydroxide, and the resulting slurry stirred at room temperature overnight. The slurry was cooled to 4° C. for one hour. The solids were isolated by filtration, washed with water (2×), and dried in vacuo at 56° C. to yield 20 g (65.4%) of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) as a white solid. Mp: >200° C. dec. ^{1}H NMR (D_2O) δ 3.49 (t, 2H); 3.94 (t, 2H); 4.39 (t, 2H); 8.13 (s, 1H); 8.22 (s, 1H).

EXAMPLE 1b



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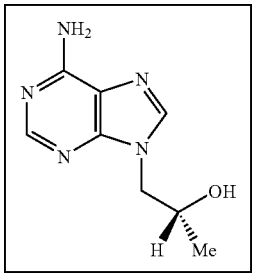
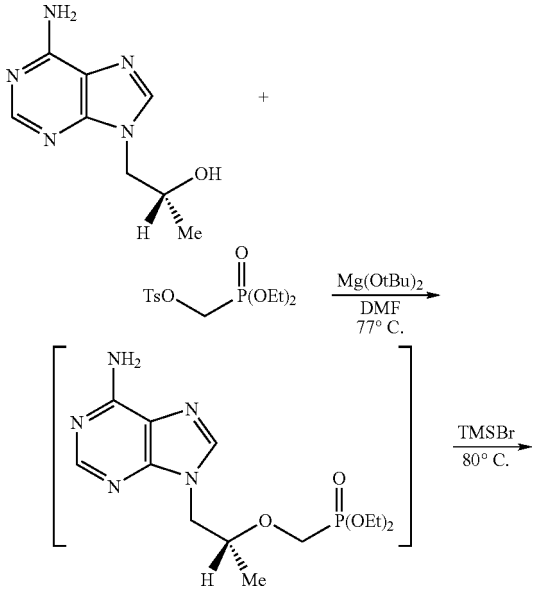


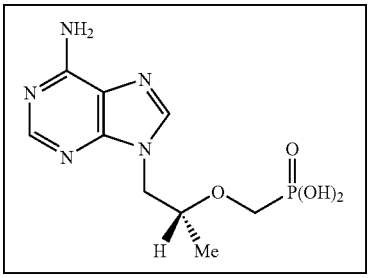
Adenine to PMPA using Magnesium t-Butoxide. To a suspension of adenine (40 g, 0.296 mol) in DMF (41.9 ml) was added (R)-propylene carbonate (34.5 g, 0.338 mol) and sodium hydroxide (0.480 g, 0.012 mol). The mixture was heated at 130° C. overnight. The reaction was cooled to 100° C. and toluene (138 ml) was added followed by methanesulfonic acid (4.7 g, 0.049 mol) while maintaining the reaction temperature between 100-110° C. Additional toluene (114 ml) was added to create a homogeneous solution. The solution was cooled to 3° C. over 7 hours and then held at 3° C. for one hour. The resulting solid was isolated by filtration and rinsed with acetone (2×). The wet solid was dried in vacuo at 80° C. to yield 42.6 g (75%) of (R)-9-[2-(hydroxy)propyl] adenine (HPA) as an off-white solid. Mp: 188-190° C.



(anhydrous)

I

-continued



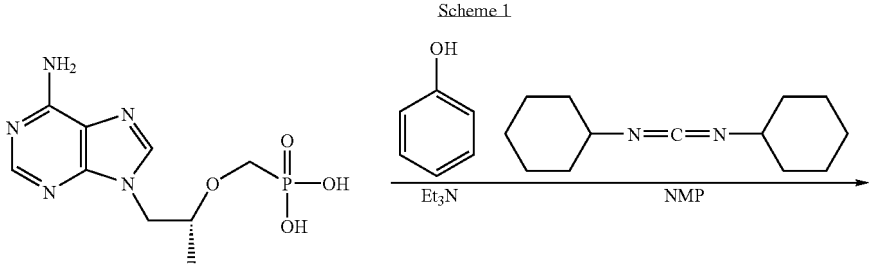
(R)-9-[2-(hydroxy)propyl]adenine (HPA) (20.0 g, 0.104 mol) was suspended in DMF (44.5 ml) and heated to 65° C. Magnesium t-butoxide (14.2 g, 0.083 mol), or alternatively magnesium isopropoxide, was added to the mixture over one hour followed by diethyl p-toluenesulfonyloxymethylphosphonate (66.0 g, 0.205 mol) over two hours while the temperature was kept at 78° C. The mixture was stirred at 75° C. for 4 hours. After cooling to below 50° C., bromotrimethylsilane (73.9 g, 0.478 mol) was added and the mixture heated to 77° C. for 3 hours. When complete, the reaction was heated to 80° C. and volatiles were removed via atmospheric distillation. The residue was dissolved into water (120 ml) at 50° C. and then extracted with ethyl acetate (101 ml). The pH of the aqueous phase was adjusted to pH 1.1 with sodium hydroxide, seeded with authentic (R)-PMPA, and the pH of the aqueous layer was readjusted to pH 2.1 with sodium hydroxide. The resulting slurry was stirred at room temperature overnight. The slurry was cooled to 4° C. for three hours. The solid was isolated by filtration, washed with water (60 ml), and dried in vacuo at 50° C. to yield 18.9 g (63.5%) of crude (R)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA) as an off-white solid.

The crude (R)-9-[2-(phosphonomethoxy)propyl]adenine was heated at reflux in water (255 ml) until all solids dissolved. The solution was cooled to room temperature over 4 hours. The resulting slurry was cooled at 4° C. for three hours. The solid was isolated by filtration, washed with water (56 ml) and acetone (56 ml), and dried in vacuo at 50° C. to yield 15.0 g (50.4%) of (R)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA) as a white solid. Mp: 278-280° C.

EXAMPLE 2

Preparation of GS-7171 (III)

Scheme 1



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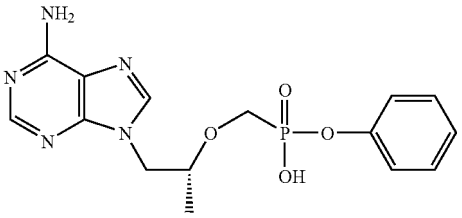
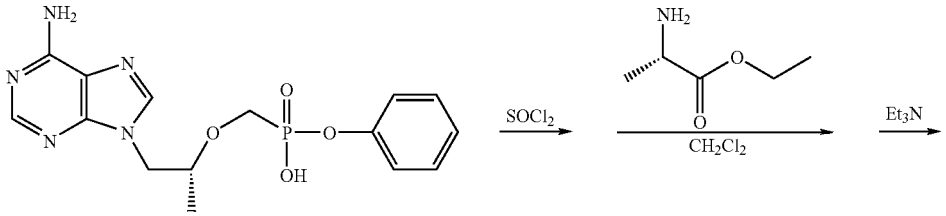
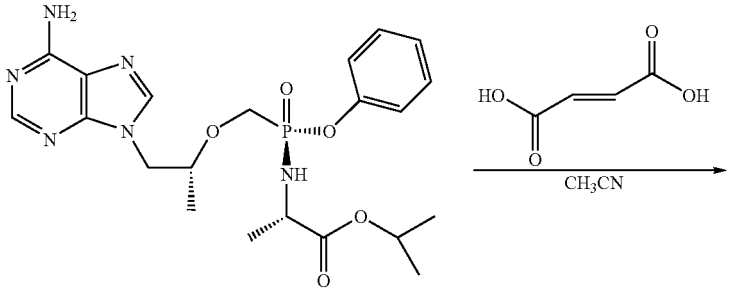


II



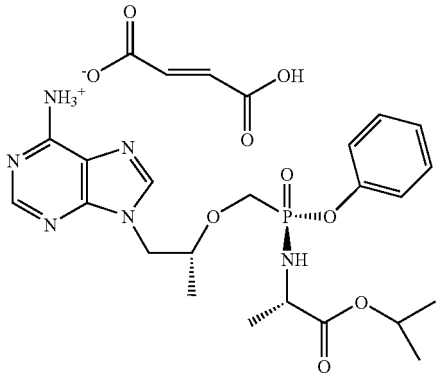
III

GS-7171



IV

GS-7340



V

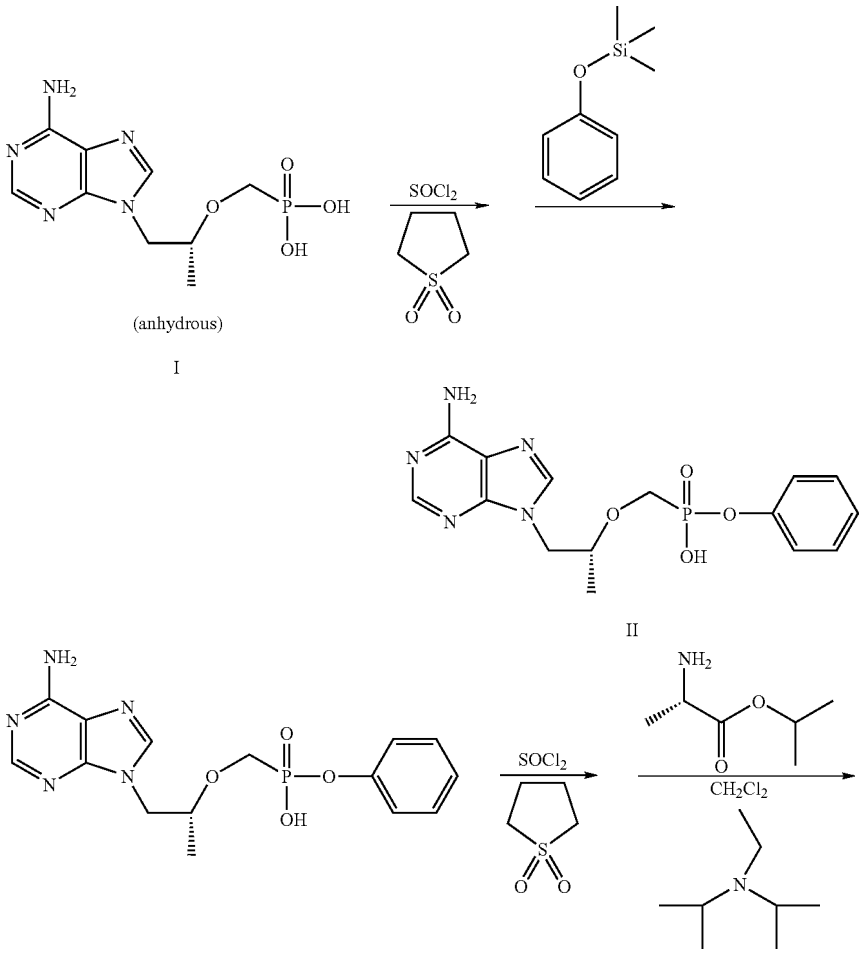
GS-7340-02

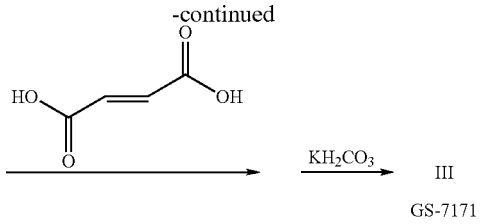
A glass-lined reactor was charged with anhydrous PMPA, (I) (14.6 kg, 50.8 mol), phenol (9.6 kg, 102 mol), and 1-methyl-2-pyrrolidinone (39 kg). The mixture was heated to 85° C. and triethylamine (6.3 kg, 62.3 mol) added. A solution of 1,3-dicyclohexylcarbodiimide (17.1 kg, 82.9 mol) in 1-methyl-2-pyrrolidinone (1.6 kg) was then added over 6 hours at 100° C. Heating was continued for 16 hours. The reaction was cooled to 45° C., water (29 kg) added, and cooled to 25° C. Solids were removed from the reaction by filtration and rinsed with water (15.3 kg). The combined filtrate and rinse was concentrated to a tan slurry under reduced pressure, water (24.6 kg) added, and adjusted to pH=11 with NaOH (25% in water). Fines were removed by filtration through diatomaceous earth (2 kg) followed by a water (4.4 kg) rinse. The combined filtrate and rinse was extracted with ethyl acetate (28 kg). The aqueous solution was adjusted to pH=3.1 with HCl (37% in water) (4 kg). Crude II was isolated by filtration and washed with methanol (12.7 kg). The crude II wet cake was slurried in methanol (58 kg). Solids were isolated by filtration, washed with methanol (8.5 kg), and dried under reduced pressure to yield 9.33 kg II as a white powder: ^{1}H NMR (D_2O) δ 1.2 (d, 3H), 3.45 (q, 2H), 3.7 (q, 2H), 4 (m, 2H), 4.2 (q, 2H), 4.35 (dd, 2H), 6.6 (d, 2H), 7 (t, 1H), 7.15 (t, 2H), 8.15 (s, 1H), 8.2 (s, 1H); ^{31}P NMR (D_2O) δ 15.0 (decoupled).

GS-7171 (III). (Scheme 1) A glass-lined reactor was charged with monophenyl PMPA, (II), (9.12 kg, 25.1 mol) and acetonitrile (30.7 kg). Thionyl chloride (6.57 kg, 56.7 mol) was added below 50° C. The mixture was heated at 75° C. until solids dissolved. Reaction temperature was increased to 80° C. and volatiles (11.4 kg) collected by atmospheric distillation under nitrogen. The pot residue was cooled to 25° C., dichloromethane (41 kg) added, and cooled to −29° C. A solution of (L)-alanine isopropyl ester (7.1 kg, 54.4 mol) in dichloromethane (36 kg) was added over 60 minutes at −18° C. followed by triethylamine (7.66 kg, 75.7 mol) over 30 minutes at −18 to −11° C. The reaction mixture was warmed to room temperature and washed five times with sodium dihydrogenphosphate solution (10% in water, 15.7 kg each wash). The organic solution was dried with anhydrous sodium sulfate (18.2 kg), filtered, rinsed with dichloromethane (28 kg), and concentrated to an oil under reduced pressure. Acetone (20 kg) was charged to the oil and the mixture concentrated under reduced pressure. Acetone (18.8 kg) was charged to the resulting oil. Half the product solution was purified by chromatography over a 38×38 cm bed of 22 kg silica gel 60, 230 to 400 mesh. The column was eluted with 480 kg acetone. The purification was repeated on the second half of the oil using fresh silica gel and acetone. Clean product bearing fractions were concentrated under reduced pressure to an oil. Acetonitrile (19.6 kg) was charged to the oil and the mixture concentrated under reduced pressure. Acetonitrile (66.4 kg) was charged and the solution chilled to 0 to −5° C. for 16 hours. Solids were removed by filtration and the filtrate concentrated under reduced pressure to 5.6 kg III as a dark oil. ^{1}H NMR ($CDCl_3$) δ 1.1 (m 12H), 3.7 (m, 1H), 4.0 (m, 5H), 4.2 (m, 1H), 5.0 (m, 1H), 6.2 (s, 2H), 7.05 (m, 5H), 8.0 (s, 1H), 8.25 (d, 1H); ^{31}P NMR ($CDCl_3$) δ 21.0, 22.5 (decoupled).

Alternate Method for GS-7171 (III)

Scheme 2





Monophenyl PMPA (II). A round-bottom flask with reflux condenser and nitrogen inlet was placed in a 70° C. oil bath. The flask was charged with anhydrous PMPA (I) (19.2 g, 67 mmol), N,N-dimethylformamide (0.29 g, 3.3 mmol), and tetramethylene sulfone (40 mL). Thionyl chloride (14.2 g, 119 mmol) was added over 4 hours. Heating was increased to 100° C. over the same time. A homogeneous solution resulted. Phenoxytrimethylsilane (11.7 g, 70 mmol) was added to the solution over 5 minutes. Heating in the 100° C. oil bath continued for two hours more. The reaction was poured into rapidly stirring acetone (400 mL) with cooling at 0° C. Solids were isolated by filtration, dried under reduced pressure, and dissolved in methanol (75 mL). The solution pH was adjusted to 3.0 with potassium hydroxide solution (45% aq.) with cooling in ice/water. The resulting solids were isolated by filtration, rinsed with methanol, and dried under reduced pressure to 20.4 g II (Scheme 2) as a white powder.

GS-7171 (III). Monophenyl PMPA (II) (3 g, 8.3 mmol), tetramethylene sulfone (5 mL), and N,N-dimethylformamide (1 drop) were combined in a round bottom flask in a 40° C. oil bath. Thionyl chloride (1.96 g, 16.5 mmol) was added. After 20 minutes the clear solution was removed from heat, diluted with dichloromethane (10 ml), and added to a solution of (L)-alanine isopropyl ester (5 g, 33 mmol) and diisopropylethylamine (5.33 g, 41 mmol) in dichloromethane (20 mL) at −10° C. The reaction mixture was warmed to room temperature and washed three times with sodium dihydrogenphosphate solution (10% aq., 10 mL each wash). The organic solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to a oil. The oil was combined with fumaric acid (0.77 g, 6.6 mmol) and acetonitrile (40 mL) and heated to reflux to give a homogeneous solution. The solution was cooled in an ice bath and solids isolated by filtration. The solid GS-7171 fumarate salt was dried under reduced pressure to 3.7 g. The salt (3.16 g, 5.3 mmol) was suspended in dichloromethane (30 mL) and stirred with potassium carbonate solution (5 mL, 2.5 M in water) until the solid dissolved. The organic layer was isolated, then washed with water (5 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 2.4 g III as a tan foam.

EXAMPLE 3

Diastereomer Separation by Batch Elution Chromatography

The diastereomers of GS-7171 (II) were resolved by batch elution chromatography using a commercially available Chiralpak AS, 20 μm, 21×250 mm semi-preparative HPLC column with a Chiralpak AS, 20 μm, 21×50 mm guard column. Chiralpak® AS is a proprietary packing material manufactured by Diacel and sold in North America by Chiral Technologies, Inc. (U.S. Pat. No. 5,202,433, RE 35,919, U.S. Pat. Nos. 5,434,298, 5,434,299 and 5,498,752). Chliralpak AS is a chiral stationary phase (CSP) comprised of amylosetris[(S)-α-methylbenzyl carbamate] coated onto a silica gel support.

The GS-7171 diastereomeric mixture was dissolved in mobile phase, and approximately 1 g aliquots of GS-7171 were pumped onto the chromatographic system. The undesired diastereomer, designated GS-7339, was the first major broad (approx. 15 min. duration) peak to elute from the column. When the GS-7339 peak had finished eluting, the mobile phase was immediately switched to 100% methyl alcohol, which caused the desired diastereomer, designated GS-7340 (IV), to elute as a sharp peak from the column with the methyl alcohol solvent front. The methyl alcohol was used to reduce the over-all cycle time. After the first couple of injections, both diastereomers were collected as a single large fractions containing one of the purified diastereomers (>99.0% single diastereomer). The mobile phase solvents were removed in vacuo to yield the purified diastereomer as a friable foam.

About 95% of the starting GS-7171 mass was recovered in the two diastereomer fractions. The GS-7340 fraction comprised about 50% of the total recovered mass.

The chromatographic conditions were as follows:

Mobile Phase	(Initial)	GS-7171 - Acetonitrile:Isopropyl Alcohol (90:10)
	(Final)	100% Methyl Alcohol
Flow		10 mL/minute
Run Time		About 45 minute
Detection		UV at 275 nm
Temperature		Ambient
Elution Profile		GS-7339 (diastereomer B) GS-7340 (diastereomer A; (IV))

Diastereomer Separation of GS-7171 by SMB Chromatography

For a general description of simulated moving bed (SMB) chromatography, see Strube et al., "Organic Process Research and Development" 2:305-319 (1998).

GS-7340 (IV). GS-7171 (III), 2.8 kg, was purified by simulated moving bed chromatography over 10 cm by 5 cm beds of packing (Chiral Technologies Inc., 20 micron Chiralpak AS coated on silica gel) (1.2 kg). The columns were eluted with 30% methanol in acetonitrile. Product bearing fractions were concentrated to a solution of IV in acetonitrile (2.48 kg). The solution solidified to a crystalline mass wet with acetonitrile on standing. The crystalline mass was dried under reduced pressure to a tan crystalline powder, 1.301 kg IV, 98.7% diastereomeric purity: mp 117-120° C.; ^{1}H NMR ($CDCl_3$) δ 1.15 (m 12H), 3.7 (t, 1H), 4.0 (m, 5H), 4.2 (dd, 1H), 5.0 (m, 1H), 6.05 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.2 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 21.0 (decoupled).

Diastereomer Separation by C18 RP-HPLC

GS-7171 (III) was chromatographed by reverse phase HPLC to separate the diastereomers using the following summary protocol.

