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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MERCK SHARP & DOHME LLC, **Plaintiff,** **v.** **HETERO USA, INC., HETERO LABS LIMITED UNIT-V, and HETERO LABS LIMITED,** **Defendants.**	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff Merck Sharp & Dohme LLC ("Merck" or "Plaintiff"), by its undersigned attorneys, for its Complaint against Defendants Hetero USA, Inc. ("Hetero USA"), Hetero Labs Limited Unit-V ("Hetero Unit-V"), and Hetero Labs Limited ("Hetero Labs") (collectively, "Hetero" or "Defendants"), alleges as follows:

Nature of the Action

1. This is an action for infringement of U.S. Patent Nos. 10,603,282 ("the '282 patent") and 10,842,751 ("the '751 patent") (collectively, "the patents-in-suit"), under the laws of the United States, 35 U.S.C. § 100, *et seq.* arising from Hetero's submission of its Abbreviated New Drug Application ("ANDA") No. 217747 to the United States Food and Drug Administration ("FDA") seeking approval to manufacture, use, import, distribute, offer to sell,

and/or sell a generic version of Merck's DELSTRIGO® drug product prior to the expiration of the patents-in-suit.

Parties

2. Plaintiff Merck is a limited liability entity organized and existing under the laws of the State of New Jersey, having a principal place of business at 126 East Lincoln Avenue, Rahway, New Jersey 07065.

3. Merck is a global, research-driven pharmaceutical company that discovers, develops, manufactures, and markets a broad range of innovative products to improve health.

4. On information and belief, Defendant Hetero USA is a corporation organized under the laws of Delaware, having a principal place of business at 1035 Centennial Avenue, Piscataway, NJ 08854. On information and belief, Hetero USA is the U.S. Regulatory Agent for Hetero Labs and Hetero Unit-V, including for ANDA No. 217747.

5. On information and belief, Defendant Hetero Labs 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 500 018, Andhra Pradesh, India.

6. On information and belief, Defendant Hetero Unit-V is a corporation organized and existing under the laws of India, having a principal place of business at Polepally, Jadcherla, Mahabubnagar – 509301, Andhra Pradesh, India.

7. On information and belief, Hetero Labs is the parent corporation of Hetero USA and Hetero Unit-V.

The Patents-in-Suit

8. On March 31, 2020, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '282 patent, entitled, "Pharmaceutical Compositions Containing

Doravirine, Tenofovir Disoproxil Fumarate and Lamivudine." Santipharp Panmai, Aditya Tatavarti, Andrew M. Farrington, Varsha Biyyala, Leonardo R. Allain, Marcela Nefliu, Gerard R. Klinzing, Jie Ren, and Matthew Lamm are the inventors of the '282 patent. The '282 patent is assigned to Merck. A copy of the '282 patent is attached hereto as Exhibit A.

9. On November 24, 2020, the USPTO duly and lawfully issued the '751 patent, entitled, "Pharmaceutical Compositions Containing Doravirine, Tenofovir Disoproxil Fumarate and Lamivudine." Santipharp Panmai, Aditya Tatavarti, Andrew M. Farrington, Varsha Biyyala, Leonardo R. Allain, Marcela Nefliu, Gerard R. Klinzing, Jie Ren, and Matthew Lamm are the inventors of the '751 patent. The '751 patent is assigned to Merck. A copy of the '751 patent is attached hereto as Exhibit B.

The DELSTRIGO® Drug Product

10. Merck holds approved New Drug Application ("NDA") No. 210807 under Section 505(a) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for doravirine, lamivudine, and tenofovir disoproxil fumarate tablets in a 100mg/300mg/300mg strength, sold under the trade name DELSTRIGO®. DELSTRIGO® is a reverse transcriptase inhibitor, indicated as a complete regimen for the treatment of HIV-1 infection in adult patients and certain pediatric patients. Merck received approval for DELSTRIGO® from the FDA in August 2018.

11. The claims of the patents-in-suit cover, *inter alia*, pharmaceutical compositions of doravirine, lamivudine, and tenofovir disoproxil fumarate in a bilayer tablet.

12. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") with respect to DELSTRIGO®.

Acts Giving Rise To This Suit

13. Pursuant to Section 505 of the FFDCA, Hetero submitted ANDA No. 217747 ("Hetero's ANDA") seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of doravirine, lamivudine, and tenofovir disoproxil fumarate tablets in a 100mg/300mg/300mg strength ("Hetero's Proposed Product"), before the patents-in-suit expire.

14. On information and belief, following FDA approval of Hetero's ANDA, Defendants Hetero Labs, Hetero Unit-V, and Hetero USA will work in concert with one another to make, use, sell, or offer to sell Hetero's Proposed Product throughout the United States, or import that generic product into the United States.

15. On information and belief, in connection with the submission of ANDA No. 217747 as described above, Hetero provided a written certification to the FDA pursuant to Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Hetero's Paragraph IV Certification"), alleging that the claims of the '282 and '751 patents are invalid, unenforceable, and/or will not be infringed by the activities described in Hetero's ANDA.

16. No earlier than October 15, 2022, Merck received Hetero's written notice of Hetero's Paragraph IV Certification ("Hetero's Notice Letter"). Hetero's Notice Letter alleged that the claims of the '282 and '751 patents are invalid, unenforceable, and/or will not be infringed by the activities described in ANDA No. 217747. Hetero's Notice Letter also informed Merck that Hetero seeks approval to market Hetero's Proposed Product before the patents-in-suit expire.

17. By filing or causing Hetero's ANDA to be filed, Hetero necessarily represented to the FDA that Hetero's Proposed Product has the same active ingredients as DELSTRIGO®, has the same method of administration, dosage form, and strengths, and is bioequivalent to DELSTRIGO®.

Jurisdiction and Venue

18. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

19. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and/or 1400(b).

20. On information and belief, Hetero USA derives substantial revenue from directly or indirectly selling generic pharmaceutical products and/or active pharmaceutical ingredient(s) used in generic pharmaceutical products sold throughout the United States, including in this Judicial District.

21. This Court has personal jurisdiction over Hetero USA because, *inter alia*, it: (1) on information and belief, maintains a regular and established, physical place of business at 1035 Centennial Avenue, Piscataway, NJ 08854; and (2) maintains extensive and systematic contacts with the State of New Jersey, including through the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Hetero Labs. On information and belief, Hetero USA is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business Id. No. 0400362826. On information and belief, Hetero USA is registered with the State of New Jersey's Department of Health as a drug wholesaler under Registration No. 5004050. By virtue of its physical presence in New Jersey, this Court has personal jurisdiction

over Hetero USA. On information and belief, Hetero USA purposefully has conducted and continues to conduct business in this Judicial District.

22. On information and belief, Hetero Labs derives substantial revenue from directly or indirectly selling generic pharmaceutical products and/or active pharmaceutical ingredient(s) used in generic pharmaceutical products sold throughout the United States, including in this Judicial District.

23. This Court has personal jurisdiction over Hetero Labs because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in the State of New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Hetero USA, a company with a regular and established place of business in New Jersey; and (2) maintains extensive and systematic contacts with the State of New Jersey, including through the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Hetero Unit-V and Hetero USA. Hetero's Notice Letter states that Hetero USA is at least the U.S. Regulatory Agent of Hetero Unit-V, a division of Hetero Labs.

24. This Court has personal jurisdiction over Hetero Unit-V because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in the State of New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Hetero USA, a company with a regular and established place of business in New Jersey; and (2) maintains extensive and systematic contacts with the State of New Jersey, including through the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Hetero USA.

25. On information and belief, Hetero Labs, Hetero Unit-V, and Hetero USA are in the business of, among other things, manufacturing, marketing, importing, offering for sale, and

selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. On information and belief, Hetero Labs, Hetero Unit-V, and Hetero USA also prepare and/or aid in the preparation and submission of ANDAs to the FDA, including Hetero's ANDA.

26. On information and belief, this Judicial District is a likely destination for Hetero's Proposed Product.

27. This Court also has personal jurisdiction over Hetero Labs, Hetero Unit-V, and Hetero USA because, *inter alia*, they have committed an act of patent infringement under 35 U.S.C. § 271(e)(2). On information and belief, Hetero Labs, Hetero Unit-V, and Hetero USA intend a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to Merck in New Jersey and in this Judicial District.

28. In the alternative, this Court has personal jurisdiction over Hetero Labs and Hetero Unit-V because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Merck's claims arise under federal law; (b) Hetero Labs and Hetero Unit-V are foreign defendants not subject to general personal jurisdiction in the courts of any state; and (c) Hetero Labs and Hetero Unit-V have sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Hetero Labs and Hetero Unit-V satisfies due process.

29. On information and belief, each of Hetero Labs, Hetero Unit-V, and Hetero USA actively participated in the submission of Hetero's ANDA. On information and belief, Hetero

Labs, Hetero Unit-V, and Hetero USA will work in privity and/or concert with one another and/or other related entities towards the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including Hetero's Proposed Product, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the patents-in-suit.

30. On information and belief, Hetero Labs, Hetero Unit-V, and Hetero USA intend to benefit directly if Hetero's ANDA is approved by participating in the manufacture, importation, distribution, and/or sale of the generic drug products that are the subject of Hetero's ANDA.

31. On information and belief, Hetero USA and Hetero Unit-V act at the direction, and for the benefit, of Hetero Labs and are controlled and/or dominated by Hetero Labs.

32. On information and belief, Hetero Labs, Hetero Unit-V, and Hetero USA act, operate, and/or hold themselves out to the public as a single integrated business.

33. On information and belief, Hetero Labs, Hetero Unit-V, and Hetero USA have previously been sued in this Judicial District and have not challenged personal jurisdiction. *See*, *e.g., Rigel Pharmaceuticals, Inc. v. Annora Pharma Private Ltd., et al.*, Civil Action No. 22-4732 (EP)(CLW) (D.N.J.) (Hetero Labs, Hetero USA); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 19-15449 (SDW)(LDW) (D.N.J.) (Hetero USA, Hetero Labs, Hetero Unit-V); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 19-5797 (ES)(MAH) (D.N.J.) (Hetero USA, Hetero Labs); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 18-17463 (SDW)(LDW) (D.N.J.) (Hetero USA, Hetero Labs); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 18-14111 (ES)(MAH) (D.N.J.) (Hetero USA, Hetero Labs); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action

No. 17-3387 (ES)(MAH) (D.N.J.) (Hetero USA, Hetero Labs); *Otsuka Pharm. Co., Ltd. v. Hetero Drugs Ltd., et al.*, Civil Action No. 15-161 (JBS)(KMW) (D.N.J.) (Hetero USA, Hetero Labs); *AstraZeneca AB, et al. v. Hetero USA Inc., et al.*, Civil Action No. 16-2442 (RMB)(JS) (D.N.J.) (Hetero USA and Hetero Labs); and *BTG Int'l Ltd., et al. v. Actavis Labs. FL, Inc., et al.*, Civil Action No. 15-5909 (KM)(JBC) (D.N.J.) (Hetero USA, Hetero Labs).