Chromatographic column:	Phenomenex Luna ™ C18(2), 5 μm, 100 Å pore size, (Phenomenex, Torrance, CA), or equivalent
Guard column:	Pellicular C18 (Alltech, Deerfield, IL), or equivalent
Mobile Phase:	A - 0.02% (85%) H_3PO_4 in water:acetonitrile (95:5) B - 0.02% (85%) H_3PO_4 in water:acetonitrile (50:50)

Mobile Phase Gradient:

Time	% Mobile Phase A	% Mobile Phase B
0	100	0
5	100	0
7	70	30
32	70	30
40	0	100
50	0	100

Run Time:	50 minutes
Equilibration Delay:	10 min at 100% mobile phase A
Flow Rate:	1.2 mL/min
Temperature:	Ambient
Detection:	UV at 260 nm
Sample Solution:	20 mM sodium phosphate buffer, pH 6
Retention Times:	GS-7339, about 25 minutes GS-7340, about 27 minutes

Diastereomer Separation by Crystallization

GS-7340 (IV). A solution of GS-7171 (III) in acetonitrile was concentrated to an amber foam (14.9 g) under reduced pressure. The foam was dissolved in acetonitrile (20 mL) and seeded with a crystal of IV. The mixture was stirred overnight, cooled to 5° C., and solids isolated by filtration. The solids were dried to 2.3 g IV as white crystals, 98% diastereomeric purity (^{31}P NMR): ^{1}H NMR ($CDCl_3$) δ 1.15 (m 12H), 3.7 (t, 1H), 3.95 (m, 2H), 4.05 (m, 2H), 4.2 (m, 2H), 5.0 (m, 1H), 6.4 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.2 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 19.5 (decoupled). X-ray crystal analysis of a single crystal selected from this product yielded the following data:

Crystal Color, Habit	colorless, column
Crystal Dimensions	0.25 × 0.12 × 0.08 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 8.352(1) Å b = 15.574(2) Å c = 18.253(2) Å V = 2374.2(5) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.333 g/cm^3
F_{000}	1008.00
μ(MoKα)	1.60 cm^{-1}

EXAMPLE 4

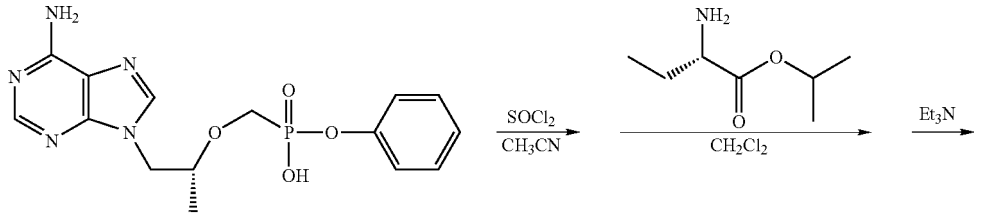
Preparation of Fumarate Salt of GS-7340

GS-7340-02 (V). (Scheme 1) A glass-lined reactor was charged with GS-730 (IV), (1.294 kg, 2.71 mol), fumaric acid (284 g, 2.44 mol), and acetonitrile (24.6 kg). The mixture was heated to reflux to dissolve the solids, filtered while hot and cooled to 5° C. for 16 hours. The product was isolated by filtration, rinsed with acetonitrile (9.2 kg), and dried to 1329 g (V) as a white powder: mp 119.7-121.1° C.; $[\alpha]_D^{20}$ −41.7° (c 1.0, acetic acid).

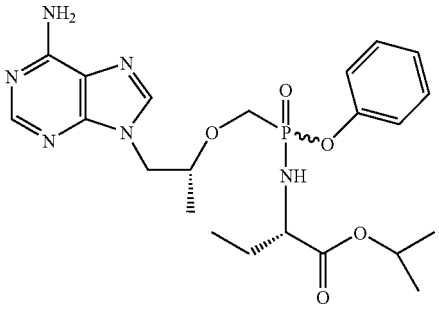
EXAMPLE 15

Preparation of GS-7120 (VI)

Scheme 3



II



VI

GS-7120

A 5 L round bottom flask was charged with monophenyl PMPA, (II), (200 g, 0.55 mol) and acetonitrile (0.629 kg). Thionyl chloride (0.144 kg, 1.21 mol) was added below 27° C. The mixture was heated at 70° C. until solids dissolved. Volatiles (0.45 L) were removed by atmospheric distillation under nitrogen. The pot residue was cooled to 25° C., dichloromethane (1.6 kg) was added and the mixture was cooled to −20° C. A solution of (L)-α aminobutyric acid ethyl ester (0.144 kg, 1.1 mol) in dichloromethane (1.33 kg) was added over 18 minutes at −20 to −10° C. followed by triethylamine (0.17 kg, 1.65 mol) over 15 minutes at −8 to −15° C. The reaction mixture was warmed to room temperature and washed four times with sodium dihydrogenphosphate solution (10% aq., 0.3 L each wash). The organic solution was dried with anhydrous sodium sulfate (0.5 kg) and filtered. The solids were rinsed with dichloromethane (0.6 kg) and the combined filtrate and rinse was concentrated to an oil under reduced pressure. The oil was purified by chromatography over a 15×13 cm bed of 1.2 kg silica gel 60, 230 to 400 mesh. The column was eluted with a gradient of dichloromethane and methanol. Product bearing fractions were concentrated under reduced pressure to afford 211 g VI (Scheme 3) as a tan foam.

EXAMPLE 5a

Diastereomer Separation of GS-7120 by Batch Elution Chromatography

The diastereomeric mixture was purified using the conditions described for GS-7171 in Example 3A except for the following:

Mobile Phase	(Initial)	GS-7120 - Acetonitrile:Isopropyl Alcohol (98:2)
	(Final)	100% Methyl Alcohol
Elution Profile		GS-7341 (diastereomer B) GS-7342 (diastereomer A)

EXAMPLE 6

Diastereomer Separation of GS-7120 by Crystallization

A 1 L round bottom flask was charged with monophenyl PMPA, (II), (50 g, 0.137 mol) and acetonitrile (0.2 L). Thionyl chloride (0.036 kg, 0.303 mol) was added with a 10° C. exotherm. The mixture was heated to reflux until solids dissolved. Volatiles (0.1 L) were removed by atmospheric distillation under nitrogen. The pot residue was cooled to 25° C., dichloromethane (0.2 kg) was added, and the mixture was cooled to −20° C. A solution of (L)-α aminobutyric acid ethyl ester (0.036 kg, 0.275 mol) in dichloromethane (0.67 kg) was added over 30 minutes at −20 to −8° C. followed by triethylamine (0.042 kg, 0.41 mol) over 10 minutes at up to −6° C. The reaction mixture was warmed to room temperature and washed four times with sodium dihydrogenphosphate solution (10% aq., 0.075 L each wash). The organic solution was dried with anhydrous sodium sulfate (0.1 kg) and filtered. The solids were rinsed with ethyl acetate (0.25 L, and the combined filtrate and rinse was concentrated to an oil under reduced pressure. The oil was diluted with ethyl acetate (0.25 L), seeded, stirred overnight, and chilled to −15° C. The solids were isolated by filtration and dried under reduced pressure to afford 17.7 g of GS-7342 (Table 5) as a tan powder: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.3 (m, 6H), 1.7, (m, 2H), 3.7 (m, 2H), 4.1 (m, 6H), 4.4 (dd, 1H), 5.8 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.4 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 21 (decoupled).

EXAMPLE 7

Diastereomer Separation of GS-7097

The diastereomeric mixture was purified using the conditions described for GS-7171 (Example 3A) except for the following:

Mobile Phase	(Initial)	GS-7120 - Acetonitrile:Isopropyl Alcohol (95:5)
	(Final)	100% Methyl Alcohol
Elution Profile		GS-7115 (diastereomer B) GS-7114 (diastereomer A)

EXAMPLE 8

Alternative Procedure for Preparation of GS-7097

GS-7097: Phenyl PMPA, Ethyl L-Alanyl Amidate. Phenyl PMPA (15.0 g, 41.3 mmol), L-alanine ethyl ester hydrochloride (12.6 g, 83 mmol) and triethylamine (11.5 mL, 83 mmol) were slurried together in 500 mL pyridine under dry N_2. This suspension was combined with a solution of triphenylphosphine (37.9 g, 145 mmol), Aldrithiol 2 (2,2'-dipyridyl disulfide) (31.8 g, 145 mmol), and 120 mL pyridine. The mixture was heated at an internal temperature of 57° C. for 15 hours. The complete reaction was concentrated under vacuum to a yellow paste, 100 g. The paste was purified by column chromatography over a 25×11 cm bed of 1.1 kg silica gel 60, 230 to 400 mesh. The column was eluted with 8 liters of 2% methanol in dichloromethane followed by a linear gradient over a course of 26 liters eluent up to a final composition of 13% methanol. Clean product bearing fractions were concentrated to yield 12.4 g crude (5), 65% theory. This material was contaminated with about 15% (weight) triethylamine hydrochloride by ^{1}H NMR. The contamination was removed by dissolving the product in 350 mL ethyl acetate, extracting with 20 mL water, drying the organic solution over anhydrous sodium sulfate, and concentrating to yield 11.1 g pure GS-7097 as a white solid, 58% yield. The process also is employed to synthesize the diastereomeric mixture of GS-7003a and GS-7003b (the phenylalanyl amidate) and the mixture GS-7119 and GS-7335 (the glycyl amidate). These diastereomers are separated using a batch elution procedure such as shown in Example 3A, 6 and 7.

EXAMPLE 9

In Vitro Studies of Prodrug Diastereomers

The in vitro anti-HIV-1 activity and cytotoxicity in MT-2 cells and stability in human plasma and MT-2 cell extracts of GS-7340 (freebase) and tenofovir disoproxil fumarate (TDF), are shown in Table 1. GS-7340 shows a 10-fold increase in antiviral activity relative to TDF and a 200-fold increase in plasma stability. This greater plasma stability is expected to result in higher circulating levels of GS-7340 than TDF after oral administration.

TABLE 1

In Vitro Activity and Stability

	HIV-1		Stability T ½ (min)		
	Activity IC_{50} μM	Cytotoxicity CC_{50} μM	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0.005	>40	90.0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	—	—	—

In order to estimate the relative intracellular PMPA resulting from the intracellular metabolism of TDF as compared to that from GS-7340, both prodrugs and PMPA were radiolabeled and spiked into intact human whole blood at equimolar concentrations. After 1 hour, plasma, red blood cells (RBCs) and peripheral blood mononuclear cells (PBMCs) were isolated and analyzed by HPLC with radiometric detection. The results are shown in Table 2.

After 1 hour, GS-7340 results in 10× and 30× the total intracellular concentration of PMPA species in PBMCs as compared to TDF and PMPA, respectively. In plasma after 1 hour, 84% of the radioactivity is due to intact GS-7340, whereas no TDF is detected at 1 hour. Since no intact TDF is detected in plasma, the 10× difference at 1 hour between TDF and GS-7340 is the minimum difference expected in vivo. The HPLC chromatogram for all three compounds in PBMCs is shown in FIG. **1**.

Met. X and Met Y (metabolites X and Y) are shown in Table 5. Lower case "p" designates phosphorylation. These results were obtained after 1 hour in human blood. With increasing time, the in vitro differences are expected to increase, since 84% of GS-7340 is still intact in plasma after one hour. Because intact GS-7340 is present in plasma after oral administration, the relative clinical efficacy should be related to the IC_{50} values seen in vitro.

In Table 3 below, IC_{50} values of tenofovir, TDF, GS-7340, several nucleosides and the protease inhibitor nelfinivir are listed. As shown, nelfinavir and GS-7340 are 2-3 orders of magnitude more potent than all other nucleotides or nucleosides.

TABLE 3

In Vitro Anti-HIV-1 Activities of Antiretroviral Compounds

Compound	IC_{50} (μM)
Adefovir (PMEA)	13.4 ± 4.2[1]
Tenofovir (PMPA)	6.3 ± 3.3[1]
AZT	0.17 ± 0.08[1]
3TC	1.8 ± 0.25[1]
d4T	8 ± 2.5[1]
Nelfinavir	0.006 ± 0.002[1]
TDF	0.05
GS 7340	0.005

[1]A. S. Mulato and J. M. Cherrington, Antiviral Research 36, 91 (1997)

Additional studies of the in vitro cell culture anti-HIV-1 activity and CC_{50} of separated diastereomers of this invention were conducted and the results tabulated below.

TABLE 4

Effect of Diastereomer

Compound	Diastereomer residue	IC_{50} (μM)	Fold change	A/B activity	CC_{50} (μM)
PMPA	—	5	1x	—	6000
Ala-methylester	Mixture 1:1	0.025	200x	20x	80
GS-6957a	A	0.0075	670x		

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, μg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 μg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 μg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 μg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

TABLE 4-continued

Effect of Diastereomer

Compound	Diastereomer residue	IC_{50} (μM)	Fold change	A/B activity	CC_{50} (μM)
GS-6957b		0.15	33x		
Phe-methylester	Mixture 1:1	0.03	170x	10x	60
GS-7003a	A	0.01	500x		
GS-7003b	B	0.1	50x		
Gly-ethylester	Mixture 1:1	0.5	10x	20x	
GS-7119	A	0.05	100x		>100
GS-7335	B	1.0	5x		
Ala-isopropyl	Mixture 1:1	0.01	500x	12x	
GS-7340	A	0.005	1,000x		40
GS-7339	B	0.06	83x		>100
ABA-ethyl	Mixture 1:1	0.008	625x	7.5x	>100
GS-7342	A	0.004	1,250x		
GS-7341	B	0.03	170x		
Ala-ethyl	Mixture 1:1	0.02	250x	10x	60
GS-7114	A	0.005	1,000x		
GS-7115	B	0.05	100x		

Assay reference: Arimilli, M N, et al., (1997) Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs. Antiviral Chemistry and Chemotherapy 8(6):557-564.

"Phe-methylester" is the methylphenylalaninyl monoamidate, phenyl monoester of tenofovir; "gly-methylester" is the methylglycyl monoamidate, phenyl monoester of tenofovir.

In each instance above, isomer A is believed to have the same absolute stereochemistry as GS-7340 (S), and isomer B is believed to have the same absolute stereochemistry that of GS-7339.

The in vitro metabolism and stability of separated diastereomers were determined in PLCE, MT-2 extract and human plasma. A biological sample listed below, 80 μL, was transferred into a screw-capped centrifuge tube and incubated at 37° C. for 5 min. A solution containing 0.2 mg/mL of the test compound in a suitable buffer, 20 μL, was added to the biological sample and mixed. The reaction mixture, 20 μL, was immediately sampled and mixed with 60 μL of methanol containing 0.015 mg/mL of 2-hydroxymethylnaphthalene as an internal standard for HPLC analysis. The sample was taken as the time-zero sample. Then, at specific time points, the reaction mixture, 20 μL, was sampled and mixed with 60 μl of methanol containing the internal standard. The mixture thus obtained was centrifuged at 15,000 G for 5 min and the supernatant was analyzed with HPLC under the conditions described below.

The biological samples evaluated are as follows,

(1) PLCE (porcine liver carboxyesterase from Sigma, 160 u/mg protein, 21 mg protein/mL) diluted 20 fold with PBS (phosphated-buffered saline).

(2) MT-2 cell extract was prepared from MT-2 cells according to the published procedure [A. Pompon, I. Lefebvre, J.-L. Imbach, S. Kahn, and D. Farquhar, "Antiviral Chemistry & Chemotherapy", 5:91-98 (1994)] except for using HEPES buffer described below as the medium.

(3) Human plasma (pooled normal human plasma from George King Biomedical Systems, Inc.)

The buffer systems used in the studies are as follows.

In the study for PLCE, the test compound was dissolved in PBS. PBS (phosphate-buffered saline, Sigma) contains 0.01 M phosphate, 0.0027 M potassium chloride, and 0.137 M sodium chloride. pH 7.4 at 37° C.

In the study for MT-2 cell extracts, the test compound was dissolved in HEPES buffer. HEPES buffer contains 0.010 M HEPES, 0.05 M potassium chloride, 0.005 M magnesium chloride, and 0.005 M dl-dithiothreitol. pH 7.4 at 37° C.

In the study for human plasma, the test compound was dissolved in TBS. TBS (tris-buffered saline, Sigma) contains 0.05 M Tris, 0.0027 M potassium chloride, and 0.138 M sodium chloride. pH 7.5 at 37° C.

The HPLC analysis was carried out under the following conditions.

Column:	Zorbax R_x-C_8, 4.6 × 250 mm, 5μ (MAC-MOD Analytical, Inc. Chadds Ford, PA)
Detection:	UV at 260 nm
Flow Rate:	1.0 mL/min
Run Time:	30 min
Injection Volume:	20 μl
Column Temperature:	Ambient temperature
Mobile Phase A:	50 mM potassium phosphate (pH 6.0)/CH_3CN = 95/5 (v/v)
Mobile Phase B:	50 mM Potassium phosphate (pH 6.0)/CH_3CN = 50/50 (v/v)
Gradient Run:	0 min 100% Mobile Phase A 25 min 100% Mobile Phase B 30 min 100% Mobile Phase B

The results are shown below in Table 5 (also including selected IC_{50} data from Table 4).

TABLE 5

In Vitro Metabolism of Isomers A and B of PMPA monoamidate at 37° C.

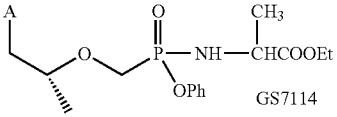
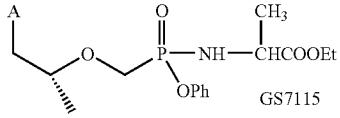
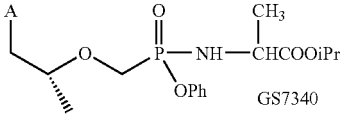
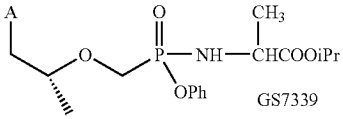
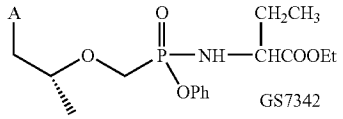
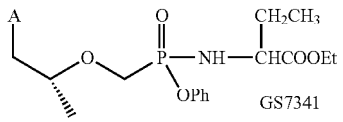
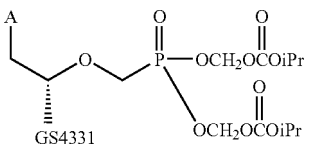
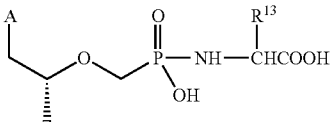
No.	PMPA monoamidate structure	HIV IC_{50} (μM)	PLCE hydrolysis rate and product	MT-2 extract hydrolysis rate and product	Human Plasma Stability (HP)
1	 Isomer A GS7114	0.005	$t_{1/2}$ = 2.9 min Met. X & PMPA	$t_{1/2}$ = 2.9 min Met. X & PMPA	$t_{1/2}$ = 148 min Met. Y

TABLE 5-continued

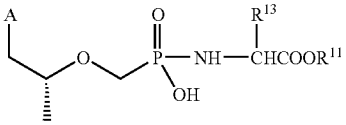
In Vitro Metabolism of Isomers A and B of PMPA monoamidate at 37° C.

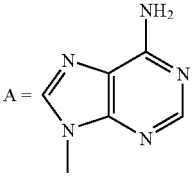
No.	PMPA monoamidate structure	HIV IC_{50} (μM)	PLCE hydrolysis rate and product	MT-2 extract hydrolysis rate and product	Human Plasma Stability (HP)
2	 GS7115 Isomer B	0.05	$t_{1/2}$ = 8.0 min Met. X & PMPA	$t_{1/2}$ = 150.6 min Met. X & PMPA	$t_{1/2}$ = 495 min Met. Y
3	 GS7340 Isomer A	0.005	$t_{1/2}$ = 3.3 min Met. X & PMPA	$t_{1/2}$ = 28.3 min Met. X & PMPA	$t_{1/2}$ = 90.0 min Met. Y
4	 GS7339 Isomer B	0.06	$t_{1/2}$ = 10.1 min Met. X & PMPA	$t_{1/2}$ > 1000 min	$t_{1/2}$ = 231 min Met. Y
5	 GS7342 Isomer A	0.004	$t_{1/2}$ = 3.9 min Met. X	$t_{1/2}$ = 49.2 min Met. X & PMPA	$t_{1/2}$ = 103 min Met. Y
6	 GS7341 Isomer B	0.03	$t_{1/2}$ = 11.3 min Met. X	$t_{1/2}$ > 1000 min	$t_{1/2}$ = 257 min Met. Y
7	 GS4331	0.05	$t_{1/2}$ < 0.14 min MonoPOC PMPA	$t_{1/2}$ = 70.7 min monoPOC PMPA	$t_{1/2}$ = 0.41 min monoPOC PMPA

Met. X:



Met. Y:





EXAMPLE 10

Plasma and PBMC Exposures Following Oral Administration of Prodrug Diastereomers to Beagle Dogs

The pharmacokinetics of GS 7340 were studied in dogs after oral administration of a 10 mg-eq/kg dose.

Formulations. The prodrugs were formulated as solutions in 50 mM citric acid within 0.5 hour prior to dose. All compounds used in the studies were synthesized by Gilead Sciences. The following lots were used:

GSI	Amidate Amino acid	AA Ester	Diastereo-isomer	Lot Number
GS-7340-2	Alanine	i-Propyl	Isomer A	1504-187-19
GS-7339	Alanine	i-Propyl	Isomer B	1509-185-31
GS7114	Alanine	Ethyl	Isomer A	1509-181-26
GS7115	Alanine	Ethyl	Isomer B	1509-181-22
GS7119	Glycine	Ethyl	Isomer A	1428-163-28
GS7342	α-Aminobutyric Acid	Ethyl	Isomer A	1509-191-12
GS7341	α-Aminobutyric Acid	Ethyl	Isomer B	1509-191-7

Dose Administration and Sample Collection. The in-life phase of this study was conducted in accordance with the recommendations of the "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health publication 86-23) and was approved by an Institutional Animal Care and Use Committee. Fasted male beagle dogs (10±2 kg) were used for the studies. Each drug was administered as a single dose by oral gavage (1.5-2 ml/kg). The dose was 10 mg-equivalent of PMPA/kg. For PBMCs, blood samples were collected at 0 (pre-dose), 2, 8, and 24 h post-dose. For plasma, blood samples were collected at 0 (pre-dose), 5, 15, and 30 min and 1, 2, 3, 4, 6, 8, 12 and 24 h post-dose. Blood (1.0 ml) was processed immediately for plasma by centrifugation at 2,000 rpm for 10 min. Plasma samples were frozen and maintained at 70° C. until analyzed.