34. On information and belief, Hetero Labs, Hetero Unit-V, and Hetero USA have previously been sued in this Judicial District and have not challenged venue. *See*, *e.g., Rigel Pharmaceuticals, Inc. v. Annora Pharma Private Ltd., et al.*, Civil Action No. 22-4732 (EP)(CLW) (D.N.J.) (Hetero Labs, Hetero USA); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 19-15449 (SDW)(LDW) (D.N.J.) (Hetero USA, Hetero Labs, Hetero Unit-V); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 19-5797 (ES)(MAH) (D.N.J.) (Hetero USA, Hetero Labs); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 18-17463 (SDW)(LDW) (D.N.J.) (Hetero USA, Hetero Labs); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 18-14111 (ES)(MAH) (D.N.J.) (Hetero USA, Hetero Labs); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 17-3387 (ES)(MAH) (D.N.J.) (Hetero USA, Hetero Labs); *Otsuka Pharm. Co., Ltd. v. Hetero Drugs Ltd., et al.*, Civil Action No. 15-161 (JBS)(KMW) (D.N.J.) (Hetero USA, Hetero Labs); *AstraZeneca AB, et al. v. Hetero USA Inc., et al.*, Civil Action No. 16-2442 (RMB)(JS) (D.N.J.) (Hetero USA and Hetero Labs); and *BTG Int'l Ltd., et al. v. Actavis Labs. FL, Inc., et al.*, Civil Action No. 15-5909 (KM)(JBC) (D.N.J.) (Hetero USA, Hetero Labs).

Count I: Infringement of the '282 Patent

35. Merck repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

36. Hetero, by the submission of Hetero's Paragraph IV Certification as part of Hetero's ANDA to the FDA and notice to Merck of same, has indicated that it seeks approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Hetero's Proposed Product, prior to the expiration of the '282 patent.

37. Hetero's submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Hetero's Proposed Product prior to the expiration of the '282 patent constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

38. There is a justiciable controversy between the parties hereto as to the infringement of the '282 patent.

39. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe, literally or under the doctrine of equivalents, one or more claims, including at least claim 1, of the '282 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States.

40. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims, including at least claim 1, of the '282 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '282 patent and knowledge that its acts are encouraging infringement by at least healthcare professionals and patients.

41. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims, including at least claim 1, of the '282 patent

under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, Hetero has had and continues to have knowledge that Hetero's Proposed Product is especially adapted for a use that constitutes a material part of the invention that infringes one or more claims of the '282 patent, and that there is no substantial non-infringing use for Hetero's Proposed Product.

42. Hetero has had knowledge of the '282 patent since at least the date Hetero submitted Hetero's ANDA and was aware that submission of its ANDA constituted an act of infringement under 35 U.S.C. § 271(e)(2). Hetero's actions render this an exceptional case under 35 U.S.C. § 285 and, therefore, Merck is entitled to attorneys' fees and costs.

43. Merck will be substantially and irreparably damaged and harmed if Hetero's infringement of the '282 patent is not enjoined.

44. Merck does not have an adequate remedy at law.

Count II: Infringement of the '751 Patent

45. Merck repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

46. Hetero, by the submission of Hetero's Paragraph IV Certification as part of Hetero's ANDA to the FDA and notice to Merck of same, has indicated that it seeks approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Hetero's Proposed Product, prior to the expiration of the '751 patent.

47. Hetero's submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Hetero's Proposed Product prior to the expiration of the '751 patent constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

48. There is a justiciable controversy between the parties hereto as to the infringement of the '751 patent.

49. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe, literally or under the doctrine of equivalents, one or more claims, including at least claim 1, of the '751 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States.

50. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims, including at least claim 1, of the '751 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '751 patent and knowledge that its acts are encouraging infringement by at least healthcare professionals and patients.

51. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims, including at least claim 1, of the '751 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, Hetero has had and continues to have knowledge that Hetero's Proposed Product is especially adapted for a use that constitutes a material part of the invention, that infringes one or more claims of the '751 patent, and that there is no substantial non-infringing use for Hetero's Proposed Product.

52. Hetero has had knowledge of the '751 patent since at least the date Hetero submitted Hetero's ANDA and was aware that submission of its ANDA constituted an act of

infringement under 35 U.S.C. § 271(e)(2). Hetero's actions render this an exceptional case under 35 U.S.C. § 285 and, therefore, Merck is entitled to attorneys' fees and costs.

53. Merck will be substantially and irreparably damaged and harmed if Hetero's infringement of the '751 patent is not enjoined.

54. Merck does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests the following relief:

(A) A Judgment that Hetero has infringed the patents-in-suit by submitting ANDA No. 217747 with the accompanying Paragraph IV Certification and notice to Merck of same;

(B) A Judgment that Hetero has infringed, and that Hetero's making, using, selling, offering to sell, or importing Hetero's Proposed Product will infringe, one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 217747 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which Merck is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Defendants and their officers, agents, attorneys, and employees, and those acting in privity and/or concert with them, from making, using, offering to sell, selling, or importing Hetero's Proposed Product until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Merck is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Hetero, its officers, agents, attorneys and employees, and those acting in privity and/or concert with it, from practicing any pharmaceutical compositions containing doravirine,

lamivudine, and tenofovir disoproxil fumarate, as claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Merck is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Hetero's Proposed Product will directly infringe, and induce and/or contribute to infringement of, the patents-in-suit;

(G) To the extent that Hetero has committed any acts with respect to the pharmaceutical compositions claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Merck damages for such acts;

(H) If Hetero engages in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Hetero's Proposed Product prior to the expiration of the patents-in-suit, a Judgment awarding damages to Merck resulting from such infringement, together with interest;

(I) A Judgment declaring that the patents-in-suit remain valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Merck its attorney's fees incurred in this action;

(K) A Judgment awarding Merck its costs and expenses incurred in this action; and

(L) Such further and other relief as this Court may deem just and proper.

Dated: November 28, 2022

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: November 28, 2022

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EXHIBIT A

US010603282B2

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

(10) **Patent No.: US 10,603,282 B2**
(45) **Date of Patent: Mar. 31, 2020**

(54) **PHARMACEUTICAL COMPOSITIONS CONTAINING DORAVIRINE, TENOFOVIR DISOPROXIL FUMARATE AND LAMIVUDINE**

(71) Applicant: **Merck Sharp & Dohme Corp.**, Rahway, NJ (US)

(72) Inventors: **Santipharp Panmai**, Cranford, NJ (US); **Aditya Tatavarti**, Chalfont, PA (US); **Andrew M. Farrington**, Collegeville, PA (US); **Varsha Biyyala**, Somerset, NJ (US); **Leonardo R. Allain**, Lansdale, PA (US); **Marcela Nefliu**, Schwenksville, PA (US); **Gerard R. Klinzing**, Wilmington, DE (US); **Jie Ren**, Chalfont, PA (US); **Matthew Lamm**, Morristown, NJ (US)

(73) Assignee: **Merck Sharp & Dohme Corp.**, Rahway, NJ (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.: **15/780,142**

(22) PCT Filed: **Nov. 29, 2016**

(86) PCT No.: **PCT/US2016/063894**
§ 371 (c)(1),
(2) Date: **May 30, 2018**

(87) PCT Pub. No.: **WO2017/095761**
PCT Pub. Date: **Jun. 8, 2017**

(65) **Prior Publication Data**

US 2019/0254977 A1 Aug. 22, 2019

Related U.S. Application Data

(60) Provisional application No. 62/261,953, filed on Dec. 2, 2015.

(51) **Int. Cl.**

A61K 9/24	(2006.01)
A61K 9/20	(2006.01)
A61K 31/4439	(2006.01)
A61K 31/675	(2006.01)
A61K 31/7068	(2006.01)
A61K 31/513	(2006.01)
A61K 31/4412	(2006.01)
A61K 9/14	(2006.01)
A61K 31/683	(2006.01)
A61K 9/16	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/209*** (2013.01); ***A61K 9/146*** (2013.01); ***A61K 9/2013*** (2013.01); ***A61K 9/2018*** (2013.01); ***A61K 9/2054*** (2013.01); ***A61K 31/4412*** (2013.01); ***A61K 31/4439*** (2013.01); ***A61K 31/513*** (2013.01); ***A61K 31/675*** (2013.01); ***A61K 31/683*** (2013.01); ***A61K 31/7068*** (2013.01); *A61K 9/1652* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Brian J Davis

(74) *Attorney, Agent, or Firm* — Nicole M. Beeler; John C. Todaro

(57) **ABSTRACT**

The instant invention relates to pharmaceutical compositions comprising doravirine, tenofovir disoproxil fumarate and lamivudine. These compositions are useful for the treatment of HIV infection. Also disclosed are processes for making said pharmaceutical compositions.

19 Claims, No Drawings

PHARMACEUTICAL COMPOSITIONS CONTAINING DORAVIRINE, TENOFOVIR DISOPROXIL FUMARATE AND LAMIVUDINE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a U.S. National Phase application under 35 U.S.C. § 371 of PCT Application No. PCT/US2016/063894 filed Nov. 29, 2016 ,which claims priority from US Ser. No. 62/261,953 filed Dec. 2, 2015.

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions comprising doravirine, tenofovir disoproxil fumarate and lamivudine. These compositions are useful for the treatment of human immunodeficiency virus (HIV) infection.

Specifically, this invention relates to single tablet fixed-dose combinations of doravirine, lamivudine and tenofovir disoproxil fumarate. A fixed-dose combination is desired and useful for the treatment of HIV infection from both compliance and convenience standpoints.

The novel pharmaceutical compositions of the instant invention address the need for incorporation of high doses of doravirine, lamivudine and tenofovir disoproxil fumarate into a compact, single-unit dosage form while still maintaining comparable bioperformance to those of co-dosed doravirine, lamivudine and tenofovir disoproxil fumarate single entity formulations.

SUMMARY OF THE INVENTION

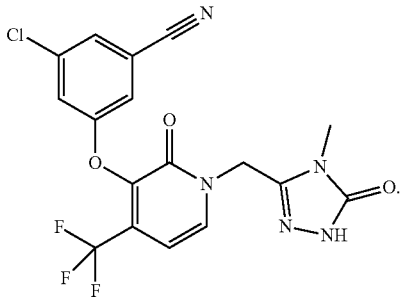
The instant invention relates to pharmaceutical compositions comprising doravirine, tenofovir disoproxil fumarate and lamivudine. These compositions are useful for the treatment of HIV infection. Also disclosed are processes for making said pharmaceutical compositions.

DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutical compositions of the present invention are useful in the treatment of HIV infection. The novel pharmaceutical compositions of the instant invention address the need for incorporation of high doses of doravirine, lamivudine and tenofovir disoproxil fumarate into a compact, single-unit dosage form while still maintaining comparable bioperformance to co-dosed single entities of doravirine, lamivudine and tenofovir disoproxil fumarate.