Peripheral Blood Mononuclear Cell (PBMC) preparation. Whole blood (8 ml) drawn at specified time points was mixed in equal proportion with phosphate buffered saline (PBS), layered onto 15 ml of Ficoll-Paque solution (Pharmacia Biotech,) and centrifuged at 400×g for 40 min. PBMC layer was removed and washed once with PBS. Formed PMBC pellet was reconstituted in 0.5 ml of PBS, cells were resuspended, counted using hemocytometer and maintained at 70° C. until analyzed. The number of cells multiplied by the mean single-cell volume was used in calculation of intracellular concentrations. A reported value of 200 femtoliters/cell was used as the resting PBMC volume (B. L. Robins, R. V. Srinivas, C. Kim, N. Bischofberger, and A. Fridland, Antimicrob. Agents Chemother. 42, 612 (1998).

Determination of PMPA and Prodrugs in plasma and PBMCs. The concentration of PMPA in dog plasma samples was determined by derivatizing PMPA with chloroacetaldehyde to yield a highly fluorescent N^2,N^6-ethenoadenine derivative (L. Naesens, J. Balzarini, and E. De Clercq, Clin. Chem. 38, 480 (1992). Briefly, plasma (100 μl) was mixed with 200 μl acetonitrile to precipitate protein. Samples were then evaporated to dryness under reduced pressure at room temperature. Dried samples were reconstituted in 200 μl derivatization cocktail (0.34% chloroacetaldehyde in 100 mM sodium acetate, pH 4.5), vortexed, and centrifuged. Supernatant was then transferred to a clean screw-cap tube and incubated at 95° C. for 40 min. Derivatized samples were then evaporated to dryness and reconstituted in 100 μl of water for HPLC analysis.

Before intracellular PMPA could be determined by HPLC, the large amounts of adenine related ribonucleotides present in the PBMC extracts had to be removed by selective oxidation. We used a modified procedure of Tanaka et al (K. Tanaka, A. Yoshioka, S. Tanaka, and Y. Wataya, Anal. Biochem., 139, 35 (1984). Briefly, PBMC samples were mixed 1:2 with methanol and evaporated to dryness under reduced pressure. The dried samples were derivatized as described in the plasma assay. The derivatized samples were mixed with 20 μL of 1M rhamnose and 30 μL of 0.1M sodium periodate and incubated at 37° C. for 5 min. Following incubation, 40 μL of 4M methylamine and 20 μL of 0.5M inosine were added. After incubation at 37° C. for 30 min, samples were evaporated to dryness under reduced pressure and reconstituted in water for HPLC analysis.

No intact prodrug was detected in any PBMC samples. For plasma samples potentially containing intact prodrugs, experiments were performed to verify that no further conversion to PMPA occurred during derivatization. Prodrug standards were added to drug-free plasma and derivatized as described. There were no detectable levels of PMPA present in any of the plasma samples, and the projected % of conversion was less than 1%.

The HPLC system was comprised of a P4000 solvent delivery system with AS3000 autoinjector and F2000 fluorescence detector (Thermo Separation, San Jose, Calif.). The column was an Inertsil ODS-2 column (4.6×150 mm). The mobile phases used were: A, 5% acetonitrile in 25 mM potassium phosphate buffer with 5 mM tetrabutyl ammonium bromide (TBABr), pH 6.0; B, 60% acetonitrile in 25 mM potassium phosphate buffer with 5 mM TBABr, pH 6.0. The flow rate was 2 ml/min and the column temperature was maintained at 35° C. by a column oven. The gradient profile was 90% A/10% B for 10 min for PMPA and 65% A/35% B for 10 min for the prodrug. Detection was by fluorescence with excitation at 236 nm and emission at 420 nm, and the injection volume was 10 μl. Data was acquired and stored by a laboratory data acquisition system (PeakPro, Beckman, Allendale, N.J.).

Pharmacokinetic Calculations. PMPA and prodrug exposures were expressed as areas under concentration curves in plasma or PBMC from zero to 24 hours (AUC). The AUC values were calculated using the trapezoidal rule.

Plasma and PBMC Concentrations. The results of this study is shown in FIGS. **2** and **3**. FIG. **2** shows the time course of GS 7340-2 metabolism summary of plasma and PBMC exposures following oral administration of pure diastereoisomers of the PMPA prodrugs.

The bar graph in FIG. **2** shows the AUC (0-24 h) for tenofovir in dog PBMCs and plasma after administration of PMPA s.c., TDF and amidate ester prodrugs. All of the amidate prodrugs exhibited increases in PBMC exposure. For example, GS 7340 results in a ~21-fold increase in PBMC exposure as compared to PMPA s.c. and TDF; and a 6.25-fold and 1.29-fold decrease in plasma exposure, respectively.

These data establish in vivo that GS 7340 can be delivered orally, minimizes systemic exposure to PMPA and greatly enhances the intracellular concentration of PMPA in the cells primarily responsible for HIV replication.

tion of GS-7340 (isopropyl alaninyl monoamidate, phenyl monoester of tenofovir) was examined following oral administration to beagle dogs. Two male animals were dosed orally with ^{14}C=GS-7340 (8.85 mg-equiv. of PMPA/kg, 33.2 μCi/kg; the 8-carbon of adenine is labeled) in an aqueous solution (50 mM citric acid, pH 2.2). Plasma and peripheral blood mononuclear cells (PBMCs) were obtained over the 24-hr period. Urine and feces were cage collected over 24 hr. At 24 h after the dose, the animals were sacrificed and tissues removed for analysis. Total radioactivity in tissues was determined by oxidation and liquid scintillation counting.

The biodistribution of PMPA after 24 hours after a single oral dose of radiolabelled GS 7340 is shown in Table 4 along with the data from a previous study with TDF (GS-4331). In the case of TDF, the prodrug concentration in the plasma is below the level of assay detection, and the main species observed in plasma is the parent drug. Levels of PMPA in the lymphatic tissues, bone marrow, and skeletal muscle are increased 10-fold after administration of GS-7340.

TABLE 6

PMPA Exposure in PBMC and Plasma from Oral Prodrugs of PMPA in Dogs

		PMPA AUC in Plasma			PMPA AUC in PBMC			Prodrug	PBMC/Plasma Exposure
GS#	Moiety	Mean	StDev	N	Mean	StDev	N	in Plasma	Ratio
GS-7114	Mono-Ala-Et-A	5.8	0.9	2	706	331	5	YES	122
GS-7115	Mono-Ala-Et-B	6.6	1.5	2	284	94	5	YES	43
GS-7340-2	Mono-Ala-iPr-A	5.0	1.1	5	805	222	5	YES	161
GS-7339	Mono-Ala-iPr-A	6.4	1.3	2	200	57	5	YES	31
GS-7119	Mono-Gly-Et-A	6.11	1.86	2	530	304	5	YES	87
GS-7342	Mono-ABA-Et-A	4.6	1.2	2	1060	511	5	YES	230
GS7341	Mono-ABA-Et-B	5.8	1.4	2	199	86	5	YES	34

EXAMPLE 11

Biodistribution of GS-7340

As part of the preclinical characterization of GS-7340, its biodistribution in dogs was determined. The tissue distribu-

Accumulation in lymphatic tissues is consistent with the data observed from the PBMC analyses, since these tissues are composed primarily of lymphocytes. Likewise, accumulation in bone marrow is probably due to the high percentage of lymphocytes (70%) in this tissue.

TABLE 7

Excretion and Tissue Distribution of Radiolabelled GS-7340 in Dogs (Mean, N = 2) Following an Oral Dose at 10 mg-eq. PMPA/kg.

	GS-4331		GS-7340		Tissue Conc.
Tissue/Fluid	% Dose	Conc. (ug-eq/g)	% Dose	Conc. (ug-eq/g)	Ratio of GS 7340 to GS-4331
Liver	12.40	38.30	16.45	52.94	1.4
Kidney	4.58	87.90	3.78	80.21	0.9
Lungs	0.03	0.53	0.34	4.33	8.2
Iliac Lymph Nodes	0.00	0.51	0.01	5.42	10.6
Axillary Lymph Nodes	0.00	0.37	0.01	5.54	14.8
Inguinal Lymph Nodes	0.00	0.28	0.00	4.12	15.0
Mesenteric Lymph Nodes	0.00	1.20	0.04	6.88	5.7
Thyroid Gland	0.00	0.30	0.00	4.78	15.8
Pituitary Gland	0.00	0.23	0.00	1.80	7.8
Salivary Gland (L + R)	0.00	0.45	0.03	5.54	12.3
Adrenal Gland	0.00	1.90	0.00	3.47	1.8
Spleen	0.00	0.63	0.17	8.13	12.8
Pancreas	0.00	0.57	0.01	3.51	6.2
Prostate	0.00	0.23	0.00	2.14	9.1

TABLE 7-continued

Excretion and Tissue Distribution of Radiolabelled GS-7340 in Dogs (Mean, N = 2) Following an Oral Dose at 10 mg-eq. PMPA/kg.

	GS-4331		GS-7340		Tissue Conc.
Tissue/Fluid	% Dose	Conc. (ug-eq/g)	% Dose	Conc. (ug-eq/g)	Ratio of GS 7340 to GS-4331
Testes (L + R)	0.02	1.95	0.02	2.01	1.0
Skeletal Muscle	0.00	0.11	0.01	1.12	10.1
Heart	0.03	0.46	0.15	1.97	4.3
Femoral Bone	0.00	0.08	0.00	0.28	3.5
Bone Marrow	0.00	0.20	0.00	2.05	10.2
Skin	0.00	0.13	0.00	0.95	7.2
Abdominal fat	0.00	0.16	0.00	0.90	5.8
Eye (L + R)	0.00	0.06	0.00	0.23	3.7
Brain	0.00	<LOD	0.00	<LOD	n.d.
Cerebrospinal Fluid	0.00	<LOD	0.00	0.00	n.d.
Spinal Cord	0.00	<LOD	0.00	0.04	n.d.
Stomach	0.11	1.92	0.26	2.68	1.4
Jejunum	1.34	3.01	0.79	4.16	1.4
Duodenum	0.49	4.96	0.44	8.77	1.8
Ileum	0.01	0.50	0.16	4.61	9.2
Large Intestine	1.63	5.97	2.65	47.20	7.9
Gall bladder	0.00	3.58	0.04	25.02	7.0
Bile	0.00	9.63	0.22	40.48	4.2
Feces	40.96	n.d.	0.19	n.d.	n.a.
Total GI Tract Contents	5.61	n.d.	21.64	n.d.	n.a.
Urine	23.72	n.d.	14.73	n.d.	n.a.
Plasma at 24 h	0.00	0.20	0.00	0.20	1.0
Plasma at 0.25 h	n.a.	3.68	n.a.	3.48	0.9
PBMC*	0.00	n.d.	0.00	63.20	n.d.
Whole Blood	0.00	0.85	0.16	0.20	0.2
Total Recovery	81.10		68.96		

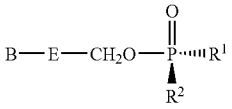
Calculated using typical recovery of 15×10^6 cells total, and mean PBMC volume of 0.2 picoliters/cell

n.s.=no sample, n.a.=not applicable, n.d.=not determined.

The invention claimed is:

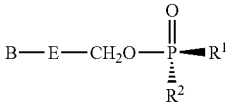
1. A method for antiviral therapy comprising administering a therapeutically effective amount of a diastereomerically enriched compound having the structure (3)

(3)



which contains less than 40% by weight of diastereomer (4)

(4)

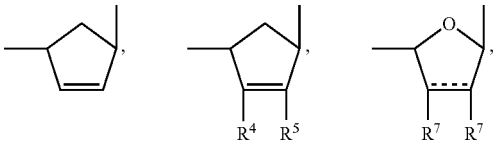


wherein R^1 is an oxyester which is hydrolyzable in vivo, or hydroxyl;

B is a heterocyclic base;

R^2 is hydroxyl, or the residue of an amino acid bonded to the P atom through an amino group of the amino acid and having each carboxy substituent of the amino acid optionally esterified, but not both of R^1 and R^2 are hydroxyl;

E is $—(CH_2)_2—$, $—CH(CH_3)CH_2—$, $—CH(CH_2F)CH_2—$, $—CH(CH_2OH)CH_2—$, $—CH(CH{=}CH_2)CH_2—$, $—CH(C{=}CH)CH_2—$, $—CH(CH_2N_3)CH_2—$,



$—CH(R^6)OCH(R^{6'})—$, $—CH(R^9)CH_2O—$ or $—CH(R^8)O—$, wherein the right hand bond is linked to the heterocyclic base;

the broken line represents an optional double bond;

R^4 and R^5 are independently hydrogen, hydroxy, halo, amino or a substituent having 1-5 carbon atoms selected from acyloxy, alkyoxy, alkylthio, alkylamino and dialkylamino;

R^6 and $R^{6'}$ are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_2-C_7 alkanoyl;

R^7 is independently H, C_1-C_6 alkyl, or are taken together to form —O— or $—CH_2—$;

R^8 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl or C_1-C_6 haloalkyl; and

R^9 is H, hydroxymethyl or acyloxymethyl;

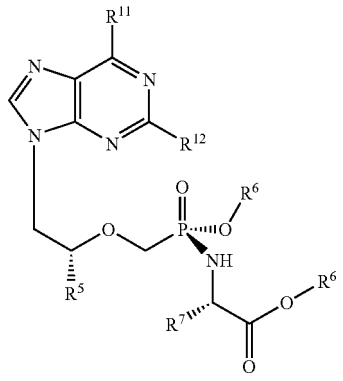
and its salts, free base, and solvates.

2. The method of claim **1**, wherein the diastereomerically enriched compound contains less than 20% by weight of the diastereomer (4).

3. The method of claim **2**, wherein the diastereomerically enriched compound contains less than 5% by weight of the diastereomer (4).

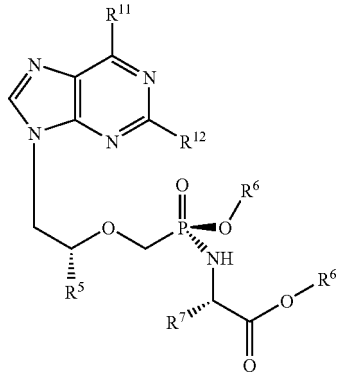
4. A method for antiviral therapy comprising administering a therapeutically effective amount of a diastereomerically enriched compound having the structure (5a)

(5a)



which contains less than 40% by weight of diastereomer (5b)

(5b)



wherein

R^5 is methyl or hydrogen;

R^6 independently is H, alkyl, alkenyl, alkynyl, aryl or arylalkyl, or R^6 independently is alkyl, alkenyl, alkynyl, aryl or arylalkyl which is substituted with from 1 to 3 substituents selected from alkylamino, alkylaminoalkyl, dialkylaminoalkyl, dialkylamino, hydroxyl, oxo, halo, amino, alkylthio, alkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylalkoxyalkyl, haloalkyl, nitro, nitroalkyl, azido, azidoalkyl, alkylacyl, alkylacylalkyl, carboxyl, or alkylacylamino;

R^7 is the side chain of any naturally-occurring or pharmaceutically acceptable amino acid and which, if the side chain comprises carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group;

R^{11} is amino, alkylamino, oxo, or dialkylamino; and

R^{12} is amino or H;

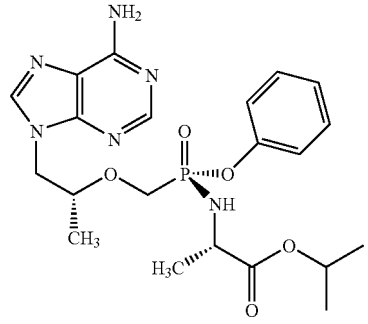
and its salts, tautomers, free base and solvates.

5. The method of claim **4**, wherein the diastereomerically enriched compound contains less than 20% by weight of the diastereomer (5b).

6. The method of claim **5**, wherein the diastereomerically enriched compound contains less than 5% by weight of the diastereomer (5b).

7. A method for antiviral therapy comprising administering a therapeutically effective amount of a diastereomerically enriched compound having the structure (6)

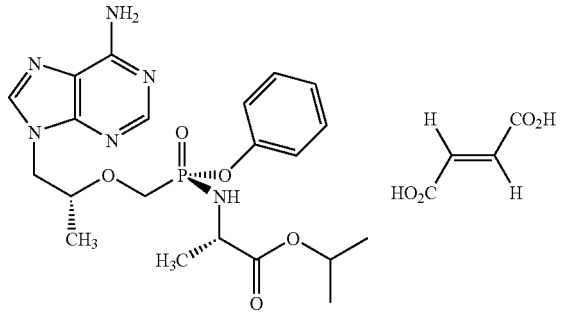
(6)



and its salts, tautomers, free base and solvates.

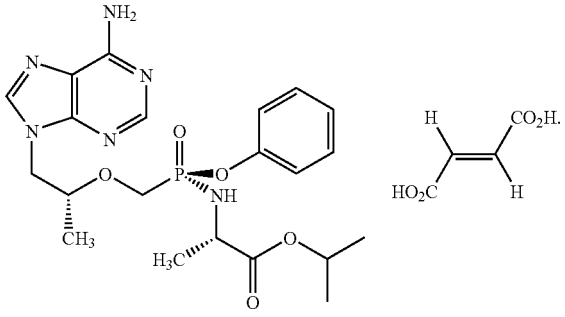
8. A method for antiviral therapy comprising administering a therapeutically effective amount of a diastereomerically enriched compound having the structure (7)

(7)



which contains less than 40% of diastereomer (7a)

(7a)



9. The method of claim **8**, wherein the diastereomerically enriched compound contains less than 20% by weight of the diastereomer (7a).

10. The method of claim **9**, wherein the diastereomerically enriched compound contains less than 5% by weight of the diastereomer (7a).

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,803,788 B2
APPLICATION NO. : 12/110829
DATED : September 28, 2010
INVENTOR(S) : Mark W. Becker et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

ON COVER PAGE [56] REFERENCES CITED:
Other Publications, "TherapeuticApplication" should read --Therapeutic Application--.

ON COVER PAGE [56] REFERENCES CITED:
Other Publications (page 2), "Thereapeutics" should read --Therapeutics--.

ON COVER PAGE [56] REFERENCES CITED:
Other Publications (page 2), "–phosphabicycIo-" should read ---phosphabicyclo--; "-octane" should read --octane--; and "Quiphos)" should read --(QUIPHOS)--.

ON COVER PAGE [56] REFERENCES CITED:
Other Publications (page 2), "retional" should read --rational--.

ON COVER PAGE [56] REFERENCES CITED:
Other Publications (page 2), "smalll" should read --small--; "glutamyicysteine" should read --glutamylcysteine--; "phnyl" should read --phenyl--; and "Opporunistic" should read ---Opportunistic--.

COLUMN 3:
Line 36, "alkyoxy" should read --alkyloxy--.

COLUMN 5:
Line 38, "Dogs" should read --dogs--.

COLUMN 8:
Line 52, "possess" should read --possesses--; and
Line 59, "toxic e.g." should read --toxic, e.g.--.

COLUMN 10:
Line 40, "therefore." should read --therefor.--.

COLUMN 13:
Line 16, "1-dezazadenyl," should read --1-dezaadenyl,--.

Signed and Sealed this
Nineteenth Day of March, 2013

Teresa Stanek Rea
Acting Director of the United States Patent and Trademark Office

COLUMN 16:
Line 31, “in is DMF” should read --in DMF--.

COLUMN 22:
Line 23, “dark oil.” should read --dark oil:--.

COLUMN 23:
Line 42, “a oil.” should read --an oil.--;
Line 60, “GS-7171 (II)” should read --GS-7171 (III)--; and
Line 67, “Chliralpak” should read --Chiralpak--.

COLUMN 24:
Line 42, “minute” should read --minutes--.

COLUMN 26:
Title, “EXAMPLE 15” should read --EXAMPLE 5--.

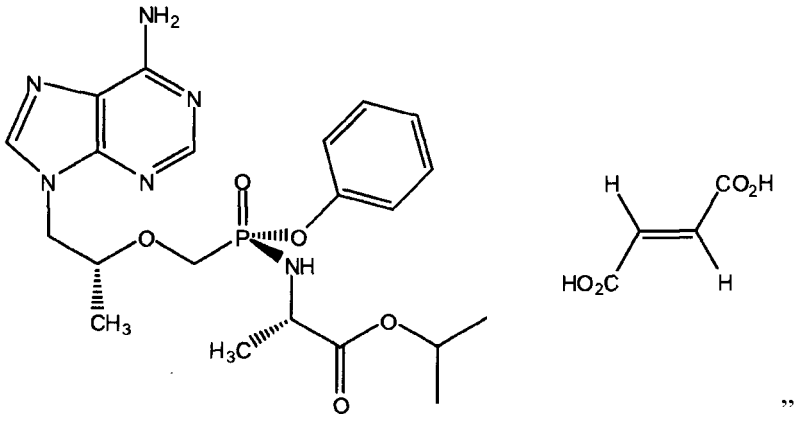
COLUMN 30:
Line 1, “Met Y” should read --Met. Y--; and
Line 10, “nelfinivir” should read --nelfinavir--.

COLUMN 31:
Line 22, “M N,” should read --MN,--; and
Line 32, “that of” should read --as that of--.

COLUMN 37:
Line 6, “is shown” should read --are shown--.

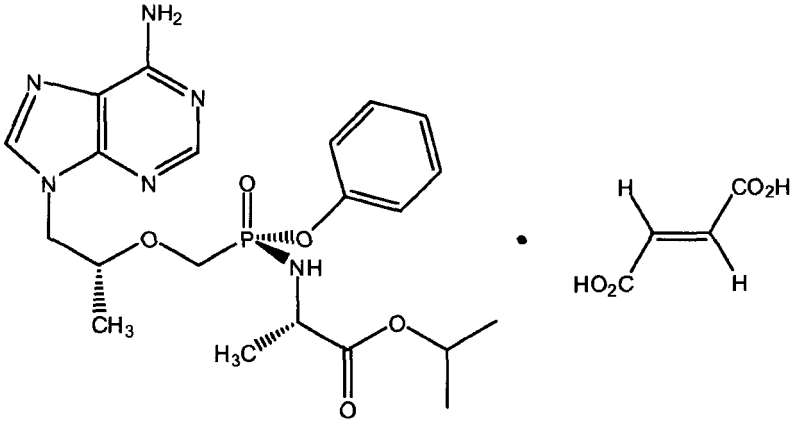
COLUMN 40:
Line 35, “–CH(C=CH)CH_2–,” should read -- –CH(C≡CH)CH_2– --; and
Line 51, “alkyoxy” should read --alkyloxy--.

COLUMN 42:
Lines 27-39,



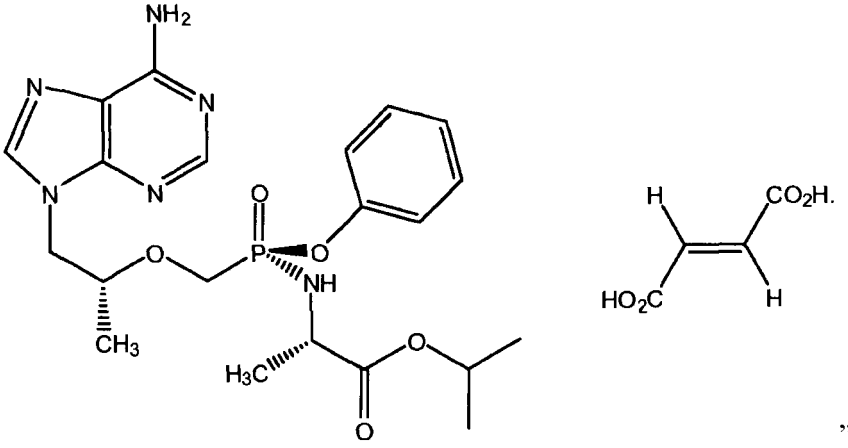
“ ”

should read



--; and

Lines 44-57,



" "

should read

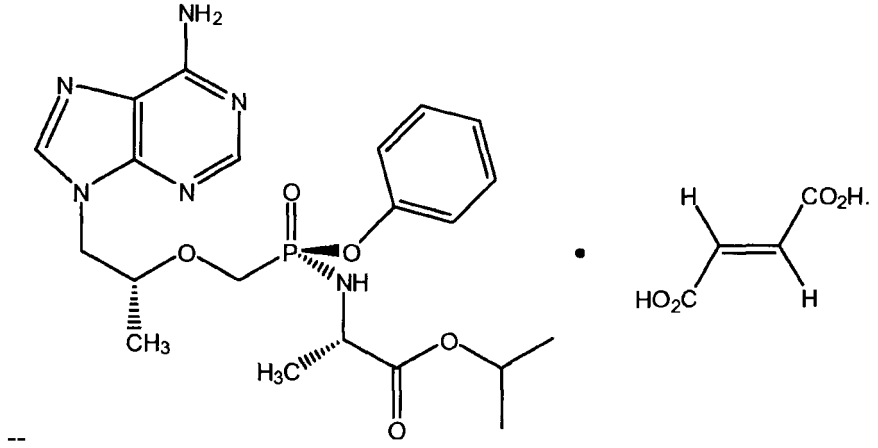


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Exhibit C

US008754065B2

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

(10) **Patent No.: US 8,754,065 B2**
(45) **Date of Patent: Jun. 17, 2014**

(54) **TENOFOVIR ALAFENAMIDE HEMIFUMARATE**

(75) Inventors: **Dazhan Liu**, Alberta (CA); **Bing Shi**, Foster City, CA (US); **Fang Wang**, Foster City, CA (US); **Richard Hung Chiu Yu**, San Francisco, CA (US)

(73) Assignee: **Gilead Sciences, Inc.** CA (US)

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

(21) Appl. No.: **13/586,358**

(22) Filed: **Aug. 15, 2012**

(65) **Prior Publication Data**

US 2013/0065856 A1 Mar. 14, 2013

Related U.S. Application Data

(60) Provisional application No. 61/524,224, filed on Aug. 16, 2011.

(51) **Int. Cl.**

A61K 31/685	(2006.01)
C07F 9/6561	(2006.01)
C07D 473/34	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 473/34*** (2013.01); ***C07F 9/65616*** (2013.01)

USPC **514/81**; 544/244

(58) **Field of Classification Search**

CPC C07D 473/34; C07F 9/65616

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,663,159	A	9/1997	Starrett, Jr. et al.	
5,798,340	A	8/1998	Bischofberger et al.	
7,390,791	B2	6/2008	Becker et al.	
7,803,788	B2	9/2010	Becker et al.	
2009/0286981	A1*	11/2009	Vasireddy et al.	544/244

FOREIGN PATENT DOCUMENTS

WO	98/04569	2/1998
WO	02/08241	1/2002

OTHER PUBLICATIONS

Jones, et al., "Minireview: nucleotide prodrugs", Antiviral Research, vol. 27 (1995) 1-17.

McIntee, et al., "Probing the Mechanism of Action and Decomposition of Amino Acid Phosphomonoester Amidates of Antiviral Nucleoside Prodrugs", J. Med. Chem., vol. 40 (1997) 3323-31.

Chapman, et al., "Practical Synthesis, Separation, and Stereochemical Assignment of the PMPA Pro-Drug GS-7340", Nucleosides, Nucleotides & Nucleic Acids, vol. 20, No. 4-7 (2001) 621-28.

Chapman, et al., "Purification of PNPA Amidate Prodrugs by SMB Chromotagraphy and X-Ray Crystallography of the Diastereomerically Pure GS-7340", Nucleosides, Nucleotides & Nucleic Acids, vol. 20, No. 4-7 (2001) 1085-90.

Non-Final Office Action for U.S. Appl. No. 13/118,122, mailed Feb. 19, 2014, 23 pages.

Supplemental Notice of Allowance for U.S. Appl. No. 12/857,238, mailed Feb. 25, 2014, 2 pages.

Non-Final Office Action for U.S. Appl. No. 14/134,933, mailed Feb. 25, 2014, 7 pages.

Non-Final Office Action for U.S. Appl. No. 14/033,245, mailed Feb. 26, 2014, 11 pages.

Patent Owner's Request for Rehearing Under 37 C.F.R. § 41.79, in Inter Partes Npls Reexamination of U.S. Patent No. 7,714,747, Control No. 95/001,517, filed Feb. 14, 2014, 11 pages.

Statement of Opposition for Venezuelan Patent Application No. 2012-001018, filed on Aug. 15, 2012, 27 pages.

* cited by examiner

Primary Examiner — James D Anderson

(74) *Attorney, Agent, or Firm* — Fitzpatrick, Cella, Harper & Scinto

(57) **ABSTRACT**

A hemifumarate form of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl] adenine (tenofovir alafenamide), and antiviral therapy using tenofovir alafenamide hemifumarate (e.g., anti-HIV and anti-HBV therapies).

31 Claims, 4 Drawing Sheets

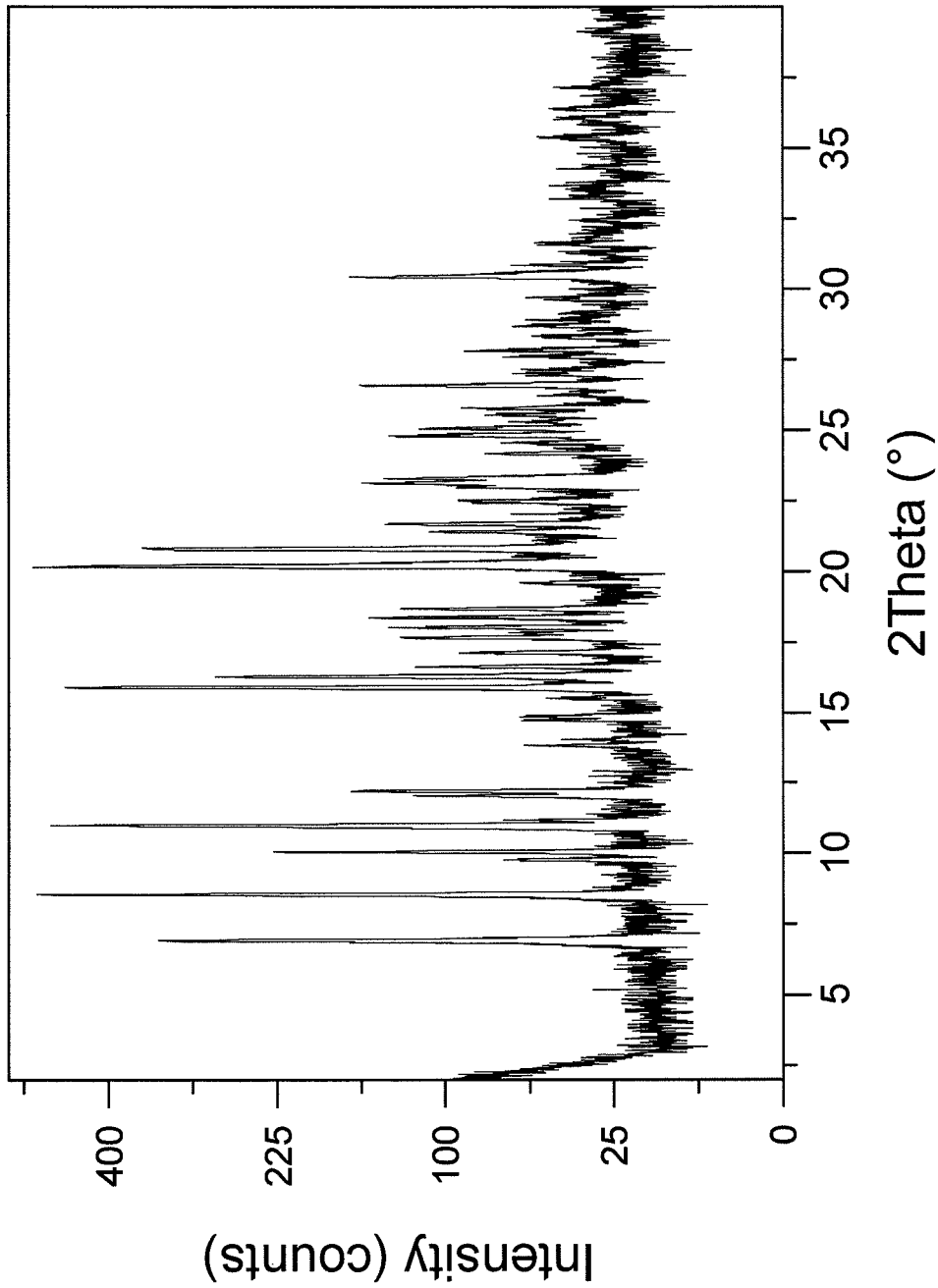


Figure 1

Figure 2

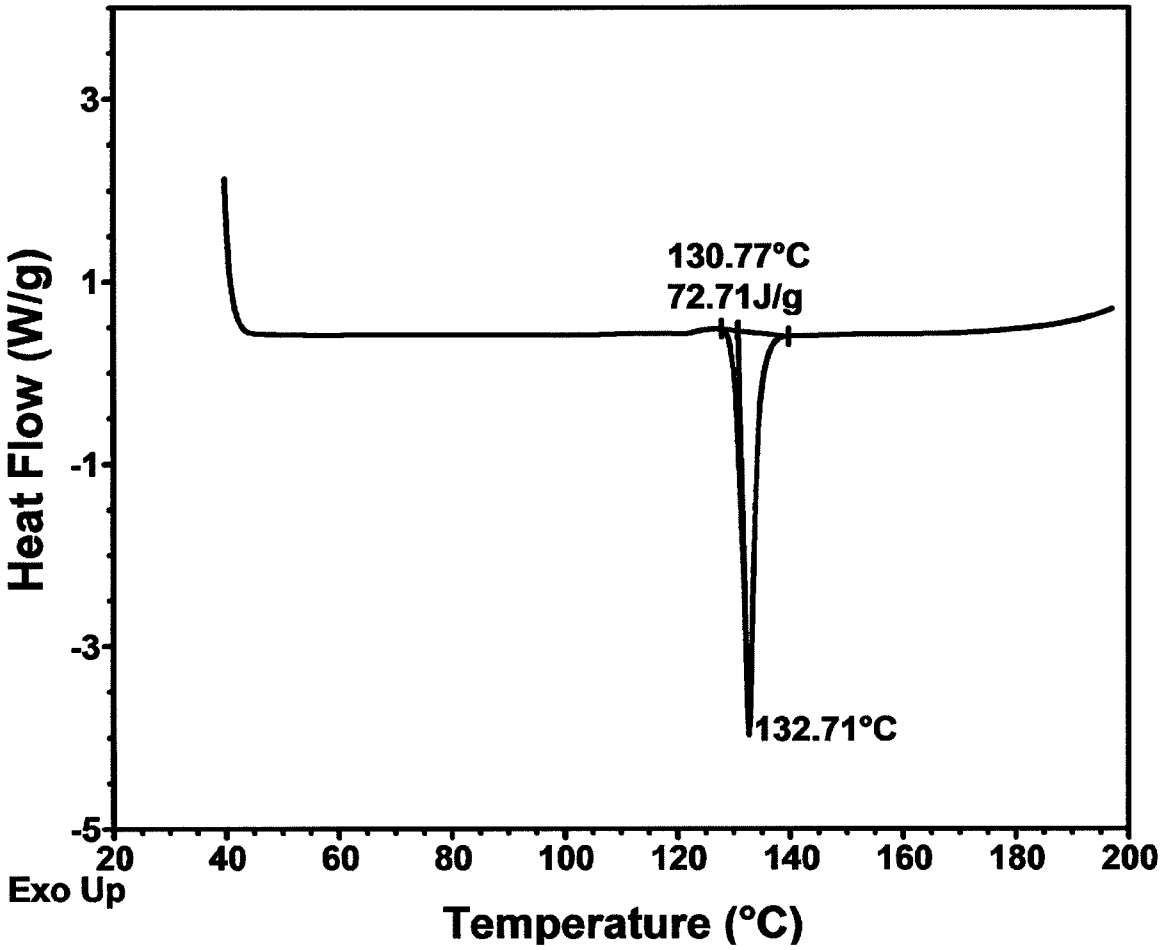

Heat Flow (W/g)
3
1
-1
-3
-5
130.77°C
72.71J/g
132.71°C
20
40
60
80
100
120
140
160
180
200
Exo Up
Temperature (°C)

Figure 3

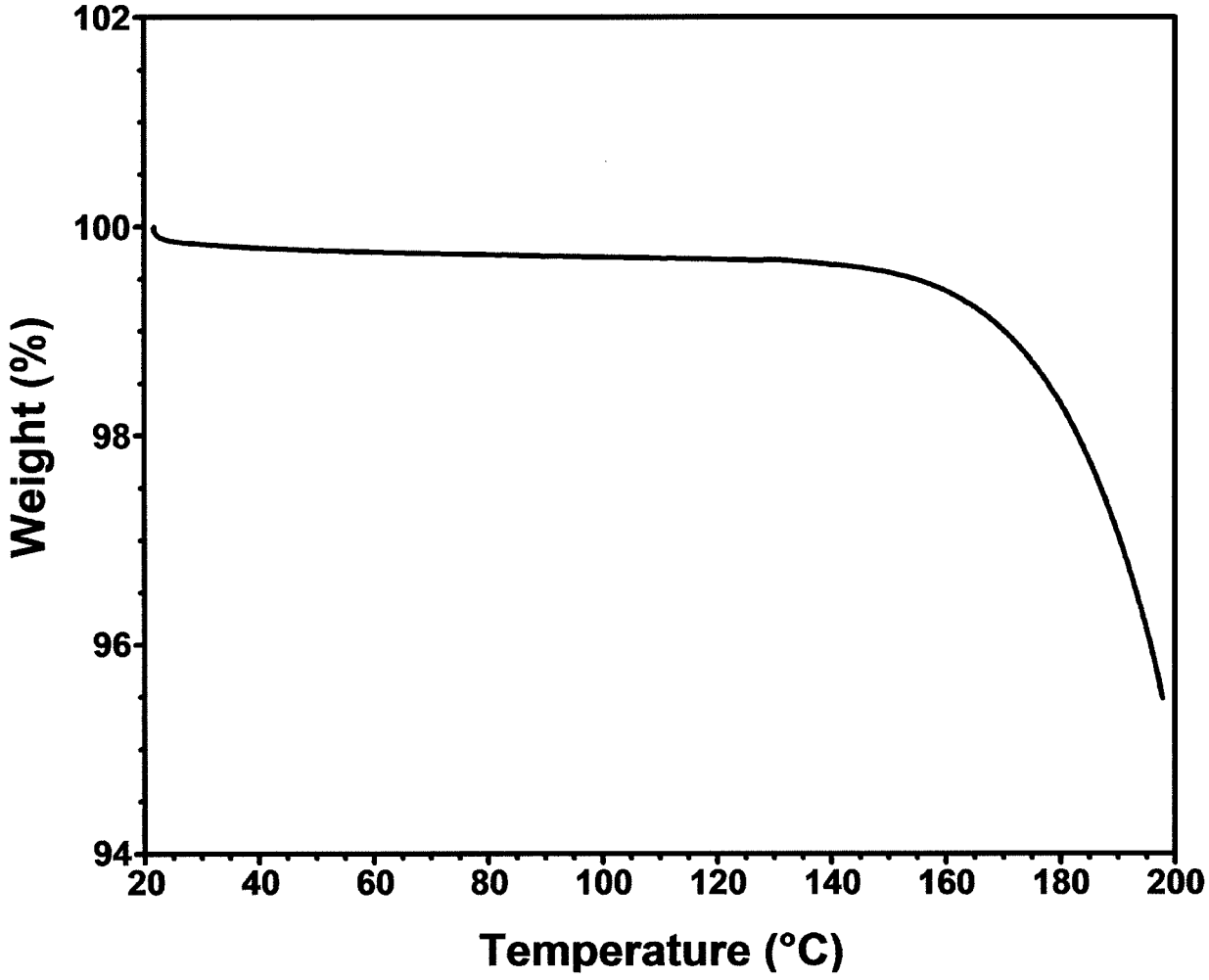
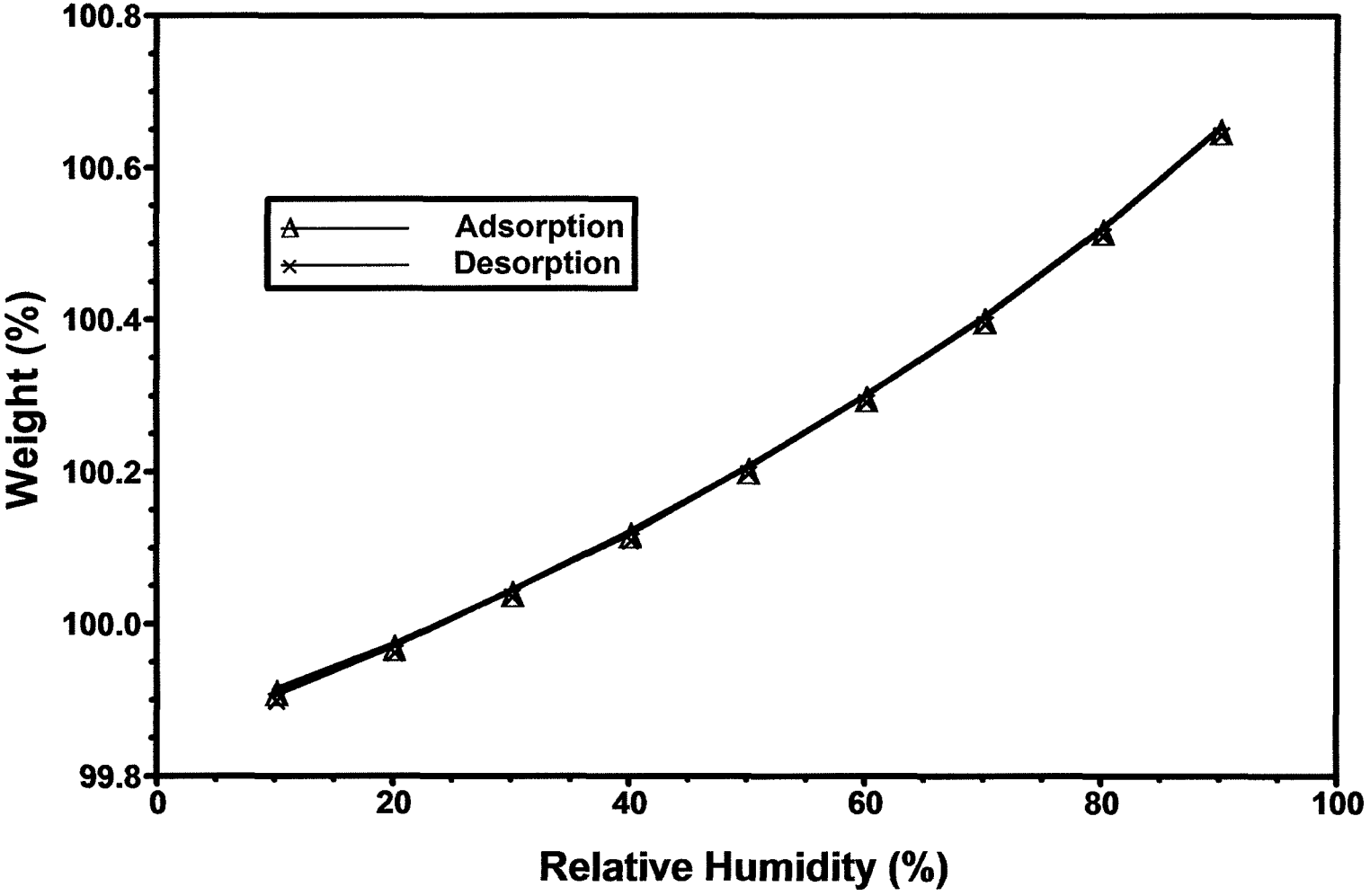

102
100
98
96
94
Weight (%)
20
40
60
80
100
120
140
160
180
200
Temperature (°C)

Figure 4


100.8
100.6
100.4
100.2
100.0
99.8
Weight (%)
Adsorption
Desorption
0
20
40
60
80
100
Relative Humidity (%)

TENOFOVIR ALAFENAMIDE HEMIFUMARATE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority from U.S. Provisional Patent Application No. 61/524,224, filed Aug. 16, 2011, the content of which is hereby incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

Description of Related Art

U.S. Pat. Nos. 7,390,791 and 7,803,788 (the content of each of which is incorporated by reference herein in its entirety) describe certain prodrugs of phosphonate nucleotide analogs that are useful in therapy. One such prodrug is 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. This compound is also known by the Chemical Abstract name L-alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester. U.S. Pat. Nos. 7,390,791 and 7,803,788 also disclose a monofumarate form of this compound and its preparation method (see, e.g., Example 4).