An embodiment of the instant invention comprises a bilayer tablet that incorporates high loading of an amorphous dispersion formulation of doravirine in one layer and high loadings of crystalline formulations of lamivudine and tenofovir disoproxil fumarate in a separate layer. The resulting bilayer tablets are compact, single-unit dosage forms that have bioperformance comparable to those of individually co-dosed doravirine, lamivudine and tenofovir disoproxil fumarate.

Doravirine is an HIV reverse transcriptase (RT) inhibitor having the chemical name 3-chloro-5-({1-[(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl}oxy)benzonitrile and the following chemical structure:



Production and the ability of doravirine to inhibit HIV reverse transcriptase is illustrated in WO 2011/120133 A1, published on Oct. 6, 2011, and U.S. Pat. No. 8,486,975, granted Jul. 16, 2013, both of which are hereby incorporated by reference in their entirety.

Tenofovir disoproxil fumarate (which can be abbreviated as "TDF") is an antiretroviral medication used to prevent and treat HIV/AIDS. It is of the nucleoside analog reverse transcriptase inhibitor (NRTI) class and is marketed under the tradename VIREAD®. TDF is disclosed in U.S. Pat. No. 5,922,695.

Lamivudine (2',3'-dideoxy-3'-thiacytidine, commonly called 3TC) is an antiretroviral medication used to prevent and treat HIV/AIDS. It is of the nucleoside analog reverse transcriptase inhibitor (NRTI) class and is marketed under the tradename EPIVIR®. Lamivudine is also abbreviated as "LAM." Lamivudine and method of treating HIV using lamivudine are disclosed in U.S. Pat. No. 5,047,407.

Doravirine is known to exist in three crystalline anhydrous forms, designated as Form I, Form II and Form III, and in an amorphous form. An amorphous dispersion formulation of doravirine can be made by spray-drying doravirine with a polymer, such as hydroxypropyl methyl cellulose acetate succinate (HPMCAS, also known as "hypromellose acetate succinate"), hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, polyvinylpyrrolidinone or polyvinylpyrrolidinone-polyvinylacetate copolymers. In a class of the invention, the amorphous dispersion formulation of doravirine is made by spray-drying doravirine with hydroxypropyl methyl cellulose acetate succinate (HPMCAS-L), which significantly improves the bioavailability of doravirine.

However, the resulting amorphous dispersion formulation of doravirine poses many unique challenges, including physical stability, since doravirine is a strong crystallizer. Doravirine was found to crystallize readily in the absence of a polymer and to have a high melting point of 286° C. (see, PCT International Publication WO 2015/077273, which is hereby incorporated by reference in its entirety). Neat amorphous doravirine generated by spray-drying crystallizes within 2 weeks when stored in an open container at 5° C./ambient relative humidity (RH), 30° C./65% RH, 40° C./75% RH, and 60° C./ambient RH. For spray-dried dispersions of doravirine and HPMCAS, crystallization was observed at 35% drug loading after 16 weeks of storage and at 40% drug loading after 8 weeks of storage at 40° C./75% RH (open). Other factors can affect physical stability, including inherent tendency of the drug to crystallize, drug loading in the dispersion, type of polymers used, hygroscopicity of the formulation and other factors.

In addition to challenges associated with physical stability, dissolution of the amorphous dispersion of doravirine is a concern due to a kinetic supersaturation effect. The composition comprising the amorphous dispersion of doravirine (doravirine and a polymer) provides a higher maximum aqueous concentration of doravirine relative to a control composition having the same concentration of doravirine but without the polymer. This supersaturation effect is transient and relies on rapid dissolution of the drug from the tablet.

Furthermore, there are processing issues due to atypical compaction properties associated with the amorphous dispersion of doravirine. The compactability of doravirine spray dried dispersion is directly correlated to the bulk density of the dispersion. Higher bulk density leads to lower tensile strength tablets. Also, recompactability of the spray dried dispersion formulations, post roller compaction is also a concern. A relatively high roller compaction force results in lower final compactability. In certain cases, tablets of formulations containing doravirine spray dried dispersions with high bulk density show failure upon compression, due to low tensile strength (see, PCT International Publication WO2015/077273).

What is needed is a formulation that can consistently deliver high doses of doravirine without encountering the observed issues related to physical stability, kinetic supersaturation effect and processing.

The pharmaceutical compositions of the present invention, which are bilayer tablets, comprise an amorphous dispersion formulation of doravirine in the first layer, and lamivudine and tenofovir disoproxil fumarate in the second layer.

In an embodiment of the invention, the first layer comprises an amorphous dispersion formulation of doravirine, a glidant, a diluent, a disintegrant and lubricants. In a class of the invention, the first layer comprises from about 25% to 75% by weight of an amorphous dispersion formulation of doravirine, and from about 25% to 75% by weight of excipients comprising glidant, diluents, disintegrants and lubricants. In a subclass of the invention, the first layer comprises from about 50% to 65% by weight of an amorphous dispersion formulation of doravirine, about 24% to 46% by weight of diluents, and about 0.1% to 1% by weight of glidants, about 4% to 8% by weight of disintegrants, about 0.25% to 2% by weight of lubricants.

In an embodiment of the invention, the second layer comprises lamivudine, tenofovir disoproxil fumarate, a glidant, a diluent, a disintegrant, and lubricants. In a class of the invention, the second layer comprises from about 15% to 45% by weight of lamivudine, from about 15% to 45% by weight of tenofovir disoproxil fumarate, and from about 10% to 70% by weight of excipients comprising glidant, diluents, disintegrants and lubricants. In a subclass of the invention, the first layer comprises from about 30% to 40% by weight of lamivudine, from about 30% to 40% by weight of tenofovir disoproxil fumarate, about 0.1% to 2% by weight of glidants, about 6% to 38% by weight of diluents, about 2% to 8% by weight of disintegrants, about 0.25% to 4% by weight of lubricants.

Optionally, the pharmaceutical compositions are film coated. The pharmaceutical compositions of the instant invention may also comprise a polishing aid such as carnauba wax, that among other uses, aids handling of the final product.

The pharmaceutical compositions of the present invention may contain one or more additional formulation ingredients that may be selected from a wide variety of excipients known in the pharmaceutical formulation art. According to the desired properties of the compositions, any number of ingredients may be selected, alone or in combination, based upon their known uses in preparing tablet compositions. Such ingredients include, but are not limited to, diluents, binders, compression aids, disintegrants, lubricants, glidants, stabilizers (such as dessicating amorphous silica), flavors, flavor enhancers, sweeteners, preservatives, colorants and coatings.

In an embodiment of the invention, the glidant, or flow aid, is colloidal silica, silicone dioxide, talc or starch. In a class of the invention, the glidant is colloidal silica.

In an embodiment of the invention, the diluents are selected from the group consisting of lactose, lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate, calcium phosphate dibasic, calcium carbonate and magnesium carbonate. In a class of the embodiment, the diluents are lactose monohydrate and microcrystalline cellulose.

In an embodiment of the invention the disintegrant is croscarmellose sodium, starch, crospovidone, sodium starch glycolate or any mixtures thereof. In a class of the embodiment, the disintegrant is croscarmellose sodium.

In an embodiment of the invention, the lubricant is magnesium stearate, stearic acid or sodium stearyl fumarate. In a class of the embodiment, the lubricants used are magnesium stearate and sodium stearyl fumarate, stearic acid or mixtures thereof.

In an embodiment of the invention, the pharmaceutical composition has a film coat. In a class of the invention, the film coating is an aqueous film coating. In a subclass of the invention, the film coating comprises hydroxypropylmethylcellulose, such as Opadry® II. Opadry® II, which is available from Colorcon, Inc., Harleysville, Pa., contains hydroxypropyl methyl cellulose (also known as "HPMC" or "hypromellose"), titanium dioxide, lactose monohydrate, triacetin and iron oxide yellow.

In an embodiment of the invention, the pharmaceutical composition has a polishing aid. In a class of the invention, the polishing aid is carnauba wax.

In an embodiment of the invention, the first layer comprises a glidant that is colloidal silica; a diluent that is microcrystalline cellulose; a disintegrant that is croscarmellose sodium; and a lubricant that is magnesium stearate.

In an embodiment of the invention, the second layer comprises a glidant that is colloidal silica; a diluent that is microcrystalline cellulose; a disintegrant that is croscarmellose sodium; and lubricants that are magnesium stearate and sodium stearyl fumarate.

The term "tablet" as used herein is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes, whether uncoated or coated. Substances which may be used for coating include hydroxypropylmethylcellulose, hydroxypropylcellulose, titanium dioxide, talc, sweeteners and colorants.

The novel pharmaceutical compositions of the instant invention address the need for incorporation of high doses of doravirine, lamivudine and tenofovir disoproxil fumarate into a compact, single-unit dosage form while still maintaining comparable bioperformance to formulations of individually co-dosed doravirine, lamivudine and tenofovir disoproxil fumarate.

Initial efforts to simply combine the three active ingredients into a homogeneous composition were unsuccessful. At first, the amorphous dispersion formulation of doravirine, lamivudine and tenofovir disoproxil fumarate were roller-compacted as a single granulation and compressed into a monolithic tablet of ≤1.6 grams. However, the tablet disintegration time was very long (more than 30 min), and the in-vitro dissolution was poor. Subsequent attempts were made to prepare separate granulations for the amorphous dispersion of doravirine and for lamivudine and tenofovir disoproxil fumarate and compress the combined granula-

tions into a monolithic tablet of ≤1.6 grams. These attempts also resulted in relatively slow tablet disintegration and slow dissolution of doravirine.

In an effort to improve the in vitro and in vivo performance of the doravirine formulation, a bilayer configuration wherein the dissolution of the doravirine moiety is not impeded by the tenofovir/lamivudine formulations was developed. Historically, a bilayer tablet configuration has been utilized to formulate active agents with physical or chemical incompatabilities resulting in degradation of interactions such as those which slow down dissolution and lower bioperformance. Doravirine is a low solubility compound classified as a class II compound based on the biopharmaceutics classification system. Hence, it is critical that the release of the active from the fixed dose combination mimics the release from the single entity formulation to ensure comparable efficacy. For the soluble actives, tenofovir disoproxil fumarate and lamivudine, co-granulating the two actives results in an eroding layer which is mechanistically different from the single entities which release the drug through layer disintegration. Separating the lamivudine and tenofovir by incorporating lamivudine in the doravirine (first) layer speeds up release of both lamivudine and tenofovir disoproxil fumarate, but considerably slows down doravirine release. Hence, achieving comparable exposure from the fixed dose combination for these actives is challenging, and the configuration in which these three moieties are presented to ensure similar performance to single entities was previously unknown

The tablets of the instant invention incorporate high loading of an amorphous dispersion formulation of doravirine in one layer and high loadings of crystalline formulations of lamivudine and tenofovir disoproxil fumarate in a separate layer. It was not until the discovery of the instant invention that a physically and chemically stable tablet could be obtained that contained all three active ingredients.