SUMMARY OF THE INVENTION

Described is a hemifumarate form of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. The name for 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine is tenofovir alafenamide. The hemifumarate form of tenofovir alafenamide is also referred to herein as tenofovir alafenamide hemifumarate.

In one embodiment of the invention is provided tenofovir alafenamide hemifumarate.

In another embodiment is provided tenofovir alafenamide hemifumarate, wherein the ratio of fumaric acid to tenofovir alafenamide is 0.5±0.1, or 0.5±0.05, or 0.5±0.01, or about 0.5.

In one embodiment is provided tenofovir alafenamide hemifumarate in a solid form.

In one embodiment is provided tenofovir alafenamide hemifumarate that has an X-ray powder diffraction (XRPD) pattern having 2theta values of 6.9±0.2° and 8.6±0.2°. In another embodiment is provided tenofovir alafenamide hemifumarate wherein the XRPD pattern comprises 2theta values of 6.9±0.2°, 8.6±0.2°, 11.0±0.2°, 15.9±0.2°, and 20.2±0.2°.

In one embodiment is provided tenofovir alafenamide hemifumarate that has a differential scanning calorimetry (DSC) onset endotherm of 131±2° C., or 131±1° C.

In one embodiment is provided a pharmaceutical composition comprising tenofovir alafenamide hemifumarate and a pharmaceutically acceptable excipient. In another embodiment is provided the pharmaceutical composition, further comprising an additional therapeutic agent. In a further embodiment, the additional therapeutic agent is selected from the group consisting of human immunodeficiency virus (HIV) protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

In one embodiment is provided a method for treating a human immunodeficiency virus (HIV) infection comprising administering to a subject in need thereof a therapeutically effective amount of tenofovir alafenamide hemifumarate. In another embodiment is provided a method for treating an HIV infection comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising tenofovir alafenamide hemifumarate. In a further embodiment, the method comprises administering to the subject one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

In one embodiment is provided a method for treating a hepatitis B virus (HBV) infection comprising administering to a subject in need thereof a therapeutically effective amount of tenofovir alafenamide hemifumarate. In another embodiment is provided a method for treating an HBV infection comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition comprising tenofovir alafenamide hemifumarate.

In one embodiment is provided a method for preparing a pharmaceutical composition comprising combining tenofovir alafenamide hemifumarate and a pharmaceutically acceptable excipient to provide the pharmaceutical composition.

In one embodiment is provided a method for preparing tenofovir alafenamide hemifumarate comprising subjecting a solution comprising a suitable solvent; fumaric acid; tenofovir alafenamide; and, optionally, one or more seeds of tenofovir alafenamide hemifumarate to conditions that provide for the crystallization of the fumaric acid and the tenofovir alafenamide. In one embodiment, the solvent comprises acetonitrile. In another embodiment, the solution is subjected to a temperature in the range of from about 0° C. to about 75° C.

In one embodiment is provided tenofovir alafenamide hemifumarate for use in medical therapy.

In one embodiment is provided the use of tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of an HIV infection. In another embodiment is provided the use of tenofovir alafenamide hemifumarate to treat an HIV infection. In a further embodiment is provided the use of tenofovir alafenamide hemifumarate for the preparation or manufacture of a medicament for the treatment of an HIV infection. In another further embodiment is provided tenofovir alafenamide hemifumarate for use in treating an HIV infection.

In one embodiment is provided the use of tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of an HBV infection. In another embodiment is provided the use of tenofovir alafenamide hemifumarate to treat an HBV infection. In a further embodiment is provided the use of tenofovir alafenamide hemifumarate for the preparation or manufacture of a medicament for the treatment of an HBV infection. In another further embodiment is provided tenofovir alafenamide hemifumarate for use in treating an HBV infection.

In some embodiments of the invention, the methods of treating and the like comprise administration of multiple daily doses. In other embodiments, the methods of treating and the like comprise administration of a single daily dose.

In one embodiment of the invention is provided a composition consisting essentially of tenofovir alafenamide hemifumarate.

BRIEF DESCRIPTIONS OF THE DRAWINGS

FIG. **1** shows the X-ray powder diffraction (XRPD) pattern of tenofovir alafenamide hemifumarate.

FIG. **2** shows a graph of the DSC analysis of tenofovir alafenamide hemifumarate.

FIG. **3** shows a graph of the thermogravimetric analysis (TGA) data for tenofovir alafenamide hemifumarate.

FIG. **4** shows a graph of the dynamic vapor sorption (DVS) analysis of tenofovir alafenamide hemifumarate.

DETAILED DESCRIPTION OF THE INVENTION

Specific values listed within the present description for radicals, substituents, and ranges are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

In one embodiment, there is provided a hemifumarate form of tenofovir alafenamide (i.e., tenofovir alafenamide hemifumarate). This form may have a ratio (i.e., a stoichiometric ratio or mole ratio) of fumaric acid to tenofovir alafenamide of 0.5±0.1, 0.5±0.05, 0.5±0.01, or about 0.5, or the like.

In one embodiment, tenofovir alafenamide hemifumarate consists of fumaric acid and tenofovir alafenamide in a ratio of 0.5±0.1.

In one embodiment, tenofovir alafenamide hemifumarate consists essentially of fumaric acid and tenofovir alafenamide in a ratio of 0.5±0.1.

In one embodiment, tenofovir alafenamide hemifumarate has an XRPD pattern comprising 2theta values of 6.9±0.2°, 8.6±0.2°, 10.0±0.2°, 11.0±0.2°, 12.2±0.2°, 15.9±0.2°, 16.3±0.2°, 20.2±0.2°, and 20.8±0.2°.

In one embodiment, tenofovir alafenamide hemifumarate has an XRPD pattern comprising at least four 2theta values selected from 6.9±0.2°, 8.6±0.2°, 10.0±0.2°, 11.0±0.2°, 12.2±0.2°, 15.9±0.2°, 16.3±0.2°, 20.2±0.2°, and 20.8±0.2°.

In one embodiment, tenofovir alafenamide hemifumarate has a DSC onset endotherm of 131±2° C., or 131±1° C.

In one embodiment, a tenofovir alafenamide hemifumarate composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate.

In one embodiment, a tenofovir alafenamide hemifumarate composition comprises less than about 1% by weight of tenofovir alafenamide monofumarate.

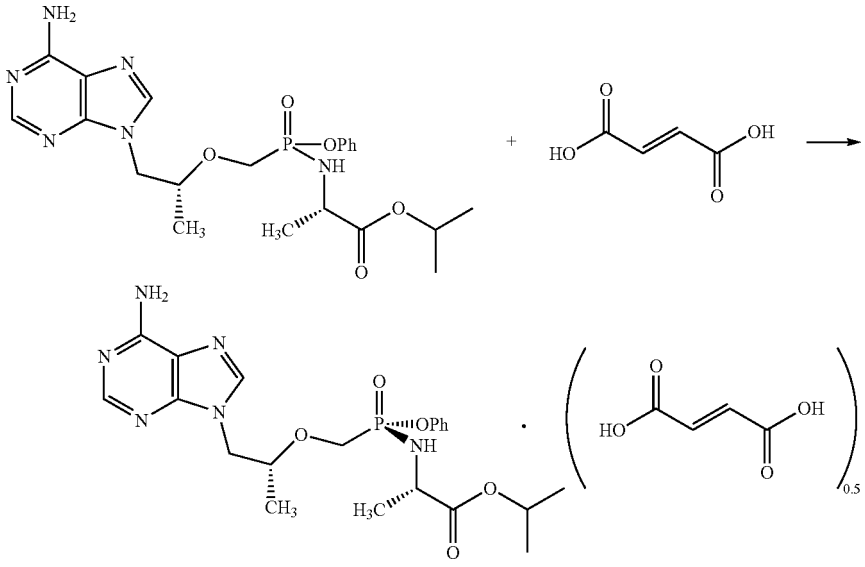
In one embodiment, a tenofovir alafenamide hemifumarate composition comprises less than about 0.5% by weight of tenofovir alafenamide monofumarate.

In one embodiment, a tenofovir alafenamide hemifumarate composition comprises no detectable tenofovir alafenamide monofumarate.

Tenofovir alafenamide (i.e., the compound 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine) can be prepared as described in U.S. Pat. No. 7,390,791.

Selective Crystallization

In one embodiment, tenofovir alafenamide hemifumarate can be prepared using selective crystallization. An example of a scheme for this preparation method is as follows.



The method can be carried out by subjecting a solution comprising: a) a suitable solvent; b) fumaric acid; c) tenofovir alafenamide; and, optionally, d) one or more seeds comprising tenofovir alafenamide hemifumarate, to conditions that provide for the crystallization of fumaric acid and tenofovir alafenamide. The starting solution can contain the single diastereomer of tenofovir alafenamide or a mixture of tenofovir alafenamide and one or more of its other diastereomers (e.g., GS-7339, as described in U.S. Pat. No. 7,390,791).

The selective crystallization can be carried out in any suitable solvent. For example, it can be carried out in a protic solvent or in an aprotic organic solvent, or in a mixture thereof In one embodiment, the solvent comprises a protic solvent (e.g., water or isopropyl alcohol). In another embodiment, the solvent comprises an aprotic organic solvent (e.g., acetone, acetonitrile (ACN), toluene, ethyl acetate, isopropyl acetate, heptane, tetrahydrofuran (THF), 2-methyl THF, methyl ethyl ketone, or methyl isobutyl ketone, or a mixture thereof). In one embodiment, the solvent comprises ACN or a mixture of ACN and up to about 50% methylene chloride (by volume). The selective crystallization also can be carried out at any suitable temperature, for example, a temperature in the range of from about 0° C. to about 70° C. In one specific embodiment, the resolution is carried out at a temperature of about 0° C.

One major advantage of the hemifumarate form of tenofovir alafenamide over the monofumarate form is its exceptional capability to purge GS-7339 (i.e., 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]

methoxy]propyl]adenine; described in, e.g., U.S. Pat. No. 7,390,791), which is the major diastereomeric impurity in the active pharmaceutical ingredient. Thus, the hemifumarate form of tenofovir alafenamide can be more readily and easily separated from impurities than the monofumarate form. Other major advantages of tenofovir alafenamide hemifumarate over the monofumarate form include improved thermodynamic and chemical stability (including long-term storage stability), superior process reproducibility, superior drug product content uniformity, and a higher melting point.

Tenofovir alafenamide hemifumarate is useful in the treatment and/or prophylaxis of one or more viral infections in man or animals, including infections caused by DNA viruses. RNA viruses, herpesviruses (e.g., CMV, HSV 1, HSV 2, VZV), retroviruses, hepadnaviruses (e.g., HBV), papillomavirus, hantavirus, adenoviruses and HIV. U.S. Pat. No. 6,043,230 (incorporated by reference herein in its entirety) and other publications describe the antiviral specificity of nucleotide analogs, such as tenofovir disoproxil. Like tenofovir disoproxil, tenofovir alafenamide is another prodrug form of tenofovir, and can be used in the treatment and/or prophylaxis of the same conditions.

Tenofovir alafenamide hemifumarate can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including ocular, buccal, and sublingual), vaginal, and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, and epidural). Generally, tenofovir alafenamide hemifumarate is administered orally, but it can be administered by any of the other routes noted herein.

Accordingly, pharmaceutical compositions include those suitable for topical or systemic administration, including oral, rectal, nasal, buccal, sublingual, vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, and epidural) administration. The formulations are in unit dosage form and are prepared by any of the methods well known in the art of pharmacy.

For oral therapeutic administration, the tenofovir alafenamide hemifumarate may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such pharmaceutical compositions and preparations will typically contain at least 0.1% of tenofovir alafenamide hemifumarate. The percentage of this active compound in the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% or more of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful pharmaceutical compositions is preferably such that an effective dosage level will be obtained upon administration of a single-unit dosage (e.g., tablet). Other dosage formulations may provide therapeutically effective amounts of tenofovir alafenamide hemifumarate upon repeated administration of subclinically effective amounts of the same. Preferred unit dosage formulations include those containing a daily dose (e.g., a single daily dose), as well as those containing a unit daily subclinical dose, or an appropriate fraction thereof (e.g., multiple daily doses), of tenofovir alafenamide hemifumarate.

Pharmaceutical compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of tenofovir alafenamide hemifumarate; as a powder or granules; as a solution or a suspension in an aqueous liquid or a nonaqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. Tenofovir alafenamide hemifumarate may also be presented as a bolus, electuary, or paste.

Tenofovir alafenamide hemifumarate is preferably administered as part of a pharmaceutical composition or formulation. Such pharmaceutical composition or formulation comprises tenofovir alafenamide hemifumarate together with one or more pharmaceutically acceptable carriers/excipients, and optionally other therapeutic ingredients. The excipient(s)/carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient. Excipients include, but are not limited to, substances that can serve as a vehicle or medium for tenofovir alafenamide hemifumarate (e.g., a diluent carrier). They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet.

Accordingly, the tablets, troches, pills, capsules, and the like may also contain, without limitation, the following: a binder(s), such as hydroxypropyl cellulose, povidone, or hydroxypropyl methylcellulose; a filler(s), such as microcrystalline cellulose, pregelatinized starch, starch, mannitol, or lactose monohydrate; a disintegrating agent(s), such as croscarmellose sodium, cross-linked povidone, or sodium starch glycolate; a lubricant(s), such as magnesium stearate, stearic acid, or other metallic stearates; a sweetening agent(s), such as sucrose, fructose, lactose, or aspartame; and/or a flavoring agent(s), such as peppermint, oil of wintergreen, or a cherry flavoring. When the unit dosage form is a capsule, it may contain, in addition to materials of the above types, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, polymers, wax, shellac, or sugar and the like. Of course, any material used in preparing any unit dosage form typically will be pharmaceutically acceptable and substantially nontoxic in the amounts employed. In addition, tenofovir alafenamide hemifumarate may be incorporated into sustained-release preparations and devices.

For infections of the eye or other external tissues, e.g., mouth and skin, the pharmaceutical compositions are preferably applied as a topical ointment or cream containing tenofovir alafenamide hemifumarate in an amount of, for example, 0.01 to 10% w/w (including active ingredient in a range between 0.1% and 5% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 3% w/w and most preferably 0.5 to 2% w/w. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base.

Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising tenofovir alafenamide hemifumarate in a flavored basis, for example, sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Pharmaceutical formulations suitable for parenteral administration are sterile and include aqueous and nonaqueous injection solutions that may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and nonaqueous sterile suspensions that may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example,

sealed ampoules and vials with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier (e.g., water for injections) immediately prior to use. Injection solutions and suspensions may be prepared from sterile powders, granules, and tablets of the kind previously described.

In addition to the ingredients particularly mentioned above, the pharmaceutical compositions/formulations may include other ingredients conventional in the art, having regard to the type of formulation in question.

In another embodiment, there is provided veterinary compositions comprising tenofovir alafenamide hemifumarate together with a veterinary carrier therefor. Veterinary carriers are materials useful for the purpose of administering the composition to cats, dogs, horses, rabbits, and other animals, and may be solid, liquid, or gaseous materials that are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally, or by any other desired route.

The tenofovir alafenamide hemifumarate can be used to provide controlled release pharmaceutical formulations containing a matrix or absorbent material and an active ingredient of the invention, in which the release of the active ingredient can be controlled and regulated to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the compound. Controlled release formulations adapted for oral administration, in which discrete units comprising a compounds of the invention, can be prepared according to conventional methods.

Useful dosages of tenofovir alafenamide hemifumarate can be determined by comparing in vitro activities, and the in vivo activities in animal models. Methods for the extrapolation of effective amounts/dosages in mice and other animals to therapeutically effective amounts/dosages in humans are known in the art.

The amount of tenofovir alafenamide hemifumarate required for use in treatment will vary with several factors, including but not limited to the route of administration, the nature of the condition being treated, and the age and condition of the patient; ultimately, the amount administered will be at the discretion of the attendant physician or clinician. The therapeutically effective amount/dose of tenofovir alafenamide hemifumarate depends, at least, on the nature of the condition being treated, any toxicity or drug interaction issues, whether the compound is being used prophylactically (e.g., sometimes requiring lower doses) or against an active disease or condition, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

In one embodiment, the oral dose of tenofovir alafenamide hemifumarate may be in the range from about 0.0001 to about 100 mg/kg body weight per day, for example, from about 0.01 to about 10 mg/kg body weight per day, from about 0.01 to about 5 mg/kg body weight per day, from about 0.5 to about 50 mg/kg body weight per day, from about 1 to about 30 mg/kg body weight per day, from about 1.5 to about 10 mg/kg body weight per day, or from about 0.05 to about 0.5 mg/kg body weight per day. As a nonlimiting example, the daily candidate dose for an adult human of about 70 kg body weight will range from about 0.1 mg to about 1000 mg, or from about 1 mg to about 1000 mg, or from about 5 mg to about 500 mg, or from about 1 mg to about 150 mg, or from about 5 mg to about 150 mg, or from about 5 mg to about 100 mg, and may take the form of single or multiple doses.

The pharmaceutical compositions described herein may further include one or more therapeutic agents in addition to tenofovir alafenamide hemifumarate. In one specific embodiment of the invention, the additional therapeutic agent can be selected from the group consisting of HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

Therapeutic methods include administering tenofovir alafenamide hemifumarate to a subject/patient in need of the same as a therapeutic or preventative treatment. Thus, tenofovir alafenamide hemifumarate may be administered to a subject/patient having a medical disorder or to a subject who may acquire the disorder. One of ordinary skill will appreciate that such treatment is given in order to ameliorate, prevent, delay, cure, and/or reduce the severity of a symptom or set of symptoms of a disorder (including a recurring disorder). The treatment may also be given to prolong the survival of a subject, e.g., beyond the survival time expected in the absence of such treatment. The medical disorders that may be treated with tenofovir alafenamide hemifumarate include those discussed herein, including without limitation, HIV infection and HBV infection.

The following are nonlimiting, illustrative Examples.