Increased complexity is imparted due to the hygroscopicity of the amorphous dispersion of doravirine in one layer owing to the polymer (for example, HPMCAS), and the susceptibility to hydrolytic degradation of the crystalline tenofovir disoproxil fumarate in the other layer. The novel pharmaceutical compositions of the instant invention address the need for adequate physical and chemical stability of the tablets. Stability of the tablet, namely, chemical stability of tenofovir disoproxil fumarate and physical stability of doravirine, was ensured by controlling water ingression into and water activity in the packaging configuration. One such way is through the use of desiccants in closed containers. Another approach to ensure chemical stability of tenofovir is through physical separation between tenofovir disoproxil fumarate and lamivudine, either within the layer or the dosage form. The separation of tenofovir and lamivudine can be done either as separate layers or as separate granulations in the second layer.

In addition, the novel pharmaceutical compositions of the instant invention address the need for process robustness upon scale up. The first layer containing doravirine is susceptible to capping and interfacial crack issues during bilayer compression as well as decapping and assay loss during processing. While interfacial cracking of bilayer tablets due to low interfacial strength or differential swelling at high temperature and relative humidity is well known, bilayer cracking due to deaeration issues of the amorphous dispersion in the first layer was not known. The low bulk density of the amorphous dispersion formulation, designed to address loss on recompaction and ensure acceptable interfacial strength between the two layers, is a key factor. Deaeration based cracking was also not seen for the single entity formulation and is exacerbated for the large bilayer image. In some cases, these cracks may not be initially present on the exterior of the tablet and hence may not be visible to the naked eye but under conditions of stress such as heat and shear in a coating pan, the cracks can propagate towards the exterior and present themselves to the naked eye. A complex interplay of roller compaction pressure, tamp force and tamp positioning optimization during bilayer compression was critical to resolving the bilayer cracking. The second layer of lamivudine and tenofovir disoproxil fumarate is prone to roll sticking during roller compaction due to the high drug loadings and the inherent sticking propensity of tenofovir. The second layer formulation is also prone to extrusion during roller compaction due to the low glass transition temperature of tenofovir. Mitigation of roll sticking and extrusion required optimal selection of lubricant systems and control of process temperature. The second layer formulation is also susceptible to layer edge chipping during film coating, due to the low tensile strength of the second layer. Edge chipping was circumvented through appropriate selection of film coating systems and optimization of coating process parameters.

Co-granulating tenofovir disoproxil fumarate and lamivudine results in an eroding layer which is mechanistically different from the formulations of the single entities, which release each drug through layer disintegration. It was not known if the mechanistically different dissolution behaviors would have an impact on bioperformance. Furthermore, in the combined tablet, it was unknown whether there would be an interaction between lamivudine and tenofovir disoproxil fumarate, which could result in chemical instability of tenofovir disoproxil fumarate.

The instant invention also addresses the chemical instability of tenofovir disoproxil fumarate, which hydrolyses to form a metabolite, tenofovir mono-POC (also known as "tenofovir monoisoproxil"). The tenofovir disoproxil fumarate stability issue is exacerbated under higher temperature and humidity conditions. These higher temperature and humidity conditions can be found in Zone III (hot, dry climate, 30° C./35% RH)/Zone IV (hot, humid climate, 30° C./75% RH) countries, which include countries in South America (Brazil), sub-Saharan Africa, South Asia (India), and Southeast Asia. Some of these geographical regions coincidentally also happen to be areas where the HIV disease is most prevalent thereby making it imperative for the product to be stable in these hot and humid regions.

The pharmaceutical compositions of the instant invention are stable at temperatures up to 25° C. and up to 60% relative humidity for at least 36 months. The pharmaceutical compositions of the instant invention are stable at temperatures up to 30° C. and up to 65% relative humidity for at least 24 months. Optionally, the packaging storage can include the use of desiccants to further enhance the stability at high relative humidity.

The instant invention also addresses the need for fixed dose pharmaceutical compositions containing doravirine, lamivudine and tenofovir disoproxil fumarate. A compact single-unit dosage form with an image size no larger than 1.6 grams was developed, comprising 100 mg of doravirine (equivalent to 500 mg of doravirine spray dried intermediate), 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate. Also, a compact dosage form for two-unit administration (taking two tablets at a time) with an image size no larger than 1.0 grams was developed, comprising 50 mg of doravirine (equivalent to 250 mg of doravirine spray

dried intermediate), 150 mg of lamivudine and 150 mg of tenofovir disoproxil fumarate.

In another embodiment, the second layer can also contain lamivudine and tenofovir disoproxil fumarate which were separately granulated. As can be seen in Example 7, lamivudine and tenofovir disoproxil fumarate were granulated separately by roller compaction. In Example 8, lamivudine and tenofovir disoproxil fumarate were granulated separately by wet granulation. Probe stability data indicated that the separate granulation approaches can improve the stability profile by reducing the rate of tenofovir mono-POC (also called "mono-POC") formation, as shown in Example 9 (accelerated study at 60° C./ambient, 3 weeks).

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope of the invention.

EXAMPLE 1

50 mg Doravirine/150 mg Lamivudine/150 mg Tenofovir Disoproxil Fumarate Bilayer Tablets

Components	Function	Amount [mg]	Percentage in Each Layer
	Layer 1		
		Intra-granular	
Doravirine[1]	Active	50.00	10.0%
Hypromellose acetate succinate - LG (HPMC-ASLG)[1]	Polymer	200.0	40.0%
Acetone[2]	Solvent	—	
Water, Purified[2]	Solvent	—	
Microcrystalline Cellulose	Diluent	107.5	21.5%
Lactose Monohydrate	Diluent	107.5	21.5%
Croscarmellose Sodium	Disintegrant	15.00	3.0%
Colloidal Silica	Glidant	2.50	0.50%
Magnesium Stearate	Lubricant	1.25	0.25%
		Extra-granular	
Croscarmellose Sodium	Disintegrant	15.00	3.0%
Magnesium Stearate	Lubricant	1.25	0.25%
Layer 1 Weight		500.0	100.0%
	Layer 2		
		Intra-granular	
Lamivudine	Active	150.0	30.0%
Tenofovir Disoproxil Fumarate	Active	150.0	30.0%
Microcrystalline Cellulose	Diluent	120.0	24.0%
Lactose Monohydrate	Diluent	55.0	11.0%
Croscarmellose Sodium	Disintegrant	10.00	2.0%
Magnesium Stearate	Lubricant	1.25	0.25%
		Extra-granular	
Croscarmellose Sodium	Disintegrant	10.00	2.0%
Magnesium Stearate	Lubricant	3.75	0.75%
Layer 2 Weight		500.0	100.0%
Core Tablet Weight		1000.0	
Opadry II 39K Film Coat	Film Coat	25.00	
Water, Purified[2]	Solvent	—	
Film-Coated Tablet Weight		1025.0	

[1]Prepared as spray dried intermediate
[2]Removed during processing

Doravirine layer granulation. Doravirine spray dried intermediate (see, PCT International Publication WO2015/077273), microcrystalline cellulose, lactose monohydrate, colloidal silica (sieved thru 30 Mesh with microcrystalline cellulose) and croscarmellose sodium were blended in V-blender at 25 rpm for 10 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 37 bars, 2.0 mm gap, 1.6 mm/0.8 mm CONIDUR screens. Then, croscarmellose sodium was added to V-blender and blended at 25 rpm for 5 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min. LAM/TDF blending and roller compaction. TDF, lamivudine, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium were sieved through 30 Mesh and blended in V-blender at 25 rpm for 10 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 55 bars, 2.0 mm gap, 1.6 mm/0.8 mm CONIDUR screens. Then, croscarmellose sodium was added to V-blender and blended at 25 rpm for 5 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min. Bilayer Compression. Doravirine lubricated granules (layer 1) and LAM/TDF lubricated granules (layer 2) were compressed into bilayer tablets on the Piccola press using the following parameters (oval tooling, 0.708"×0.354", 500 mg layer 1 fill weight, 500 mg layer 2 fill weight, 20 kp hardness, 7.3 mm thickness, 1.7 kN tamping force, 18 kN main compression force, 10 rpm turret speed).

Film Coating. An aqueous suspension of Opadry 39K, 15% by weight, was prepared. The compressed tablets were film-coated in the O'Hara (19" pan) using the following parameters (2.5 kg tablet load, exhaust temp=45° C., air flow=400 ft^3/min, pan speed=10 rpm, spray rate=10 g/min).

EXAMPLE 2

100 mg Doravirine/300 mg Lamivudine/300 mg Tenofovir Disoproxil Fumarate Bilayer Tablets

Components	Function	Amount [mg]	Percentage in Each Layer
	Layer 1		
		Intra-granular	
Doravirine[1]	Active	100.0	12.8%
Hypromellose acetate succinate - LG (HPMC-ASLG)[1]	Polymer	400.0	51.3%
Acetone[2]	Solvent	—	
Water, Purified[2]	Solvent	—	
Microcrystalline Cellulose	Diluent	224.0	28.7%
Croscarmellose Sodium	Disintegrant	24.0	3.1%
Colloidal Silica	Glidant	4.00	0.51%
Magnesium Stearate	Lubricant	2.00	0.26%
		Extra-granular	
Croscarmellose Sodium	Disintegrant	24.00	3.1%
Magnesium Stearate	Lubricant	2.00	0.26%
Layer 1 Weight		780.0	100%

-continued

Components	Function	Amount [mg]	Percentage in Each Layer
	Layer 2		
		Intra-granular	
Lamivudine	Active	300.0	38.5%
Tenofovir Disoproxil Fumarate	Active	300.0	38.5%
Microcrystalline Cellulose	Diluent	103.8	13.3%
Croscarmellose Sodium	Disintegrant	23.4	3.0%
Colloidal Silica	Glidant	7.80	1.0%
Magnesium Stearate	Lubricant	7.80	1.0%
Sodium Stearyl Fumarate	Lubricant	7.80	1.0%
		Extra-granular	
Croscarmellose Sodium	Disintegrant	23.40	3.0%
Magnesium Stearate	Lubricant	6.00	0.77%
Layer 2 Weight		780.0	100%
Core Tablet Weight		1560	
Opadry II 39K Film Coat	Film Coat	39.00	
Water, Purified[2]	Solvent	—	
Carnauba Wax	Polishing Aid	0.05	
Film-Coated Tablet Weight		1599	

[1]Prepared as spray dried intermediate
[2]Removed during processing

Doravirine layer granulation. Doravirine spray dried intermediate, microcrystalline cellulose, colloidal silica (sieved thru 30 Mesh with microcrystalline cellulose) and croscarmellose sodium were blended in 1800-L Bohle bin at 6 rpm for 30 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 6 rpm for 10 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-200 at the following settings: 75 mm knurled roll, 5.6 kN/cm, 2.0 mm gap, 2.0 mm/1.0 mm CONIDUR screens. Then, croscarmellose sodium was added to the Bohle bin and blended at 6 rpm for 30 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 6 rpm for additional 10 min.