Example 1

Tenofovir alafenamide monofumarate solids (5.0 g) and 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]methoxy]propyl]adenine (GS-7339) monofumarate solids (0.75 g) were charged into 35 g MTBE at 22° C. and the mixture was stirred for 1 hour. A slurry was formed and was dried in a rotary evaporator. 58 g acetonitrile (ACN) was charged into the solids and the mixture was heated to reflux to dissolve the solids. The resulting solution was allowed to cool naturally while agitated. A slurry was formed, and the slurry was further cooled by ice-water-bath. The solids were isolated by filtration and washed with 5 g ACN. The solids were dried in a vacuum oven at 40° C. overnight. 5.52 g off-white solids were obtained. The solids were analyzed by XRPD and found to contain tenofovir alafenamide monofumarate, GS-7339 monofumarate, and tenofovir alafenamide hemifumarate.

Example 2

Preparation of Tenofovir Alafenamide Hemifumarate via Selective Crystallization

9-[(R)-2-[[[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine as a slurry in ACN (9.7 kg slurry, 13.8 wt %, a diastereomeric mixture of 1.0 kg (2.10 mol, 1 mol equiv) of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy] propyl]adenine and 0.35 kg of 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl] methoxy]propyl]adenine was charged into a reactor and rinsed forward with dichloromethane (5 kg). The mixture was concentrated under vacuum to about 3 L with jacket temperature below 40° C. The concentrate was then coevaporated with ACN (6 kg) under vacuum to about 3 L with jacket temperature below 40° C. The concentrate was diluted with ACN (8.5 kg) and warmed to 40-46° C. The warm mixture was filtered into a second reactor and the filtrate was cooled to 19-25° C.

To the above solution was charged fumaric acid (0.13 kg, 1.12 mol, 0.542 mole equiv) followed by ACN (1 kg), and the mixture was heated to 67-73° C. The hot mixture was trans-

ferred into a reactor via a polishing filter, and then adjusted to 54-60° C. Seed crystals (5 g) of the hemifumarate form of tenofovir alafenamide were charged (for example, the mixture can be seeded with tenofovir alafenamide hemifumarate formed in Example 1 or a subsequent production), and the resulting mixture was agitated at 54-60° C. for about 30 minutes. The mixture was cooled over a minimum of 4 hours to 0-6° C., and then agitated at 0-6° C. for a minimum of 1 hour. The resulting slurry was filtered and rinsed with chilled (0-6° C.) ACN (2 kg). The product was dried under vacuum below 45° C. until loss on drying (LOD) and organic volatile impurities (OVI) limits were met (LOD≤1.0%, dichloromethane content≤0.19%, acetonitrile content≤0.19%) to afford the final compound of the hemifumarate form of tenofovir alafenamide as a white to off-white powder (typical yield is about 0.95 kg). ^{1}H NMR (400 MHz, d6 DMSO): δ 1.06 (d, J=5.6 Hz, 3H), 1.12-1.16 (m, 9H), 3.77 (dd, J=10.4, 11.6 Hz, 1H), 3.84-3.90 (m, 2H), 3.94 (m, 1H), 4.14 (dd, J=6.8, 14.8 Hz, 1H), 4.27 (m, 1H), 4.85 (heptet, J=6.0 Hz, 1H), 5.65 (t, J=11.2 Hz, 1H), 6.63 (s, 1H), 7.05 (d. J=7.6 Hz, 2H), 7.13 (t, J=7.2 Hz, 1H), 7.24 (s, 2H), 7.29 (t, J=7.6 Hz, 2H), 8.13 (t, J=13.6 Hz, 2H), ^{31}P NMR (162 MHz, d6 DMSO): δ 23.3.

Example 3

Preparation of Tenofovir Alafenamide Hemifumarate

To a jacketed reactor equipped with overhead agitator, was charged 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine (10 g), fumaric acid (1.22 g), and ACN (100 mL). The mixture was heated to 70-75° C. to dissolve the solids. Any undissolved particulates were removed by filtration through a cartridge filter. The filtered solution was cooled to 60-65° C., and seeded with 1% (by weight) of tenofovir alafenamide hemifumarate. The slurry was aged for 30 minutes and cooled to 0-5° C. over 2 hours. The temperature was maintained for 1-18 hours, and the resulting slurry was filtered and washed with 2 ml of cold ACN (0-5° C.). The solids were dried under vacuum at 50° C. to provide the hemifumarate form of tenofovir alafenamide, which was characterized as described below.

Characterization of Tenofovir Alafenamide Hemifumarate from Example 3

Tenofovir alafenamide hemifumarate from Example 3 consists of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine and one-half an equivalent of fumaric acid. Tenofovir alafenamide hemifumarate is anhydrous, nonhygroscopic, and has a DSC onset endotherm of about 131° C.

X-Ray Powder Diffraction

The XRPD pattern of tenofovir alafenamide hemifumarate was obtained in the following experimental setting: 45 KV, 45 mA, Kα1=1.5406 Å, scan range 2.-40°, step size 0.0084°, counting time: 8.25 s. The XRPD pattern for tenofovir alafenamide hemifumarate is shown in FIG. **1**. The characteristic peaks include: 6.9±0.2°, 8.6±0.2°, 10.0±0.2°, 11.0±0.2°, 12.2±0.2°, 15.9±0.2°, 16.3±0.2°, 20.2±0.2°, and 20.8±0.2°.

Single-Crystal X-Ray Diffraction

The crystal size was 0.32×0.30×0.20 mm^3. The sample was held at 123 K and the data was collected using a radiation source with a wavelength of 0.71073 Å in the theta range of 1.59 to 25.39°. Conditions of, and data collected from the single-crystal X-ray diffraction are shown in Table 1.

TABLE 1

Single-Crystal X-ray Diffraction

Empirical formula	$C_{23}H_{31}N_6O_7P$	
Formula weight	534.50	
Temperature	123(2) K	
Crystal size	0.32 × 0.30 × 0.20 mm^3	
Theta range for data collection	1.59 to 25.39°	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	P4(2)2(1)2	
Unit cell dimensions	a = 18.1185(12) Å	α = 90°
	b = 18.1185(12) Å	β = 90°
	c = 17.5747(11) Å	γ = 90°
Volume	5769.4(6) Å^3	
Z	8	
Density (calculated)	1.231 g/cm^3	

DSC Analysis

The DSC analysis was conducted using 2.517 mg of tenofovir alafenamide hemifumarate. It was heated at 10° C./min over the range of 40-200° C. The onset endotherm was found to be about 131° C. (FIG. **2**).

TGA Data

The TGA data were obtained using 4.161 mg of tenofovir alafenamide hemifumarate. It was heated at 10° C./min over the range of 25-200° C. The sample lost 0.3% weight before melting (FIG. **3**). It was determined to be an anhydrous form.

DVS Analysis

DVS analysis was conducted using 4.951 mg of tenofovir alafenamide hemifumarate. The material was kept at 25° C. in nitrogen at humidities ranging from 10% to 90% relative humidity; each step was equilibrated for 120 minutes. The sorption isotherm is shown at FIG. **4**. The material was found to be nonhygroscopic, and to absorb 0.65% water at a relative humidity of 90%.

Purging of Diastereomeric Impurity

In the prior syntheses of tenofovir alafenamide, one of the major impurities is typically the diastereomer 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. The hemifumarate form of tenofovir alafenamide from Example 3 has an exceptional capability to purge this diastereomeric impurity, as compared with the capability of the monofumarate form (described in U.S. Pat. No. 7,390,791). The data in Table 2 (below) demonstrates that tenofovir alafenamide hemifumarate (Batch 2) purged the diastereomeric impurity to less than one-tenth of the starting concentration, whereas the monofumarate form of tenofovir alafenamide (Batch 1) only slightly purged the diastereomeric impurity.

TABLE 2

Purging Capability Comparison

Batch	Diastereomeric Impurity in Starting Material	Solvent	Fumaric acid charge (mole equivalent)	Product obtained	Diastereomeric Impurity in Product
1	9.3%	ACN	0.9	Monofumarate form	7.6%
2	10.0%	ACN	0.5	Hemifumarate form	0.65%

Chemical Stability

Chemical stability of the hemifumarate form of tenofovir alafenamide was compared with the monofumarate form. As shown in Table 3 (below), under identical conditions, the hemifumarate form of tenofovir alafenamide was chemically

more stable and exhibited better long-term storage stability, with significantly less degradation (% Total Deg. Products) than the monofumarate form. Conditions evaluated include temperature, relative humidity (RH), and the open or closed state of the container cap.

TABLE 3

Chemical Stability Comparison

		Monofumarate form		Hemifumarate form	
Storage Condition	Time Points (weeks)	% TA * Area Normalized	% Total Deg. Products	% TA Area Normalized	% Total Deg. Products
40° C./	0	97.1	0.69	98.4	0.05
75% RH	1	97.0	0.87	98.4	0.14
Cap	2	96.6	1.18	98.5	0.14
Closed	4	96.4	1.49	98.4	0.25
	8	95.4	2.36	98.0	0.49
40° C./	0	97.1	0.69	98.4	0.05
75% RH	1	96.9	0.90	98.5	0.15
Cap	2	96.6	1.10	98.5	0.14
Open	4	96.2	1.67	98.4	0.26
	8	95.0	2.74	98.1	0.50
70° C.	0	97.1	0.69	98.4	0.05
Cap	2	96.2	1.83	98.5	0.22
Closed	4	93.3	4.78	98.4	0.33

* TA is tenofovir alafenamide

Thermodynamic Stability

Stable form screening of tenofovir alafenamide hemifumarate showed that it is thermodynamically stable in most solvents, such as ACN, toluene, ethyl acetate, methyl tert-butyl ether (MTBE), acetone, THF, and 2-methyl THF. A similar stable form screening of the monofumarate form showed that this form is not thermodynamically stable in the above-listed solvents. When suspended in these solvents, the monofumarate form of tenofovir alafenamide fully converts to the hemifumarate form in THF and 2-methyl THF, and partially converts to the hemifumarate form in ACN, ethyl acetate, MTBE, and acetone, as well as at ambient temperatures.

Thermal Stability

As shown by the DSC data, the hemifumarate form of tenofovir alafenamide has a melting point that is about 10° C. higher than that of the monofumarate form, indicating that the hemifumarate form has improved thermal stability as compared with the monofumarate form.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. Tenofovir alafenamide hemifumarate.

2. The hemifumarate of claim **1** that has a differential scanning calorimetry (DSC) onset endotherm of 131±2° C.

3. The hemifumarate of claim **2** that has a DSC onset endotherm of 131±1° C.

4. Tenofovir alafenamide hemifumarate, having an X-ray powder diffraction (XRPD) pattern comprises 2theta values of 6.9±0.2° and 8.6±0.2°.

5. The hemifumarate of claim **4**, wherein the XRPD pattern comprises 2theta values of 6.9±0.2°, 8.6±0.2°, 11.0±0.2°, 15.9±0.2°, and 20.2±0.2°.

6. A composition comprising tenofovir alafenamide hemifumarate according to claim **1**, wherein the ratio of fumaric acid to tenofovir alafenamide in said composition is 0.5±0.1.

7. The composition of claim **6**, wherein the ratio of fumaric acid to tenofovir alafenamide is 0.5±0.05.

8. The composition of claim **6**, wherein the ratio of fumaric acid to tenofovir alafenamide is 0.5±0.01.

9. The composition of claim **6**, wherein the ratio of fumaric acid to tenofovir alafenamide is about 0.5.

10. The composition of claim **6**, which is a solid.

11. A pharmaceutical composition comprising the hemifumarate of claim **1** and a pharmaceutically acceptable excipient.

12. The pharmaceutical composition of claim **11**, further comprising an additional therapeutic agent.

13. The pharmaceutical composition of claim **12**, wherein the additional therapeutic agent is selected from the group consisting of human immunodeficiency virus (HIV) protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

14. The composition of claim **7**, which is a solid.

15. The composition of claim **8**, which is a solid.

16. The composition of claim **9**, which is a solid.

17. A method for treating a human immunodeficiency virus (HIV) infection comprising administering to a subject in need thereof a therapeutically effective amount of the hemifumarate of claim **1**.

18. A method for treating an HIV infection comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of claim **11**.

19. The method for treating an HIV infection of claim **17**, further comprising administering to the subject one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

20. A method for treating a hepatitis B virus (HBV) infection comprising administering to a subject in need thereof a therapeutically effective amount of the hemifumarate of claim **1**.

21. A method for treating an HBV infection comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of claim **11**.

22. The method for treating an HIV infection of claim **17**, wherein the hemifumarate is administered in multiple daily doses.

23. The method for treating an HIV infection of claim **17**, wherein the hemifumarate is administered in a single daily dose.

24. The method for treating an HBV infection of claim **20**, wherein the hemifumarate is administered in multiple daily doses.

25. The method for treating an HBV infection of claim **20**, wherein the hemifumarate is administered in a single daily dose.

26. A method for preparing a pharmaceutical composition comprising combining the hemifumarate of claim **1** and a pharmaceutically acceptable excipient to provide the pharmaceutical composition.

27. A method for preparing tenofovir alafenamide hemifumarate comprising admixing a) aprotic organic solvent; b) fumaric acid; c) tenofovir alafenamide; and d) one or more seeds of tenofovir alafenamide hemifumarate; and

crystallizing additional tenofovir alafenamide hemifumarate.

28. The method of claim **27**, wherein the solvent comprises acetonitrile.

29. The method of claim **27**, wherein the solution is subjected to a temperature in the range of from about 0° C. to about 75° C.

30. A method for preparing tenofovir alafenamide hemifumarate, comprising the steps of:

admixing a) a solvent comprising water, isopropyl alcohol, acetone, acetonitrile, toluene, ethyl acetate, isopropyl acetate, heptane, tetrahydrofuran, 2-methyl tetrahydrofuran, methyl ethyl ketone, methyl isobutyl ketone or mixtures thereof; b) fumaric acid; c) tenofovir alafenamide; and d) one or more seeds of tenofovir alafenamide hemifumarate; and

crystallizing additional tenofovir alafenamide hemifumaratre at a temperature from about 0° C. to about 70° C.

31. The method of claim **30**, wherein the solvent comprises acetonitrile and up to about 50% by volume methylene chloride.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,754,065 B2
APPLICATION NO. : 13/586358
DATED : June 17, 2014
INVENTOR(S) : Dazhan Liu et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

TITLE PAGE:

Page one, second column, line 19, please delete "Non-Final Office Action for U.S. Appl. No. 13/118,122, mailed Feb.".

Page one, second column, line 20, please delete "19, 2014, 23 pages.".

Page one, second column, line 21, please delete "Supplemental Notice of Allowance for U.S. Appl. No. 12/857,238,".

Page one, second column, line 22, please delete "mailed Feb. 25, 2014, 2 pages.".

Page one, second column, line 23, please delete "Non-Final Office Action for U.S. Appl. No. 14/134,933, mailed Feb.".

Page one, second column, line 24, please delete "25, 2014, 7 pages.".

Page one, second column, line 25, please delete "Non-Final Office Action for U.S. Appl. No. 14/033,245 mailed Feb.".

Page one, second column, line 26, please delete "26, 2014, 11 pages.".

Page one, second column, line 27, please delete "Patent Owner's Request for Rehearing Under 37 C.F.R. § 41.79, in".

Page one, second column, line 28, please delete "Inter Partes Npls Reexamination of U.S. Patent No. 7,714,747, Con-".

Page one, second column, line 29, please delete "trol No. 95/001,517, filed Feb. 14, 2014, 11 pages.".

Signed and Sealed this
Ninth Day of December, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

CLAIMS:

Claim 4:

Column 11, line 60; please replace "pattern comprises" with -- pattern that comprises --.

Claim 29:

Column 13, line 6; please replace "0° C." with -- 0° C --.

Claim 30:

Column 13, lines 17 and 18; please replace "hemifumaratre at a temperature from about 0° C." with -- hemifumarate at a temperature of from about 0° C --.

Exhibit D

US009296769B2

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

(10) **Patent No.: US 9,296,769 B2**
(45) **Date of Patent: *Mar. 29, 2016**

(54) **TENOFOVIR ALAFENAMIDE HEMIFUMARATE**

(71) Applicant: **Gilead Sciences, Inc.**, Foster City, CA (US)

(72) Inventors: **Dazhan Liu**, Edmonton (CA); **Bing Shi**, Foster City, CA (US); **Fang Wang**, Foster City, CA (US); **Richard Hung Chiu Yu**, San Francisco, CA (US)

(73) Assignee: **Gilead Sciences, Inc.**, Foster City, CA (US)

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

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/197,873**

(22) Filed: **Mar. 5, 2014**

(65) **Prior Publication Data**

US 2014/0187773 A1 Jul. 3, 2014

Related U.S. Application Data

(63) Continuation of application No. 13/586,358, filed on Aug. 15, 2012, now Pat. No. 8,754,065.

(60) Provisional application No. 61/524,224, filed on Aug. 16, 2011.

(51) **Int. Cl.**

A61K 31/685	(2006.01)
C07F 9/6561	(2006.01)
A61K 31/52	(2006.01)
C07D 473/34	(2006.01)

(52) **U.S. Cl.**

CPC ***C07F 9/65616*** (2013.01); ***A61K 31/52*** (2013.01); ***A61K 31/685*** (2013.01); ***C07D 473/34*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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WO	WO-2009/135179	A2	11/2009
WO	WO-2009/135179	A3	11/2009
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Primary Examiner — James D Anderson

(74) *Attorney, Agent, or Firm* — Morrison & Foerster LLP

(57) **ABSTRACT**

A hemifumarate form of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl] adenine (tenofovir alafenamide), and antiviral therapy using tenofovir alafenamide hemifumarate (e.g., anti-HIV and anti-HBV therapies).