LAM/TDF blending and roller compaction. TDF, lamivudine, microcrystalline cellulose, colloidal silica (sieved thru 30 mesh with microcrystalline cellulose), and croscarmellose sodium were blended in 1800-L Bohle bin at 6 rpm for 30 min. Sodium stearyl fumarate and magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 6 rpm for 10 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-200 at the following settings: 75 mm knurled roll, 7.1 kN/cm, 2.0 mm gap, 2.0 mm/1.0 mm wire screens. Then, croscarmellose sodium was added to the Bohle bin and blended at 6 rpm for 30 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 6 rpm for 10 min.

Bilayer Compression. Doravirine lubricated granules (layer 1) and LAM/TDF lubricated granules (layer 2) were compressed into bilayer tablets on the Fette 3090 press (49 stations) using the following parameters (oval tooling, 0.850"×0.445", 780 mg layer 1 fill weight, 780 mg layer 2 fill weight, 23 kp hardness, 7.3 mm thickness, 5 kN tamping force, 37 kN main compression force, 10 rpm turret speed).

Film Coating. An aqueous suspension of Opadry 39K, yellow, 18% by weight, was prepared. The compressed tablets were film-coated in the Vector FC 150L, using the following parameters (88 kg tablet load, exhaust temp=45° C., air flow=1250 m^3/hr, pan speed=4-5 rpm, spray rate=175-200 g/min). Carnauba wax was added to the film-coated tablets at the end.

EXAMPLE 3

100 mg Doravirine/300 mg Lamivudine/300 mg Tenofovir Disoproxil Fumarate Monolithic Tablets

Components	Function	Amount [mg]
	Granulation 1 (695 mg)	
Doravirine[1]	Active	100.0
Hypromellose acetate succinate - LG (HPMC-ASLG)[1]	Polymer	400.0
Acetone[2]	Solvent	—
Water, Purified[2]	Solvent	—
Microcrystalline Cellulose	Diluent	100.0
Lactose Monohydrate	Diluent	50.00
Croscarmellose Sodium	Disintegrant	40.00
Colloidal Silica	Glidant	3.00
Magnesium Stearate	Lubricant	2.00
	Granulation 2 (700 mg)	
Lamivudine	Active	300.0
Tenofovir Disoproxil Fumarate	Active	300.0
Microcrystalline Cellulose	Diluent	50.00
Lactose Monohydrate	Diluent	25.00
Croscarmellose Sodium	Disintegrant	20.00
Magnesium Stearate	Lubricant	5.00
	Extragranular (165 mg)	
Microcrystalline Cellulose	Diluent	100.0
Croscarmellose Sodium	Disintegrant	60.00
Magnesium Stearate	Lubricant	5.00
Core Tablet Weight		1560
Opadry II 39K Film Coat	Film Coat	39.00
Water, Purified[2]	Solvent	—
Film-Coated Tablet Weight		1599

[1]Prepared as spray dried intermediate
[2]Removed during processing

Doravirine blending and roller compaction. Doravirine spray dried intermediate, microcrystalline cellulose, lactose monohydrate, colloidal silica and croscarmellose sodium were sieved through 30 Mesh and blended in V-blender at 25 rpm for 15 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 28 bars, 2.0 mm gap, 1.6 mm/0.8 mm CONIDUR screens.

LAM/TDF blending and roller compaction. TDF, lamivudine, microcrystalline cellulose, lactose monohydrate, and croscarmellose sodium were sieved through 30 Mesh and blended in V-blender at 25 rpm for 15 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 20 bars, 2.0 mm gap, 1.6 mm/0.8 mm CONIDUR screens.

Granulation blending and lubrication. Doravirine roller-compacted granules, LAM/TDF roller-compacted granules, microcrystalline cellulose (thru 30 Mesh), and croscarmellose sodium (thru 30 Mesh) were added to V-blender and

blended at 25 rpm for 5 min. Then, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min.

Compression. The lubricated blends were compressed on the Piccola press using the following parameters (oval tooling, 0.745"×0.383", 1560 mg fill weight, 20 kp hardness, 9.7 mm thickness, 15 kN main compression force, 8 rpm turret speed).

Film Coating. An aqueous suspension of Opadry 39K, 15% by weight, was prepared. The compressed tablets were film-coated in the O'Hara (19" pan) using the following parameters (2.82 kg tablet load, exhaust temp=45° C., air flow=250 ft^3/min, pan speed=8 rpm, spray rate=30 g/min).

EXAMPLE 4

Biocomparabiliy of Bilayer Tablets (50 mg/150 mg/150 mg), Monolithic Tablets (100 mg/300 mg/300 mg) and Co-Dosings

A biocomparability study was conducted to evaluate the relative bioavailability of the triple combinations of doravirine, lamivudine, and tenofovir disoproxil fumarate (two 50-mg bilayer tablets and a 100-mg monolithic tablet) compared to the bioavailability of doravirine, lamivudine, and tenofovir disoproxil fumarate co-administered as individual tablets (reference). The 50-mg bilayer formulation contained 50 mg doravirine, 150 mg lamivudine, and 150 mg tenofovir disoproxil fumarate, while the 100-mg monolithic formulation contained 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate. The data are summarized in the table below.

Doravirine				
PK	2 × 50/150/150 Bilayer[a]		1 × 100/300/300 Monolithic[b]	
Parameter	GMR[c]	90% CI	GMR	90% CI
AUC0-∞	1.00	0.931-1.08	0.858	0.800-0.919
Cmax	0.977	0.893-1.07	0.713	0.652-0.781
C24 hr	1.02	0.926-1.12	0.871	0.817-0.929
PK	2 × 50/150/150 Bilayer		1 × 100/300/300 Monolithic	
Parameter	GMR	90% CI	GMR	90% CI
Lamivudine				
AUC0-∞	1.02	0.975-1.07	1.09	1.05-1.12
Cmax	0.926	0.859-0.999	1.08	1.02-1.15
TDF				
AUC0-∞	0.994	0.946-1.04	0.975	0.923-1.03
Cmax	0.912	0.808-1.03	0.868	0.786-0.959

References: individual tablets of doravirine (100 mg), lamivudine (300 mg), TDF (300 mg)
[a]Bilayer Formulation: 2 tablets of 50 mg doravirine/150 mg lamivudine/150 mg TDF
[b]Monolithic Formulation: 1 tablet of 100 mg doravirine/300 mg lamivudine/300 mg TDF
[c]Geometric Mean Ratio

The relative bioavailability of doravirine after administration of either the bilayer or monolithic formulation was comparable to the reference. The geometric mean ratios (GMR) of $AUC_{0-\infty}$, C_{max} and $C_{24\ hr}$ of doravirine were 1.00, 0.977, and 1.02, respectively, for the bilayer tablet, indicating that bioavailability was the same as the reference. Slight decreases of 14%, 29%, and 13% were noted in $AUC_{0-\infty}$, C_{max} and $C_{24\ hr}$ of doravirine, respectively, after administration of the monolithic tablet compared to the reference with GMRs of 0.858, 0.713, and 0.871, respectively. Doravirine was absorbed with a median t_{max} of 3 hr for the bilayer tablet and 4 hr for the monolithic tablet, comparable to the t_{max} of the reference (3 hr). The elimination $t_{1/2}$ of doravirine (~17-19 hr) was similar after all three treatments.

The relative bioavailability of lamivudine was similar to the reference with GMRs of $AUC_{0-\infty}$ and C_{max} of 1.02 and 0.926, respectively, for the bilayer tablet, and the corresponding values for the monolithic tablet were 1.09 and 1.08, respectively. Following administration as a monolithic or bilayer tablet, elimination $t_{1/2}$ of lamivudine was not altered compared to the reference (12.5 hr, and 12.6 hr respectively, compared to 11.6 hr). Lamivudine t_{max} was 2 hr for bilayer tablet and 1 hr for the monolithic tablet, similar to the t_{max} of the reference (1 hr).

The relative bioavailability of tenofovir disoproxil fumarate when administered in both the bilayer and monolithic formulations was comparable to the reference. The geometric mean ratios of $AUC_{0-\infty}$ and C_{max} of tenofovir disoproxil fumarate were 0.994 and 0.912, respectively, for the bilayer tablet, similar to the reference, while the values for the monolithic tablet were 0.975 and 0.868, respectively. A slight decrease (~13%) of the geometric mean C_{max} was observed for the monolithic tablet vs. the reference.

The median t_{max} for tenofovir disoproxil fumarate was 1 hr for both the bilayer and monolithic tablets, and was similar to the t_{max} of the reference (1 hr). The elimination $t_{1/2}$ of tenofovir disoproxil fumarate was similar after administration of the bilayer tablet (18.0 hr), or monolithic tablet (17.8 hr) or as a co-administered tablet with lamivudine and tenofovir disoproxil fumarate tablets (18.1 hr).

EXAMPLE 5

Biocomparabiliy of Bilayer Tablets (100 mg/300 mg/300 mg) and Co-Dosings

A biocomparability study was conducted to evaluate the comparative bioavailability of a bilayer fixed-dose combination ("FDC") tablet comprised of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate (TDF) to the bioavailability of co-administration of:

- Doravirine 100 mg oral tablet from Merck Sharp & Dohme Corp., USA
- Epivir® (lamivudine) 300 mg tablets from ViiV Healthcare UK Limited, United Kingdom and
- Viread® (tenofovir disoproxil fumarate) 245 mg tablets from Gilead Sciences International Limited, United Kingdom

The FDC is a film-coated, bilayer tablet with doravirine in one layer and lamivudine and TDF in the other layer, as described herein.

1 × 100/300/300 Bilayer[a] vs Co-Dosings[b]		
Doravirine		
PK Parameter	GMR[c]	90% CI
$AUC_{0-\infty}$	1.01	0.94-1.08
AUC_{0-last}	1.02	0.95-1.09
C_{max}	0.99	0.91-1.09
$C_{24\ hr}$	1.02	0.94-1.12
PK Parameter	GMR	90% CI
Lamivudine		
AUC0-∞	1.04	1.00-1.09
AUC_{0-last}	1.04	1.00-1.08
C_{max}	1.00	0.91-1.09

-continued

1 × 100/300/300 Bilayer[a] vs Co-Dosings[b]		
TDF		
$AUC_{0-\infty}$	0.98	0.93-1.03
AUC_{0-last}	0.99	0.94-1.04
C_{max}	0.87	0.78-0.97

[a]Bilayer Formulation: 1 tablet of 100 mg doravirine/300 mg lamivudine/300 mg TDF
[b]Reference: individual tablets of DORAVIRINE (100 mg), Epivir ® (300 mg), Viread ® (245 mg)
[c]Geometric Mean Ratio

As shown above, the pharmacokinetics of doravirine, lamivudine, and tenofovir disoproxil fumarate were generally similar when administered as a bilayer fixed-dose combination or the individual components. While tenofovir disoproxil fumarate C_{max} was slightly decreased after administration of the bilayer fixed-dose combination tablet, compared to administration as Viread®, this decrease is not expected to be clinically meaningful.

EXAMPLE 6

Chemical Stability Data for Bilayer Tablets (100 mg/300 mg/300 mg)

The re-evaluation date ("RED") for the FDC (100 mg doravirine/300 mg tenofovir disoproxil fumarate/300 mg lamuvidine) film-coated bilayer tablet is 24 months (worldwide) stored at 2 to 25° C., based on 12-month probe stability data generated at 30° C./65% RH. The tablets were packaged in 120-mL high-density polyethylene ("HDPE") bottles with induction-sealed caps and 4 g or more of desiccant. Alternative packaging configurations, such as 90 mL or 100 mL HDPE bottles with at least 3 g or 4 g of desiccant, respectively, could be used. The alternative packaging configurations should provide similar, if not better humidity control compared to the primary package. The RED is the currently assigned shelf-life, based on the available data at the time, and can be extended with additional stability data from later timepoints. Hence, the eventual or achievable commercial shelf life can be and is expected to be longer than the mentioned RED. The tables below provide analysis of the assay and degradates for each of DORAVIRINE, lamivudine and TDF, after storage at various temperature/RH conditions at various time points. The mono-POC degradate in TDF is the key degradate which governs the shelf-life. The specification for mono-POC in the fixed-dose combination tablet is 3.5% wt.

Assay/Degradates for Film-Coated Bilaver Tablet ("FCT") 100 mg/300 mg/300 mg: Doravirine

Storage Condition	Timepoints (months)	Assay (% claim)	1.28RRT (% claim)
5° C./amb RH closed	1	97.99	0.03
25° C./60% RH closed	1	96.39	0.04
30° C./65% RH closed	1	95.20	0.05
40° C./75% RH closed	1	97.36	0.07
25° C./60% RH closed	2	98.22	0.05
30° C./65% RH closed	2	98.82	0.06
40° C./75% RH closed	2	97.92	0.09
25° C./60% RH closed	5	96.73	0.07
30° C./65% RH closed	5	96.98	0.09
40° C./75% RH closed	5	97.79	0.10
25° C./60% RH closed	8	96.34	0.07
30° C./65% RH closed	8	96.33	0.09
30° C./65% RH closed	12	98.32	0.10

Assay/Degradates for Film-Coated Bilayer Tablet 100 mg/300 mg/300 mg FCT: Lamivudine

Storage Condition	Timepoints (months)	Assay (% claim)	0.39RRT (% claim)
5° C./amb RH closed	1	100.06	ND
25° C./60% RH closed	1	100.86	ND
30° C./65% RH closed	1	101.03	ND
40° C./75% RH closed	1	100.51	ND
25° C./60% RH closed	2	100.15	ND
30° C./65% RH closed	2	99.88	ND
40° C./75% RH closed	2	100.49	ND
25° C./60% RH closed	5	99.67	ND
30° C./65% RH closed	5	100.7	ND
40° C./75% RH closed	5	99.33	0.07
25° C./60% RH closed	8	100.94	ND
30° C./65% RH closed	8	98.87	ND
30° C./65% RH closed	12	99.67	ND

Assay/Degradates for Film-Coated Bilaver Tablet 100 mg/300 mg/300 mg FCT: TDF

Storage	Timespoints	Assay	Degradates (% claim)				
Condition	(months)	(% claim)	0.53RRT	0.59RRT	0.62RRT	0.66RRT	0.69RRT
5° C./amb RH	1	102.12	0.58	ND	ND	ND	ND
25° C./60% R	1	100.88	0.62	0.01	ND	ND	ND
30° C./65% R	1	101.40	0.66	0.02	ND	ND	ND
40° C./75% R	1	101.01	0.85	0.09	ND	ND	ND
25° C./60% R	2	103.28	0.68	0.01	ND	ND	ND
30° C./65% R	2	102.13	0.75	0.03	ND	ND	ND
40° C./75% R	2	101.69	1.06	0.13	0.04	ND	ND
25° C./60% R	5	100.29	0.77	0.04	ND	ND	ND
30° C./65% R	5	101.13	0.92	0.07	ND	ND	ND
40° C./75% R	5	100.54	1.53	0.22	0.15	0.09	0.08
25° C./60% R	8	101.78	0.84	0.05	0.04	ND	ND
30° C./65% R	8	98.83	1.01	0.09	0.05	0.04	0.04
30° C./65% R	12	100.49	1.20	0.10	0.05	0.05	0.06

(*) mono-POC is expressed as % LC by weight relative to TDF
ND: Not detected
RH: Relative Humidity
RRT: Relative Retention Time (compared to the parent drug in a column)

EXAMPLE 7

100 mg Doravirine/300 mg Lamivudine/300 mg Tenofovir Disoproxil Fumarate Bilayer Tablets

Components	Function	Amount [mg]	Percentage in Each Layer
	Layer 1		
		Intra-granular	
Doravirine[1]	Active	100.0	12.8%
Hypromellose acetate succinate - LG (HPMC-ASLG)[1]	Polymer	400.0	51.3%
Acetone[2]	Solvent	—	
Water, Purified[2]	Solvent	—	
Microcrystalline Cellulose	Diluent	224.0	28.7%
Croscarmellose Sodium	Disintegrant	24.0	3.1%
Colloidal Silica	Glidant	4.00	0.51%
Magnesium Stearate	Lubricant	2.00	0.26%
		Extra-granular	
Croscarmellose Sodium	Disintegrant	24.00	3.1%
Magnesium Stearate	Lubricant	2.00	0.26%
Layer 1 Weight		780	100%
	Layer 2		
		Intra-granular	
Tenofovir Disoproxil Fumarate	Active	300.0	38.5%
Microcrystalline Cellulose	Diluent	51.93	6.7%
Croscarmellose Sodium	Disintegrant	11.70	1.5%
Colloidal Silica	Glidant	3.12	0.40%
Sodium Stearyl Fumarate	Lubricant	4.50	0.58%
Magnesium Stearate	Lubricant	4.50	0.58%
Lamivudine	Active	300.0	38.5%
Microcrystalline Cellulose	Diluent	55.68	7.1%
Croscarmellose Sodium	Disintegrant	11.70	1.5%
Colloidal Silica	Glidant	3.12	0.40%
Sodium Stearyl Fumarate	Lubricant	2.25	0.29%
Magnesium Stearate	Lubricant	2.25	0.29%
		Extra-granular	
Croscarmellose Sodium	Disintegrant	23.40	3.0%
Magnesium Stearate	Lubricant	6.00	0.77%
Layer 2 Weight		780	100%
Core Tablet Weight		1560	
Opadry II 39K Film Coat	Film Coat	39.00	
Water, Purified[2]	Solvent	—	
Film-Coated Tablet Weight		1599	

[1]Prepared as spray dried intermediate
[2]Removed during processing

Doravirine layer granulation. Doravirine spray dried intermediate, microcrystalline cellulose, colloidal silica (sieved thru 34 T Mesh with microcrystalline cellulose) and croscarmellose sodium were blended in 40 L Bohle bin at 25 rpm for 10 min. Magnesium stearate was sieved through 74 T Mesh and added to the blender, which was blended at 25 rpm for 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 33 bars, 2.0 mm gap, 2.0 mm/1.0 mm wire mesh screens. Then, croscarmellose sodium was added to Bohle bin and blended at 25 rpm for 10 min. Finally, magnesium stearate was sieved through 74 T Mesh and added to the blender, which was blended at 25 rpm for additional 5 min.

LAM/TDF layer blend. (i) LAM Blending and Roller Compaction. Lamivudine (sieved thru 22 T Mesh), microcrystalline cellulose, colloidal silica (sieved thru 34 T Mesh with microcrystalline cellulose) and croscarmellose sodium were blended in 40 L Bohle bin at 25 rpm for 10 min. Sodium stearyl fumarate and magnesium stearate was sieved through 74 T Mesh and added to the blender, which was blended at 25 rpm for 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 36 bars, 2.0 mm gap, 2.0 mm/1.0 mm wire screens. (ii) TDF blending and roller compaction. TDF, microcrystalline cellulose, colloidal silica (sieved thru 34 T mesh with microcrystalline cellulose), croscarmellose sodium were blended in 40 L Bohle bin at 25 rpm for 10 min. Sodium stearyl fumarate and magnesium stearate was sieved through 74 T Mesh and added to the blender, which was blended at 25 rpm for 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 22 bars, 2.0 mm gap, 2.0 mm/1.0 mm wire screens. (iii) LAM and TDF granulations blending and lubrication. LAM granulation, TDF granulation and croscarmellose sodium were added to a Bohle bin and blended at 25 rpm for 10 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for 5 min.

Bilayer Compression. Doravirine lubricated granules (layer 1) and LAM/TDF lubricated granules (layer 2) were compressed into bilayer tablets on the Fette 3090 press (14 stations) using the following parameters (oval tooling, 0.850"×0.445", 780 mg layer 1 fill weight, 780 mg layer 2 fill weight, 24 kp hardness, 5 kN tamping force, 35 kN main compression force, 10 rpm turret speed).

Film Coating. An aqueous suspension of Opadry 39K, yellow, 18% by weight, was prepared. The compressed tablets were film-coated in the Vector LCDS 2.5 L, using the following parameters (1.5 kg tablet load, exhaust temp=40° C., air flow=40 cfm, pan speed=12 rpm, spray rate=7.0 g/min).

EXAMPLE 8

100 mg Doravirine/300 mg Lamivudine/300 mg Tenofovir Disoproxil Fumarate Bilayer Tablets

Components	Function	Amount [mg]	Percentage in Each Layer
	Layer 1		
		Intra-granular	
Doravirine[1]	Active	100.0	12.8%
Hypromellose acetate succinate - LG (HPMC-ASLG)[1]	Polymer	400.0	51.3%
Acetone[2]	Solvent	—	
Water, Purified[2]	Solvent	—	
Microcrystalline Cellulose	Diluent	224.0	28.7%
Croscarmellose Sodium	Disintegrant	24.0	3.1%
Colloidal Silica	Glidant	4.00	0.51%
Magnesium Stearate	Lubricant	2.00	0.26%
		Extra-granular	
Croscarmellose Sodium	Disintegrant	24.00	3.1%
Magnesium Stearate	Lubricant	2.00	0.26%
Layer 1 Weight		780	100%

-continued

Components	Function	Amount [mg]	Percentage in Each Layer
	Layer 2		
		Intra-granular	
Tenofovir Disoproxil Fumarate	Active	300.0	43.80
Croscarmellose Sodium	Disintegrant	13.19	1.93%
Hydroxypropylcellulose - EXF	Binder	16.49	2.41%
Lamivudine	Active	300.0	43.80%
Croscarmellose Sodium	Disintegrant	13.19	1.93%
Hydroxypropylcellulose - EXF	Binder	16.49	2.41%
		Extra-granular	
Croscarmellose Sodium	Disintegrant	20.80	3.0%
Magnesium Stearate	Lubricant	4.80	0.70%
Layer 2 Weight		685	100%
Core Tablet Weight		1465	
Opadry II 39K Film Coat	Film Coat	36.6	
Water, Purified[2]	Solvent	—	
Film-Coated Tablet Weight		1501.6	

[1]Prepared as spray dried intermediate
[2]Removed during processing

Doravirine layer granulation. Doravirine spray dried intermediate, microcrystalline cellulose, colloidal silica (sieved thru 30 Mesh with microcrystalline cellulose), croscarmellose sodium were blended in 40 L Bohle bin at 25 rpm for 10 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 34 bars, 2.0 mm gap, 2.0 mm/1.0 mm wire mesh screens. Then, croscarmellose sodium was added to the Bohle bin and blended at 25 rpm for 10 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min.