19 Claims, 4 Drawing Sheets

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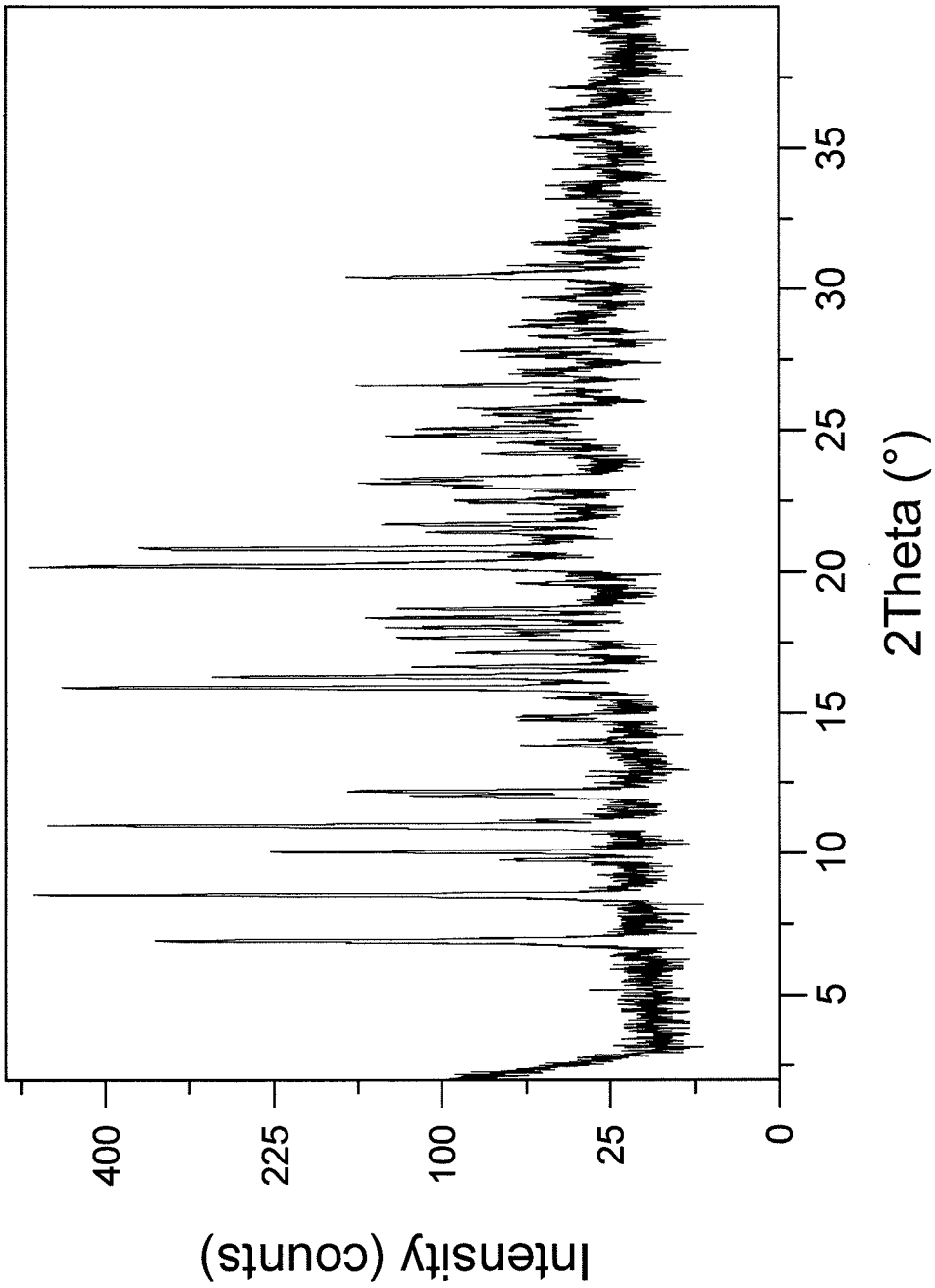
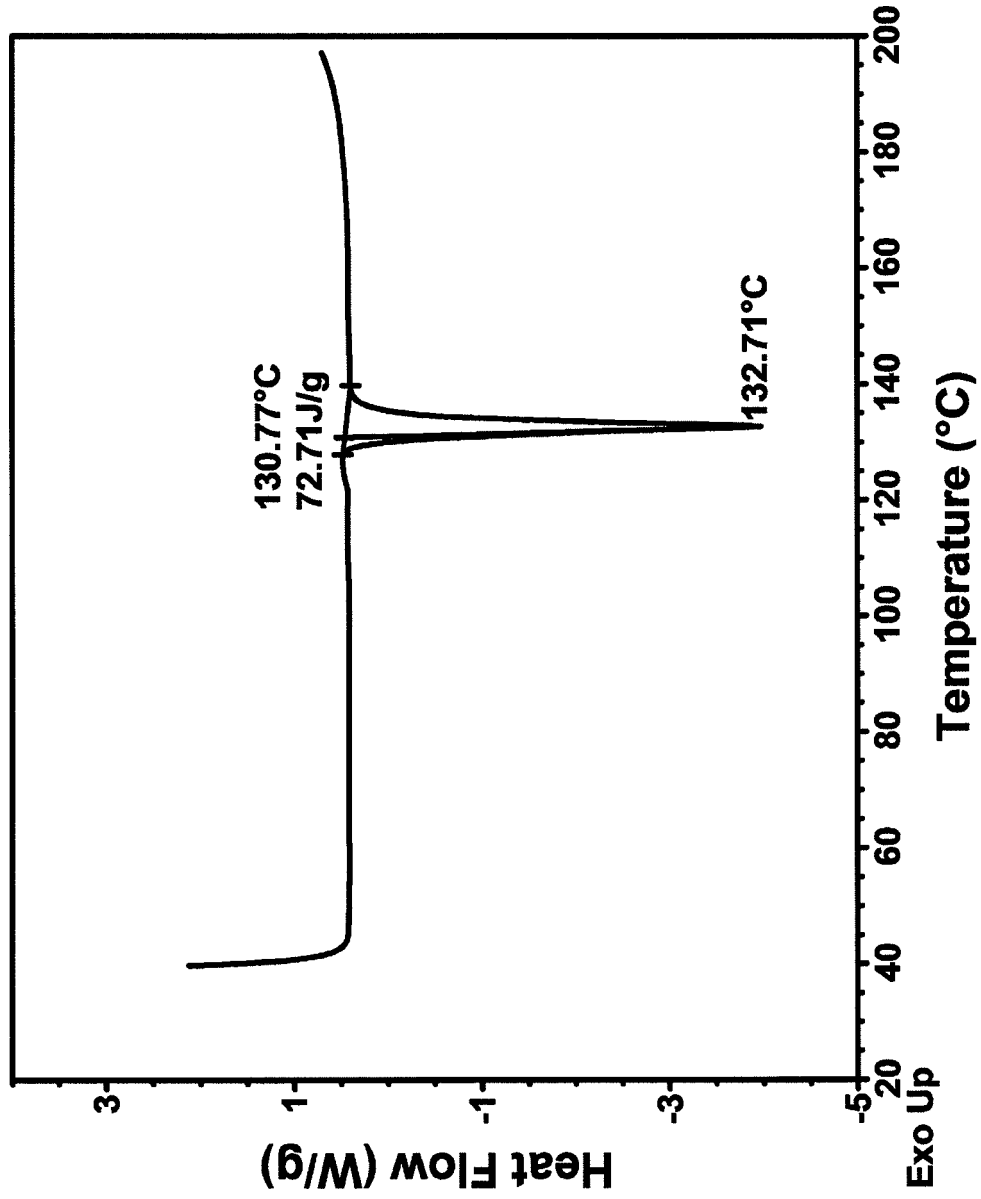


Figure 1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132.71°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
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-3
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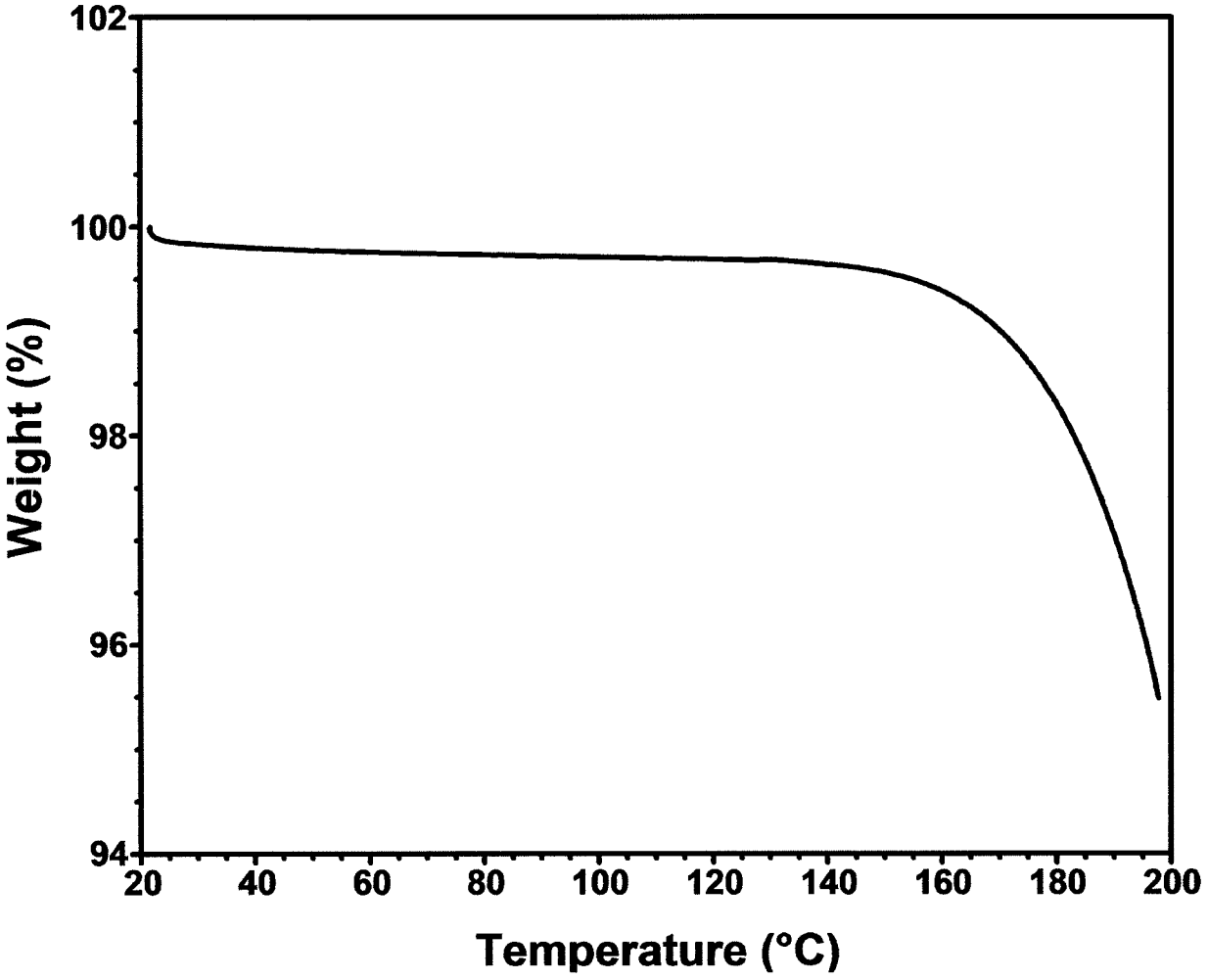
60
80
100
120
140
160
180
200

Figure 2

Figure 3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100
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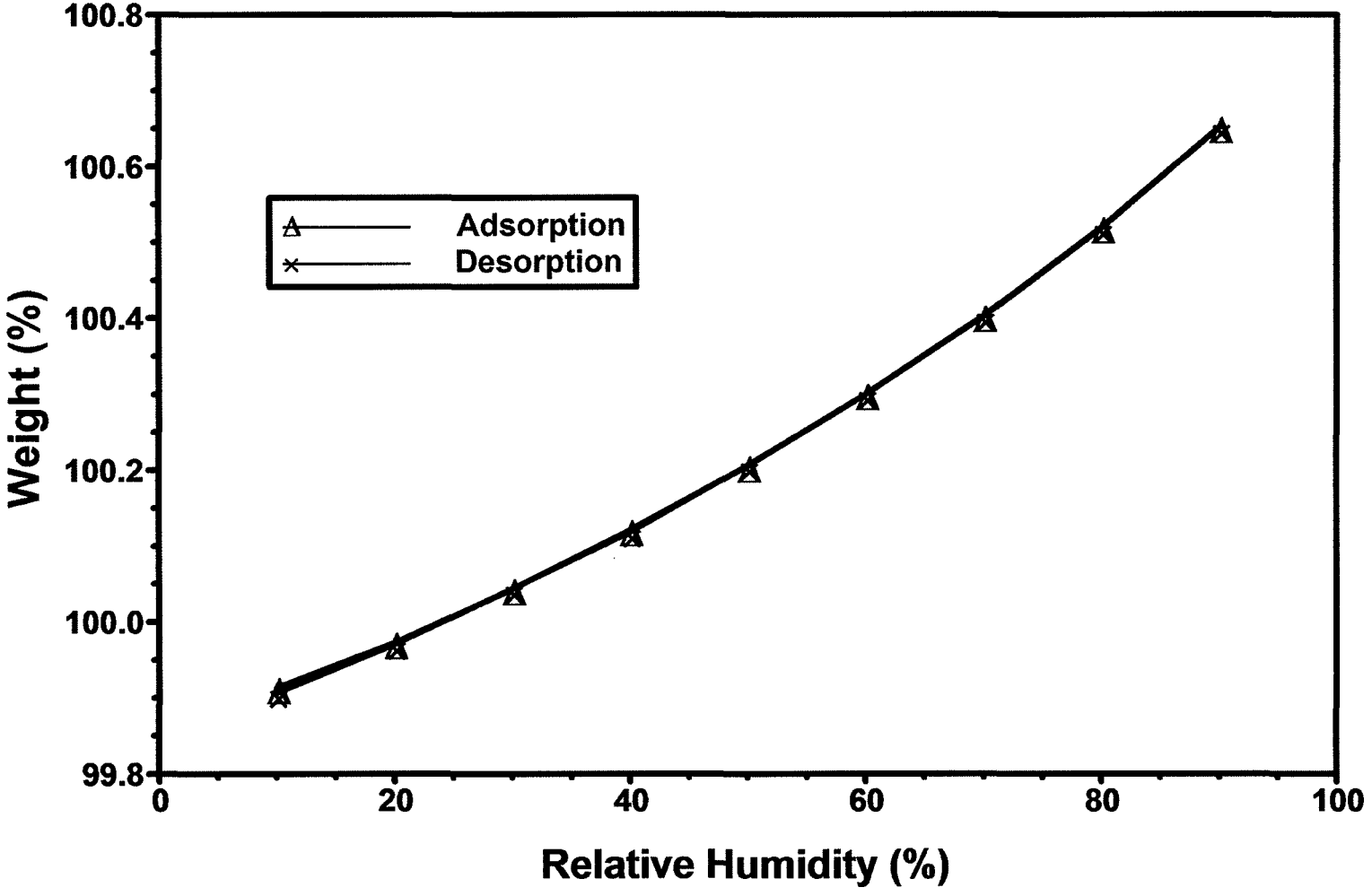
160
180
200
Temperature (°C)

Figure 4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100.2
100.0
99.8
Weight (%)
Adsorption
Desorption
0
20
40
60
80
100
Relative Humidity (%)

TENOFOVIR ALAFENAMIDE HEMIFUMARATE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 13/586,358 filed Aug. 15, 2012, which in turn claims the benefit of priority from U.S. Provisional Patent Application No. 61/524,224, filed Aug. 16, 2011, the content of each of which is hereby incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

Description of Related Art

U.S. Pat. Nos. 7,390,791 and 7,803,788 (the content of each of which is incorporated by reference herein in its entirety) describe certain prodrugs of phosphonate nucleotide analogs that are useful in therapy. One such prodrug is 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. This compound is also known by the Chemical Abstract name L-alanine, N—[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester. U.S. Pat. Nos. 7,390,791 and 7,803,788 also disclose a monofumarate form of this compound and its preparation method (see, e.g., Example 4).

SUMMARY OF THE INVENTION

Described is a hemifumarate form of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. The name for 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine is tenofovir alafenamide. The hemifumarate form of tenofovir alafenamide is also referred to herein as tenofovir alafenamide hemifumarate.

In one embodiment of the invention is provided tenofovir alafenamide hemifumarate.

In another embodiment is provided tenofovir alafenamide hemifumarate, wherein the ratio of fumaric acid to tenofovir alafenamide is 0.5±0.1, or 0.5±0.05, or 0.5±0.01, or about 0.5.

In one embodiment is provided tenofovir alafenamide hemifumarate in a solid form.

In one embodiment is provided tenofovir alafenamide hemifumarate that has an X-ray powder diffraction (XRPD) pattern having 2theta values of 6.9±0.2° and 8.6±0.2°. In another embodiment is provided tenofovir alafenamide hemifumarate wherein the XRPD pattern comprises 2theta values of 6.9±0.2°, 8.6±0.2°, 11.0±0.2°, 15.9±0.2°, and 20.2±0.2°.

In one embodiment is provided tenofovir alafenamide hemifumarate that has a differential scanning calorimetry (DSC) onset endotherm of 131±2° C., or 131±1° C.

In one embodiment is provided a pharmaceutical composition comprising tenofovir alafenamide hemifumarate and a pharmaceutically acceptable excipient. In another embodiment is provided the pharmaceutical composition, further comprising an additional therapeutic agent. In a further embodiment, the additional therapeutic agent is selected from the group consisting of human immunodeficiency virus (HIV) protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

In one embodiment is provided a method for treating a human immunodeficiency virus (HIV) infection comprising administering to a subject in need thereof a therapeutically effective amount of tenofovir alafenamide hemifumarate. In another embodiment is provided a method for treating an HIV infection comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising tenofovir alafenamide hemifumarate. In a further embodiment, the method comprises administering to the subject one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

In one embodiment is provided a method for treating a hepatitis B virus (HBV) infection comprising administering to a subject in need thereof a therapeutically effective amount of tenofovir alafenamide hemifumarate. In another embodiment is provided a method for treating an HBV infection comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition comprising tenofovir alafenamide hemifumarate.

In one embodiment is provided a method for preparing a pharmaceutical composition comprising combining tenofovir alafenamide hemifumarate and a pharmaceutically acceptable excipient to provide the pharmaceutical composition.

In one embodiment is provided a method for preparing tenofovir alafenamide hemifumarate comprising subjecting a solution comprising a suitable solvent; fumaric acid; tenofovir alafenamide; and, optionally, one or more seeds of tenofovir alafenamide hemifumarate to conditions that provide for the crystallization of the fumaric acid and the tenofovir alafenamide. In one embodiment, the solvent comprises acetonitrile. In another embodiment, the solution is subjected to a temperature in the range of from about 0° C. to about 75° C.

In one embodiment is provided tenofovir alafenamide hemifumarate for use in medical therapy.

In one embodiment is provided the use of tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of an HIV infection. In another embodiment is provided the use of tenofovir alafenamide hemifumarate to treat an HIV infection. In a further embodiment is provided the use of tenofovir alafenamide hemifumarate for the preparation or manufacture of a medicament for the treatment of an HIV infection. In another further embodiment is provided tenofovir alafenamide hemifumarate for use in treating an HIV infection.

In one embodiment is provided the use of tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of an HBV infection. In another embodiment is provided the use of tenofovir alafenamide hemifumarate to treat an HBV infection. In a further embodiment is provided the use of tenofovir alafenamide hemifumarate for the preparation or manufacture of a medicament for the treatment of an HBV infection. In another further embodiment is provided tenofovir alafenamide hemifumarate for use in treating an HBV infection.

In some embodiments of the invention, the methods of treating and the like comprise administration of multiple daily doses. In other embodiments, the methods of treating and the like comprise administration of a single daily dose.

In one embodiment of the invention is provided a composition consisting essentially of tenofovir alafenamide hemifumarate.

BRIEF DESCRIPTIONS OF THE DRAWINGS

FIG. **1** shows the X-ray powder diffraction (XRPD) pattern of tenofovir alafenamide hemifumarate.

FIG. **2** shows a graph of the DSC analysis of tenofovir alafenamide hemifumarate.

FIG. **3** shows a graph of the thermogravimetric analysis (TGA) data for tenofovir alafenamide hemifumarate.

FIG. **4** shows a graph of the dynamic vapor sorption (DVS) analysis of tenofovir alafenamide hemifumarate.

DETAILED DESCRIPTION OF THE INVENTION

Specific values listed within the present description for radicals, substituents, and ranges are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

In one embodiment, there is provided a hemifumarate form of tenofovir alafenamide (i.e., tenofovir alafenamide hemifumarate). This form may have a ratio (i.e., a stoichiometric ratio or mole ratio) of fumaric acid to tenofovir alafenamide of 0.5±0.1, 0.5±0.05, 0.5±0.01, or about 0.5, or the like.

In one embodiment, tenofovir alafenamide hemifumarate consists of fumaric acid and tenofovir alafenamide in a ratio of 0.5±0.1.

In one embodiment, tenofovir alafenamide hemifumarate consists essentially of fumaric acid and tenofovir alafenamide in a ratio of 0.5±0.1.

In one embodiment, tenofovir alafenamide hemifumarate has an XRPD pattern comprising 2theta values of 6.9±0.2°, 8.6±0.2°, 10.0±0.2°, 11.0±0.2°, 12.2±0.2°, 15.9±0.2°, 16.3±0.2°, 20.2±0.2°, and 20.8±0.2°.

In one embodiment, tenofovir alafenamide hemifumarate has an XRPD pattern comprising at least four 2theta values selected from 6.9±0.2°, 8.6±0.2°, 10.0±0.2°, 11.0±0.2°, 12.2±0.2°, 15.9±0.2°, 16.3±0.2°, 20.2±0.2°, and 20.8±0.2°.

In one embodiment, tenofovir alafenamide hemifumarate has a DSC onset endotherm of 131±2° C., or 131±1° C.

In one embodiment, a tenofovir alafenamide hemifumarate composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate.

In one embodiment, a tenofovir alafenamide hemifumarate composition comprises less than about 1% by weight of tenofovir alafenamide monofumarate.

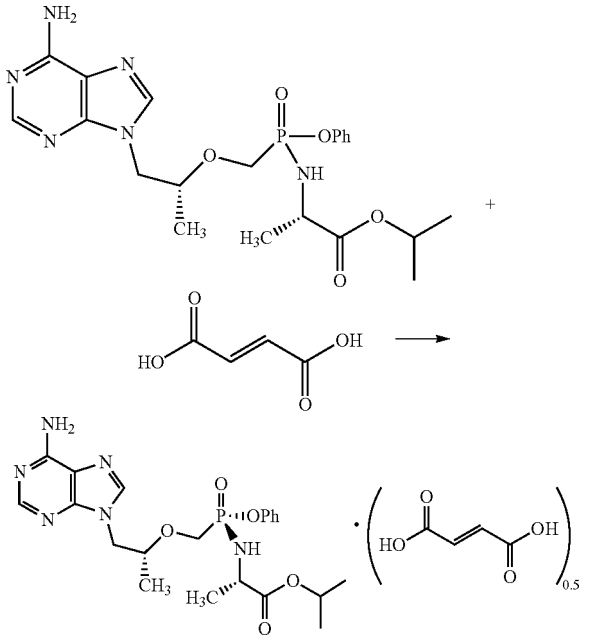
In one embodiment, a tenofovir alafenamide hemifumarate composition comprises less than about 0.5% by weight of tenofovir alafenamide monofumarate.

In one embodiment, a tenofovir alafenamide hemifumarate composition comprises no detectable tenofovir alafenamide monofumarate.

Tenofovir alafenamide (i.e., the compound 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine) can be prepared as described in U.S. Pat. No. 7,390,791.

Selective Crystallization

In one embodiment, tenofovir alafenamide hemifumarate can be prepared using selective crystallization. An example of a scheme for this preparation method is as follows.



The method can be carried out by subjecting a solution comprising: a) a suitable solvent; b) fumaric acid; c) tenofovir alafenamide; and, optionally, d) one or more seeds comprising tenofovir alafenamide hemifumarate, to conditions that provide for the crystallization of fumaric acid and tenofovir alafenamide. The starting solution can contain the single diastereomer of tenofovir alafenamide or a mixture of tenofovir alafenamide and one or more of its other diastereomers (e.g., GS-7339, as described in U.S. Pat. No. 7,390,791).

The selective crystallization can be carried out in any suitable solvent. For example, it can be carried out in a protic solvent or in an aprotic organic solvent, or in a mixture thereof. In one embodiment, the solvent comprises a protic solvent (e.g., water or isopropyl alcohol). In another embodiment, the solvent comprises an aprotic organic solvent (e.g., acetone, acetonitrile (ACN), toluene, ethyl acetate, isopropyl acetate, heptane, tetrahydrofuran (THF), 2-methyl THF, methyl ethyl ketone, or methyl isobutyl ketone, or a mixture thereof). In one embodiment, the solvent comprises ACN or a mixture of ACN and up to about 50% methylene chloride (by volume). The selective crystallization also can be carried out at any suitable temperature, for example, a temperature in the range of from about 0° C. to about 70° C. In one specific embodiment, the resolution is carried out at a temperature of about 0° C.