LAM/TDF layer blend. (i) LAM wet granulation. Lamivudine, croscarmellose sodium and hydropropyl cellulose were charged into a 10 L FIELDER blender (1.8 kg total) and blended for 1 min at impeller speed of 300 rpm. Then, the blend was wet-granulated with water as a granulation solution at the following settings: 300 rpm impeller speed, 1800 rpm chopper speed, 66 g/min solution delivery for 10 min. The wet granules were tray-dried at 35° C. The dried granules were milled using a Co-Mil with 40G screen at 1500 rpm. (ii) TDF wet granulation. TDF, croscarmellose sodium and hydropropyl cellulose were charged into 10 L Fielder (2 kg total) and blended for 1 min at impeller speed of 300 rpm. Then, the blend was wet-granulated with water as a granulation solution at the following settings: 300 rpm impeller speed, 1800 rpm chopper speed, 100 g/min solution delivery for 10 min. The wet granules were tray-dried at 35° C. The dried granules were milled using a Co-Mil with 40G screen at 1500 rpm. (iii) LAM and TDF granulations blending and lubrication. LAM granulation, TDF granulation, and croscarmellose sodium were added to a Bohle bin and blended at 25 rpm for 10 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for 5 min.

Bilayer Compression. Doravirine lubricated granules (layer 1) and LAM/TDF lubricated granules (layer 2) were compressed into bilayer tablets on the Fette 3090 press (7 stations) using the following parameters (oval tooling, 0.850"×0.445", 780 mg layer 1 fill weight, 685 mg layer 2 fill weight, 26 kp hardness, 5 kN tamping force, 25 kN main compression force, 10 rpm turret speed).

Film Coating. An aqueous suspension of Opadry 39K, yellow, 18% by weight, was prepared. The compressed tablets were film-coated in the Vector LCDS 2.5 L, using the following parameters (1.5 kg tablet load, exhaust temp=40° C., air flow=40 cfm, pan speed=12 rpm, spray rate=6.5 g/min).

EXAMPLE 9

Chemical Stability Data for Bilayer Tablets (100 mg/300 mg/300 mg)

	0.53RRT mono-POC (% area)		mono-POC Growth
Formulation Example	5° C.	60° C.	(% area) over 3 weeks
EXAMPLE 2	0.71	3.47	2.76
EXAMPLE 7	0.69	2.31	1.62
EXAMPLE 8	0.65	1.67	1.02

The stability of different configurations of bilayer tablets in relation to tenofovir mono-POC formation is shown above. The different configurations are described in Examples 2, 7 and 8 wherein the doravirine layer is similar but the TDF/lamivudine consisting second layer is either co-granulated or separately granulated via dry or wet granulation techniques. The stability when TDF and lamivudine are spatially separated is improved relative to that when TDF and lamivudine are co-granulated.

What is claimed is:

1. A pharmaceutical composition, which is a bilayer tablet, comprising an amorphous dispersion formulation of doravirine in the first layer, and lamivudine and tenofovir disoproxil fumarate in the second layer.

2. The pharmaceutical composition of claim **1** wherein the amorphous dispersion formulation of doravirine comprises doravirine and a polymer.

3. The pharmaceutical composition of claim **2** wherein the polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxpropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, polyvinylpyrrolidinone and polyvinylpyrrolidinone-polyvinylacetate copolymers.

4. The pharmaceutical composition of claim **3** wherein the polymer is hydroxypropyl methyl cellulose acetate succinate.

5. The pharmaceutical composition of claim **1** wherein the first layer comprises an amorphous dispersion formulation of doravirine, a glidant, a diluent, a disintegrant, and a lubricant.

6. The pharmaceutical composition of claim **5** wherein the first layer comprises a glidant that is selected from the group consisting of colloidal silica, silicone dioxide, talc and starch; a diluent that is selected from the group consisting of lactose, lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate dibasic, calcium carbonate and magnesium carbonate; a disintegrant that is selected from the group consisting of croscarmellose

sodium, starch, crospovidone, and sodium starch glycolate; and a lubricant that is selected from the group consisting of magnesium stearate, stearic acid or sodium stearyl fumarate.

7. The pharmaceutical composition of claim **6** wherein the first layer comprises a glidant that is colloidal silica; a diluent that is microcrystalline cellulose; a disintegrant that is croscarmellose sodium; and a lubricant that is magnesium stearate.

8. The pharmaceutical composition of claim **1** wherein the second layer comprises lamivudine, tenofovir disoproxil fumarate, a glidant, a diluent, a disintegrant, and lubricants.

9. The pharmaceutical composition of claim **8** wherein the second layer comprises a glidant that is selected from the group consisting of colloidal silica, silicone dioxide, talc and starch; a diluent that is selected from the group consisting of lactose, lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate dibasic, calcium carbonate and magnesium carbonate; a disintegrant that is selected from the group consisting of croscarmellose sodium, starch, crospovidone, and sodium starch glycolate; lubricants that are selected from the group consisting of magnesium stearate, stearic acid and sodium stearyl fumarate.

10. The pharmaceutical composition of claim **9** wherein the second layer comprises a glidant that is colloidal silica; a diluent that is microcrystalline cellulose; a disintegrant that is croscarmellose sodium; and lubricants that are magnesium stearate and sodium stearyl fumarate.

11. The pharmaceutical composition of claim **1** wherein lamivudine and tenofovir disoproxil fumarate are co-granulated.

12. The pharmaceutical composition of claim **1** wherein lamivudine and tenofovir disoproxil fumarate are separately granulated.

13. The pharmaceutical composition of claim **1** comprising a film coat.

14. The pharmaceutical composition of claim **1** comprising a polishing aid.

15. The pharmaceutical composition of claim **1** comprising 50 mg of doravirine, 150 mg of lamivudine and 150 mg of tenofovir disoproxil fumarate.

16. The pharmaceutical composition of claim **1** comprising 100 mg of doravirine, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate.

17. The pharmaceutical composition of claim **1** comprising:

Components	Amount [mg]
Layer 1	
Intragranular	
Doravirine	50.00
Hypromellose acetate succinate - LG (HPMC-ASLG)	200.0
Microcrystalline Cellulose	107.5
Lactose Monohydrate	107.5
Croscarmellose Sodium	15.00
Colloidal Silica	2.50
Magnesium Stearate	1.25
Extragranular	
Croscarmellose Sodium	15.00
Magnesium Stearate	1.25
Layer 1 Weight	500.0
Layer 2	
Intragranular	
Lamivudine	150.0
Tenofovir Disoproxil Fumarate	150.0
Microcrystalline Cellulose	120.0
Lactose Monohydrate	55.0
Croscarmellose Sodium	10.00
Magnesium Stearate	1.25
Extragranular	
Croscarmellose Sodium	10.00
Magnesium Stearate	3.75
Layer 2 Weight	500.0
Core Tablet Weight	1000.0
Opadry II 39K Film Coat	25.00
Film-Coated Tablet Weight	1025.0.

18. The pharmaceutical composition of claim **1** comprising:

Components	Amount [mg]
Layer 1	
Intragranular	
Doravirine	100.0
Hypromellose acetate succinate - LG (HPMC-ASLG)	400.0
Microcrystalline Cellulose	224.0
Croscarmellose Sodium	24.0
Colloidal Silica	4.00
Magnesium Stearate	2.00
Extragranular	
Croscarmellose Sodium	24.00
Magnesium Stearate	2.00
Layer 1 Weight	780.0
Layer 2	
Intragranular	
Lamivudine	300.0
Tenofovir Disoproxil Fumarate	300.0
Microcrystalline Cellulose	103.8
Croscarmellose Sodium	23.4
Colloidal Silica	7.80
Magnesium Stearate	7.80
Sodium Stearyl Fumarate	7.80
Extragranular	
Croscarmellose Sodium	23.40
Magnesium Stearate	6.00
Layer 2 Weight	780.0
Core Tablet Weight	1560
Opadry II 39K Film Coat	39.00
Carnauba Wax	0.05
Film-Coated Tablet Weight	1599.

19. The pharmaceutical composition of claim **1** comprising:

Components	Amount [mg]
Layer 1	
Intragranular	
Doravirine	100.0
Hypromellose acetate succinate - LG (HPMC-ASLG)	400.0
Microcrystalline Cellulose	224.0
Croscarmellose Sodium	24.0
Colloidal Silica	4.00
Magnesium Stearate	2.00
Extragranular	
Croscarmellose Sodium	24.00
Magnesium Stearate	2.00
Layer 1 Weight	780
Layer 2	
Intragranular	
Tenofovir Disoproxil Fumarate	300.0
Microcrystalline Cellulose	51.93
Croscarmellose Sodium	11.70
Colloidal Silica	3.12

-continued

Components	Amount [mg]
Sodium Stearyl Fumarate	4.50
Magnesium Stearate	4.50
Intragranular	
Lamivudine	300.0
Microcrystalline Cellulose	55.68
Croscarmellose Sodium	11.70
Colloidal Silica	3.12
Sodium Stearyl Fumarate	2.25
Magnesium Stearate	2.25
Extragranular	
Croscarmellose Sodium	23.40
Magnesium Stearate	6.00
Layer 2 Weight	780
Core Tablet Weight	1560
Opadry II 39K Film Coat	39.00
Film-Coated Tablet Weight	1599.

* * * * *

EXHIBIT B

US010842751B2

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

(10) **Patent No.: US 10,842,751 B2**
(45) **Date of Patent: *Nov. 24, 2020**

(54) **PHARMACEUTICAL COMPOSITIONS CONTAINING DORAVIRINE, TENOFOVIR DISOPROXIL FUMARATE AND LAMIVUDINE**

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(*) 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.

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(22) Filed: **Feb. 14, 2020**

(65) **Prior Publication Data**

US 2020/0179291 A1 Jun. 11, 2020

Related U.S. Application Data

(63) Continuation of application No. 15/780,142, filed as application No. PCT/US2016/063894 on Nov. 29, 2016, now Pat. No. 10,603,282.

(60) Provisional application No. 62/261,953, filed on Dec. 2, 2015.