One major advantage of the hemifumarate form of tenofovir alafenamide over the monofumarate form is its exceptional capability to purge GS-7339 (i.e., 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine; described in, e.g., U.S. Pat. No. 7,390,791), which is the major diastereomeric impurity in the active pharmaceutical ingredient. Thus, the hemifumarate form of tenofovir alafenamide can be more readily and easily separated from impurities than the monofumarate form. Other major advantages of tenofovir alafenamide hemifumarate over the monofumarate form include improved thermodynamic and chemical stability (including long-term storage stability), superior process reproducibility, superior drug product content uniformity, and a higher melting point.

Tenofovir alafenamide hemifumarate is useful in the treatment and/or prophylaxis of one or more viral infections in man or animals, including infections caused by DNA viruses. RNA viruses, herpesviruses (e.g., CMV, HSV 1, HSV 2, VZV), retroviruses, hepadnaviruses (e.g., HBV), papillomavirus, hantavirus, adenoviruses and HIV. U.S. Pat. No. 6,043,230 (incorporated by reference herein in its entirety) and other publications describe the antiviral specificity of nucleotide analogs, such as tenofovir disoproxil. Like tenofovir disoproxil, tenofovir alafenamide is another prodrug form of tenofovir, and can be used in the treatment and/or prophylaxis of the same conditions.

Tenofovir alafenamide hemifumarate can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including ocular, buccal, and sublingual), vaginal, and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, and epidural). Generally, tenofovir alafenamide hemifumarate is administered orally, but it can be administered by any of the other routes noted herein.

Accordingly, pharmaceutical compositions include those suitable for topical or systemic administration, including oral, rectal, nasal, buccal, sublingual, vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, and epidural) administration. The formulations are in unit dosage form and are prepared by any of the methods well known in the art of pharmacy.

For oral therapeutic administration, the tenofovir alafenamide hemifumarate may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such pharmaceutical compositions and preparations will typically contain at least 0.1% of tenofovir alafenamide hemifumarate. The percentage of this active compound in the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% or more of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful pharmaceutical compositions is preferably such that an effective dosage level will be obtained upon administration of a single-unit dosage (e.g., tablet). Other dosage formulations may provide therapeutically effective amounts of tenofovir alafenamide hemifumarate upon repeated administration of subclinically effective amounts of the same. Preferred unit dosage formulations include those containing a daily dose (e.g., a single daily dose), as well as those containing a unit daily subclinical dose, or an appropriate fraction thereof (e.g., multiple daily doses), of tenofovir alafenamide hemifumarate.

Pharmaceutical compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of tenofovir alafenamide hemifumarate; as a powder or granules; as a solution or a suspension in an aqueous liquid or a nonaqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. Tenofovir alafenamide hemifumarate may also be presented as a bolus, electuary, or paste.

Tenofovir alafenamide hemifumarate is preferably administered as part of a pharmaceutical composition or formulation. Such pharmaceutical composition or formulation comprises tenofovir alafenamide hemifumarate together with one or more pharmaceutically acceptable carriers/excipients, and optionally other therapeutic ingredients. The excipient(s)/carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient. Excipients include, but are not limited to, substances that can serve as a vehicle or medium for tenofovir alafenamide hemifumarate (e.g., a diluent carrier). They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet.

Accordingly, the tablets, troches, pills, capsules, and the like may also contain, without limitation, the following: a binder(s), such as hydroxypropyl cellulose, povidone, or hydroxypropyl methylcellulose; a filler(s), such as microcrystalline cellulose, pregelatinized starch, starch, mannitol, or lactose monohydrate; a disintegrating agent(s), such as croscarmellose sodium, cross-linked povidone, or sodium starch glycolate; a lubricant(s), such as magnesium stearate, stearic acid, or other metallic stearates; a sweetening agent(s), such as sucrose, fructose, lactose, or aspartame; and/or a flavoring agent(s), such as peppermint, oil of wintergreen, or a cherry flavoring. When the unit dosage form is a capsule, it may contain, in addition to materials of the above types, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, polymers, wax, shellac, or sugar and the like. Of course, any material used in preparing any unit dosage form typically will be pharmaceutically acceptable and substantially nontoxic in the amounts employed. In addition, tenofovir alafenamide hemifumarate may be incorporated into sustained-release preparations and devices.

For infections of the eye or other external tissues, e.g., mouth and skin, the pharmaceutical compositions are preferably applied as a topical ointment or cream containing tenofovir alafenamide hemifumarate in an amount of, for example, 0.01 to 10% w/w (including active ingredient in a range between 0.1% and 5% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 3% w/w and most preferably 0.5 to 2% w/w. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base.

Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising tenofovir alafenamide hemifumarate in a flavored basis, for example, sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Pharmaceutical formulations suitable for parenteral administration are sterile and include aqueous and nonaqueous injection solutions that may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and nonaqueous sterile suspensions that may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier (e.g., water for injections) immediately prior to use. Injection solutions and suspensions may be prepared from sterile powders, granules, and tablets of the kind previously described.

In addition to the ingredients particularly mentioned above, the pharmaceutical compositions/formulations may include other ingredients conventional in the art, having regard to the type of formulation in question.

In another embodiment, there is provided veterinary compositions comprising tenofovir alafenamide hemifumarate together with a veterinary carrier therefor. Veterinary carriers are materials useful for the purpose of administering the composition to cats, dogs, horses, rabbits, and other animals, and may be solid, liquid, or gaseous materials that are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally, or by any other desired route.

The tenofovir alafenamide hemifumarate can be used to provide controlled release pharmaceutical formulations containing a matrix or absorbent material and an active ingredient of the invention, in which the release of the active ingredient can be controlled and regulated to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the compound. Controlled release formulations adapted for oral administration, in which discrete units comprising a compounds of the invention, can be prepared according to conventional methods.

Useful dosages of tenofovir alafenamide hemifumarate can be determined by comparing in vitro activities, and the in vivo activities in animal models. Methods for the extrapolation of effective amounts/dosages in mice and other animals to therapeutically effective amounts/dosages in humans are known in the art.

The amount of tenofovir alafenamide hemifumarate required for use in treatment will vary with several factors, including but not limited to the route of administration, the nature of the condition being treated, and the age and condition of the patient; ultimately, the amount administered will be at the discretion of the attendant physician or clinician. The therapeutically effective amount/dose of tenofovir alafenamide hemifumarate depends, at least, on the nature of the condition being treated, any toxicity or drug interaction issues, whether the compound is being used prophylactically (e.g., sometimes requiring lower doses) or against an active disease or condition, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

In one embodiment, the oral dose of tenofovir alafenamide hemifumarate may be in the range from about 0.0001 to about 100 mg/kg body weight per day, for example, from about 0.01 to about 10 mg/kg body weight per day, from about 0.01 to about 5 mg/kg body weight per day, from about 0.5 to about 50 mg/kg body weight per day, from about 1 to about 30 mg/kg body weight per day, from about 1.5 to about 10 mg/kg body weight per day, or from about 0.05 to about 0.5 mg/kg body weight per day. As a nonlimiting example, the daily candidate dose for an adult human of about 70 kg body weight will range from about 0.1 mg to about 1000 mg, or from about 1 mg to about 1000 mg, or from about 5 mg to about 500 mg, or from about 1 mg to about 150 mg, or from about 5 mg to about 150 mg, or from about 5 mg to about 100 mg, and may take the form of single or multiple doses.

The pharmaceutical compositions described herein may further include one or more therapeutic agents in addition to tenofovir alafenamide hemifumarate. In one specific embodiment of the invention, the additional therapeutic agent can be selected from the group consisting of HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

Therapeutic methods include administering tenofovir alafenamide hemifumarate to a subject/patient in need of the same as a therapeutic or preventative treatment. Thus, tenofovir alafenamide hemifumarate may be administered to a subject/patient having a medical disorder or to a subject who may acquire the disorder. One of ordinary skill will appreciate that such treatment is given in order to ameliorate, prevent, delay, cure, and/or reduce the severity of a symptom or set of symptoms of a disorder (including a recurring disorder). The treatment may also be given to prolong the survival of a subject, e.g., beyond the survival time expected in the absence of such treatment. The medical disorders that may be treated with tenofovir alafenamide hemifumarate include those discussed herein, including without limitation, HIV infection and HBV infection.

The following are nonlimiting, illustrative Examples.

EXAMPLE 1

Tenofovir alafenamide monofumarate solids (5.0 g) and 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]methoxy]propyl]adenine (GS-7339) monofumarate solids (0.75 g) were charged into 35 g MTBE at 22° C. and the mixture was stirred for 1 hour. A slurry was formed and was dried in a rotary evaporator. 58 g acetonitrile (ACN) was charged into the solids and the mixture was heated to reflux to dissolve the solids. The resulting solution was allowed to cool naturally while agitated. A slurry was formed, and the slurry was further cooled by ice-water-bath. The solids were isolated by filtration and washed with 5 g ACN. The solids were dried in a vacuum oven at 40° C. overnight. 5.52 g off-white solids were obtained. The solids were analyzed by XRPD and found to contain tenofovir alafenamide monofumarate, GS-7339 monofumarate, and tenofovir alafenamide hemifumarate.

EXAMPLE 2

Preparation of Tenofovir Alafenamide Hemifumarate Via Selective Crystallization

9-[(R)-2-[[[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine as a slurry in ACN (9.7 kg slurry, 13.8 wt %, a diastereomeric mixture of 1.0 kg (2.10 mol, 1 mol equiv) of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy] propyl]adenine and 0.35 kg of 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl] methoxy]propyl]adenine was charged into a reactor and rinsed forward with dichloromethane (5 kg). The mixture was concentrated under vacuum to about 3 L with jacket temperature below 40° C. The concentrate was then coevaporated with ACN (6 kg) under vacuum to about 3 L with jacket temperature below 40° C. The concentrate was diluted with ACN (8.5 kg) and warmed to 40-46° C. The warm mixture was filtered into a second reactor and the filtrate was cooled to 19-25° C.

To the above solution was charged fumaric acid (0.13 kg, 1.12 mol, 0.542 mole equiv) followed by ACN (1 kg), and the mixture was heated to 67-73° C. The hot mixture was transferred into a reactor via a polishing filter, and then adjusted to 54-60° C. Seed crystals (5 g) of the hemifumarate form of tenofovir alafenamide were charged (for example, the mixture can be seeded with tenofovir alafenamide hemifumarate formed in Example 1 or a subsequent production), and the resulting mixture was agitated at 54-60° C. for about 30 minutes. The mixture was cooled over a minimum of 4 hours to 0-6° C., and then agitated at 0-6° C. for a minimum of 1 hour. The resulting slurry was filtered and rinsed with chilled (0-6° C.) ACN (2 kg). The product was dried under vacuum

below 45° C. until loss on drying (LOD) and organic volatile impurities (OVI) limits were met (LOD≤1.0%, dichloromethane content ≤0.19%, acetonitrile content ≤0.19%) to afford the final compound of the hemifumarate form of tenofovir alafenamide as a white to off-white powder (typical yield is about 0.95 kg). ^{1}H NMR (400 MHz, d6 DMSO): δ 1.06 (d, J=5.6 Hz, 3H), 1.12-1.16 (m, 9H), 3.77 (dd, J=10.4, 11.6 Hz, 1H), 3.84-3.90 (m, 2H), 3.94 (m, 1H), 4.14 (dd, J=6.8, 14.8 Hz, 1H), 4.27 (m, 1H), 4.85 (heptet, J=6.0 Hz, 1H), 5.65 (t, J=11.2 Hz, 1H), 6.63 (s, 1H), 7.05 (d. J=7.6 Hz, 2H), 7.13 (t, J=7.2 Hz, 1H), 7.24 (s, 2H), 7.29 (t, J=7.6 Hz, 2H), 8.13 (t, J=13.6 Hz, 2H), ^{31}P NMR (162 MHz, d6 DMSO): δ 23.3.

EXAMPLE 3

Preparation of Tenofovir Alafenamide Hemifumarate

To a jacketed reactor equipped with overhead agitator, was charged 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl] amino]phenoxyphosphinyl]methoxy]propyl]adenine (10 g), fumaric acid (1.22 g), and ACN (100 mL). The mixture was heated to 70-75° C. to dissolve the solids. Any undissolved particulates were removed by filtration through a cartridge filter. The filtered solution was cooled to 60-65° C., and seeded with 1% (by weight) of tenofovir alafenamide hemifumarate. The slurry was aged for 30 minutes and cooled to 0-5° C. over 2 hours. The temperature was maintained for 1-18 hours, and the resulting slurry was filtered and washed with 2 ml of cold ACN (0-5° C.). The solids were dried under vacuum at 50° C. to provide the hemifumarate form of tenofovir alafenamide, which was characterized as described below.

Characterization of Tenofovir Alafenamide Hemifumarate from Example 3

Tenofovir alafenamide hemifumarate from Example 3 consists of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl) ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine and one-half an equivalent of fumaric acid. Tenofovir alafenamide hemifumarate is anhydrous, nonhygroscopic, and has a DSC onset endotherm of about 131° C.

X-Ray Powder Diffraction

The XRPD pattern of tenofovir alafenamide hemifumarate was obtained in the following experimental setting: 45 KV, 45 mA, Kα1=1.5406 Å, scan range 2.-40°, step size 0.0084°, counting time: 8.25 s. The XRPD pattern for tenofovir alafenamide hemifumarate is shown in FIG. **1**. The characteristic peaks include: 6.9±0.2°, 8.6±0.2°, 10.0±0.2°, 11.0±0.2°, 12.2±0.2°, 15.9±0.2°, 16.3±0.2°, 20.2±0.2°, and 20.8±0.2°.

Single-Crystal X-Ray Diffraction

The crystal size was 0.32×0.30×0.20 mm^3. The sample was held at 123 K and the data was collected using a radiation source with a wavelength of 0.71073 Å in the theta range of 1.59 to 25.39°. Conditions of, and data collected from the single-crystal X-ray diffraction are shown in Table 1.

TABLE 1

Single-Crystal X-ray Diffraction	
Empirical formula	$C_{23}H_{31}N_6O_7P$
Formula weight	534.50
Temperature	123(2) K
Crystal size	0.32 × 0.30 × 0.20 mm^3
Theta range for data collection	1.59 to 25.39°
Wavelength	0.71073 Å
Crystal system	Tetragonal
Space group	P4(2)2(1)2

TABLE 1-continued

Single-Crystal X-ray Diffraction		
Unit cell dimensions	a = 18.1185(12) Å	α = 90°
	b = 18.1185(12) Å	β = 90°
	c = 17.5747(11) Å	γ = 90°
Volume	5769.4(6) Å^3	
Z	8	
Density (calculated)	1.231 g/cm^3	

DSC Analysis

The DSC analysis was conducted using 2.517 mg of tenofovir alafenamide hemifumarate. It was heated at 10° C./min over the range of 40-200° C. The onset endotherm was found to be about 131° C. (FIG. **2**).

TGA Data

The TGA data were obtained using 4.161 mg of tenofovir alafenamide hemifumarate. It was heated at 10° C./min over the range of 25-200° C. The sample lost 0.3% weight before melting (FIG. **3**). It was determined to be an anhydrous form.

DVS Analysis

DVS analysis was conducted using 4.951 mg of tenofovir alafenamide hemifumarate. The material was kept at 25° C. in nitrogen at humidities ranging from 10% to 90% relative humidity; each step was equilibrated for 120 minutes. The sorption isotherm is shown at FIG. **4**. The material was found to be nonhygroscopic, and to absorb 0.65% water at a relative humidity of 90%.

Purging of Diastereomeric Impurity

In the prior syntheses of tenofovir alafenamide, one of the major impurities is typically the diastereomer 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. The hemifumarate form of tenofovir alafenamide from Example 3 has an exceptional capability to purge this diastereomeric impurity, as compared with the capability of the monofumarate form (described in U.S. Pat. No. 7,390,791). The data in Table 2 (below) demonstrates that tenofovir alafenamide hemifumarate (Batch 2) purged the diastereomeric impurity to less than one-tenth of the starting concentration, whereas the monofumarate form of tenofovir alafenamide (Batch 1) only slightly purged the diastereomeric impurity.

TABLE 2

Purging Capability Comparison

Batch	Diastereomeric Impurity in Starting Material	Solvent	Fumaric acid charge (mole equivalent)	Product obtained	Diastereomeric Impurity in Product
1	9.3%	ACN	0.9	Monofumarate form	7.6%
2	10.0%	ACN	0.5	Hemifumarate form	0.65%

Chemical Stability

Chemical stability of the hemifumarate form of tenofovir alafenamide was compared with the monofumarate form. As shown in Table 3 (below), under identical conditions, the hemifumarate form of tenofovir alafenamide was chemically more stable and exhibited better long-term storage stability, with significantly less degradation (% Total Deg. Products) than the monofumarate form. Conditions evaluated include temperature, relative humidity (RH), and the open or closed state of the container cap.

TABLE 3

Chemical Stability Comparison

		Monofumarate form		Hemifumarate form	
Storage Condition	Time Points (weeks)	% TA* Area Normalized	% Total Deg. Products	% TA Area Normalized	% Total Deg. Products
40° C./	0	97.1	0.69	98.4	0.05
75% RH	1	97.0	0.87	98.4	0.14
Cap	2	96.6	1.18	98.5	0.14
Closed	4	96.4	1.49	98.4	0.25
	8	95.4	2.36	98.0	0.49
40° C./	0	97.1	0.69	98.4	0.05
75% RH	1	96.9	0.90	98.5	0.15
Cap	2	96.6	1.10	98.5	0.14
Open	4	96.2	1.67	98.4	0.26
	8	95.0	2.74	98.1	0.50
70° C.	0	97.1	0.69	98.4	0.05
Cap	2	96.2	1.83	98.5	0.22
Closed	4	93.3	4.78	98.4	0.33

*TA is tenofovir alafenamide

Thermodynamic Stability

Stable form screening of tenofovir alafenamide hemifumarate showed that it is thermodynamically stable in most solvents, such as ACN, toluene, ethyl acetate, methyl tert-butyl ether (MTBE), acetone, THF, and 2-methyl THF. A similar stable form screening of the monofumarate form showed that this form is not thermodynamically stable in the above-listed solvents. When suspended in these solvents, the monofumarate form of tenofovir alafenamide fully converts to the hemifumarate form in THF and 2-methyl THF, and partially converts to the hemifumarate form in ACN, ethyl acetate, MTBE, and acetone, as well as at ambient temperatures.

Thermal Stability

As shown by the DSC data, the hemifumarate form of tenofovir alafenamide has a melting point that is about 10° C. higher than that of the monofumarate form, indicating that the hemifumarate form has improved thermal stability as compared with the monofumarate form.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A composition comprising tenofovir alafenamide hemifumarate, wherein the composition comprises less than about 5% by weight of tenofovir alafenamide monofumarate.

2. The composition of claim **1**, wherein the composition comprises less than about 1% by weight of tenofovir alafenamide monofumarate.

3. The composition of claim **1**, wherein the composition comprises less than about 0.5% by weight of tenofovir alafenamide monofumarate.

4. The composition of claim **1**, wherein the ratio of fumaric acid to tenofovir alafenamide in said composition is 0.5±0.1.

5. The composition of claim **1**, wherein the ratio of fumaric acid to tenofovir alafenamide in said composition is 0.5±0.01.

6. The composition of claim **1**, having an X-ray powder diffraction pattern that comprises 2theta values of 6.9±0.2° and 8.6±0.2°.

7. A pharmaceutical composition comprising the composition of claim **1** and a pharmaceutically acceptable excipient.

8. The pharmaceutical composition of claim **7**, further comprising an additional therapeutic agent.

9. The pharmaceutical composition of claim **8**, wherein the additional therapeutic agent is selected from the group consisting of human immunodeficiency virus (HIV) protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

10. A method for treating a human immunodeficiency virus (HIV) infection comprising administering to a subject in need thereof a therapeutically effective amount of the composition of claim **1**.

11. A method for treating an HIV infection comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of claim **7**.

12. The method for treating an HIV infection of claim **10**, further comprising administering to the subject one or more additional therapeutic agents selected from the group consisting of human immunodeficiency virus (HIV) protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

13. A method for treating a hepatitis B virus (HBV) infection comprising administering to a subject in need thereof a therapeutically effective amount of the composition of claim **1**.

14. A method for treating an HBV infection comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of claim **7**.

15. A method for preparing a pharmaceutical composition comprising combining the composition of claim **1** and a pharmaceutically acceptable excipient to provide the pharmaceutical composition.

16. The method for treating an HIV infection of claim **10**, wherein the composition is administered in multiple daily doses.

17. The method for treating an HIV infection of claim **10**, wherein the composition is administered in a single daily dose.

18. The method for treating an HBV infection of claim **13**, wherein the composition is administered in multiple daily doses.

19. The method for treating an HBV infection of claim **13**, wherein the composition is administered in a single daily dose.

* * * * *