(51) **Int. Cl.**

A61K 9/24	(2006.01)
A61K 9/20	(2006.01)
A61K 31/4439	(2006.01)
A61K 31/675	(2006.01)
A61K 31/7068	(2006.01)
A61K 31/513	(2006.01)
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A61K 9/14	(2006.01)
A61K 31/683	(2006.01)
A61K 9/16	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/209*** (2013.01); ***A61K 9/146*** (2013.01); ***A61K 9/2013*** (2013.01); ***A61K 9/2018*** (2013.01); ***A61K 9/2054*** (2013.01); ***A61K 31/4412*** (2013.01); ***A61K 31/4439*** (2013.01); ***A61K 31/513*** (2013.01); ***A61K 31/675*** (2013.01); ***A61K 31/683*** (2013.01); ***A61K 31/7068*** (2013.01); *A61K 9/1652* (2013.01)

(58) **Field of Classification Search**

CPC A61K 9/209

See application file for complete search history.

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Primary Examiner — Brian J Davis

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(57) **ABSTRACT**

The instant invention relates to pharmaceutical compositions comprising doravirine, tenofovir disoproxil fumarate and lamivudine. These compositions are useful for the treatment of HIV infection. Also disclosed are processes for making said pharmaceutical compositions.

11 Claims, No Drawings

PHARMACEUTICAL COMPOSITIONS CONTAINING DORAVIRINE, TENOFOVIR DISOPROXIL FUMARATE AND LAMIVUDINE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. Ser. No. 15/780,142, filed May 30, 2018, which is a national stage application under 35 U.S.C. 371 of International Patent Application No. PCT/US2016/063894, filed Nov. 29, 2016, which claims priority to U.S. Provisional Application No. 62/261,953, filed Dec. 2, 2015. Each of the aforementioned US, PCT and priority applications is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions comprising doravirine, tenofovir disoproxil fumarate and lamivudine. These compositions are useful for the treatment of human immunodeficiency virus (HIV) infection.

Specifically, this invention relates to single tablet fixed-dose combinations of doravirine, lamivudine and tenofovir disoproxil fumarate. A fixed-dose combination is desired and useful for the treatment of HIV infection from both compliance and convenience standpoints.

The novel pharmaceutical compositions of the instant invention address the need for incorporation of high doses of doravirine, lamivudine and tenofovir disoproxil fumarate into a compact, single-unit dosage form while still maintaining comparable bioperformance to those of co-dosed doravirine, lamivudine and tenofovir disoproxil fumarate single entity formulations.

SUMMARY OF THE INVENTION

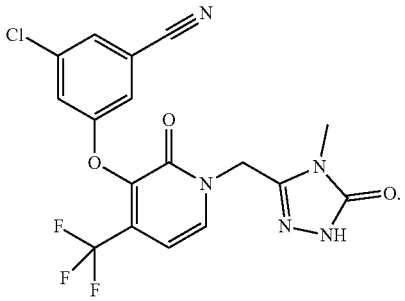
The instant invention relates to pharmaceutical compositions comprising doravirine, tenofovir disoproxil fumarate and lamivudine. These compositions are useful for the treatment of HIV infection. Also disclosed are processes for making said pharmaceutical compositions.

DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutical compositions of the present invention are useful in the treatment of HIV infection. The novel pharmaceutical compositions of the instant invention address the need for incorporation of high doses of doravirine, lamivudine and tenofovir disoproxil fumarate into a compact, single-unit dosage form while still maintaining comparable bioperformance to co-dosed single entities of doravirine, lamivudine and tenofovir disoproxil fumarate.

An embodiment of the instant invention comprises a bilayer tablet that incorporates high loading of an amorphous dispersion formulation of doravirine in one layer and high loadings of crystalline formulations of lamivudine and tenofovir disoproxil fumarate in a separate layer. The resulting bilayer tablets are compact, single-unit dosage forms that have bioperformance comparable to those of individually co-dosed doravirine, lamivudine and tenofovir disoproxil fumarate.

Doravirine is an HIV reverse transcriptase (RT) inhibitor having the chemical name 3-chloro-5-({1-[(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl}oxy)benzonitrile and the following chemical structure:



Production and the ability of doravirine to inhibit HIV reverse transcriptase is illustrated in WO 2011/120133 A1, published on Oct. 6, 2011, and U.S. Pat. No. 8,486,975, granted Jul. 16, 2013, both of which are hereby incorporated by reference in their entirety.

Tenofovir disoproxil fumarate (which can be abbreviated as "TDF") is an antiretroviral medication used to prevent and treat HIV/AIDS. It is of the nucleoside analog reverse transcriptase inhibitor (NRTI) class and is marketed under the tradename VIREAD®. TDF is disclosed in U.S. Pat. No. 5,922,695.

Lamivudine (2',3'-dideoxy-3'-thiacytidine, commonly called 3TC) is an antiretroviral medication used to prevent and treat HIV/AIDS. It is of the nucleoside analog reverse transcriptase inhibitor (NRTI) class and is marketed under the tradename EPIVIR®. Lamivudine is also abbreviated as "LAM." Lamivudine and method of treating HIV using lamivudine are disclosed in U.S. Pat. No. 5,047,407.

Doravirine is known to exist in three crystalline anhydrous forms, designated as Form I, Form II and Form III, and in an amorphous form. An amorphous dispersion formulation of doravirine can be made by spray-drying doravirine with a polymer, such as hydroxypropyl methyl cellulose acetate succinate (HPMCAS, also known as "hypromellose acetate succinate"), hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, polyvinylpyrrolidinone or polyvinylpyrrolidinone-polyvinylacetate copolymers. In a class of the invention, the amorphous dispersion formulation of doravirine is made by spray-drying doravirine with hydroxypropyl methyl cellulose acetate succinate (HPMCAS-L), which significantly improves the bioavailability of doravirine.

However, the resulting amorphous dispersion formulation of doravirine poses many unique challenges, including physical stability, since doravirine is a strong crystallizer. Doravirine was found to crystallize readily in the absence of a polymer and to have a high melting point of 286° C. (see, PCT International Publication WO 2015/077273, which is hereby incorporated by reference in its entirety). Neat amorphous doravirine generated by spray-drying crystallizes within 2 weeks when stored in an open container at 5° C./ambient relative humidity (RH), 30° C./65% RH, 40° C./75% RH, and 60° C./ambient RH. For spray-dried dispersions of doravirine and HPMCAS, crystallization was observed at 35% drug loading after 16 weeks of storage and at 40% drug loading after 8 weeks of storage at 40° C./75%

RH (open). Other factors can affect physical stability, including inherent tendency of the drug to crystallize, drug loading in the dispersion, type of polymers used, hygroscopicity of the formulation and other factors.

In addition to challenges associated with physical stability, dissolution of the amorphous dispersion of doravirine is a concern due to a kinetic supersaturation effect. The composition comprising the amorphous dispersion of doravirine (doravirine and a polymer) provides a higher maximum aqueous concentration of doravirine relative to a control composition having the same concentration of doravirine but without the polymer. This supersaturation effect is transient and relies on rapid dissolution of the drug from the tablet.

Furthermore, there are processing issues due to atypical compaction properties associated with the amorphous dispersion of doravirine. The compactability of doravirine spray dried dispersion is directly correlated to the bulk density of the dispersion. Higher bulk density leads to lower tensile strength tablets. Also, recompactability of the spray dried dispersion formulations, post roller compaction is also a concern. A relatively high roller compaction force results in lower final compactability. In certain cases, tablets of formulations containing doravirine spray dried dispersions with high bulk density show failure upon compression, due to low tensile strength (see, PCT International Publication WO2015/077273).

What is needed is a formulation that can consistently deliver high doses of doravirine without encountering the observed issues related to physical stability, kinetic supersaturation effect and processing.

The pharmaceutical compositions of the present invention, which are bilayer tablets, comprise an amorphous dispersion formulation of doravirine in the first layer, and lamivudine and tenofovir disoproxil fumarate in the second layer.

In an embodiment of the invention, the first layer comprises an amorphous dispersion formulation of doravirine, a glidant, a diluent, a disintegrant and lubricants. In a class of the invention, the first layer comprises from about 25% to 75% by weight of an amorphous dispersion formulation of doravirine, and from about 25% to 75% by weight of excipients comprising glidant, diluents, disintegrants and lubricants. In a subclass of the invention, the first layer comprises from about 50% to 65% by weight of an amorphous dispersion formulation of doravirine, about 24% to 46% by weight of diluents, and about 0.1% to 1% by weight of glidants, about 4% to 8% by weight of disintegrants, about 0.25% to 2% by weight of lubricants.

In an embodiment of the invention, the second layer comprises lamivudine, tenofovir disoproxil fumarate, a glidant, a diluent, a disintegrant, and lubricants. In a class of the invention, the second layer comprises from about 15% to 45% by weight of lamivudine, from about 15% to 45% by weight of tenofovir disoproxil fumarate, and from about 10% to 70% by weight of excipients comprising glidant, diluents, disintegrants and lubricants. In a subclass of the invention, the first layer comprises from about 30% to 40% by weight of lamivudine, from about 30% to 40% by weight of tenofovir disoproxil fumarate, about 0.1% to 2% by weight of glidants, about 6% to 38% by weight of diluents, about 2% to 8% by weight of disintegrants, about 0.25% to 4% by weight of lubricants.

Optionally, the pharmaceutical compositions are film coated. The pharmaceutical compositions of the instant invention may also comprise a polishing aid such as carnauba wax, that among other uses, aids handling of the final product.

The pharmaceutical compositions of the present invention may contain one or more additional formulation ingredients that may be selected from a wide variety of excipients known in the pharmaceutical formulation art. According to the desired properties of the compositions, any number of ingredients may be selected, alone or in combination, based upon their known uses in preparing tablet compositions. Such ingredients include, but are not limited to, diluents, binders, compression aids, disintegrants, lubricants, glidants, stabilizers (such as dessicating amorphous silica), flavors, flavor enhancers, sweeteners, preservatives, colorants and coatings.

In an embodiment of the invention, the glidant, or flow aid, is colloidal silica, silicone dioxide, talc or starch. In a class of the invention, the glidant is colloidal silica.

In an embodiment of the invention, the diluents are selected from the group consisting of lactose, lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate, calcium phosphate dibasic, calcium carbonate and magnesium carbonate. In a class of the embodiment, the diluents are lactose monohydrate and microcrystalline cellulose.

In an embodiment of the invention the disintegrant is croscarmellose sodium, starch, crospovidone, sodium starch glycolate or any mixtures thereof. In a class of the embodiment, the disintegrant is croscarmellose sodium.

In an embodiment of the invention, the lubricant is magnesium stearate, stearic acid or sodium stearyl fumarate. In a class of the embodiment, the lubricants used are magnesium stearate and sodium stearyl fumarate, stearic acid or mixtures thereof.

In an embodiment of the invention, the pharmaceutical composition has a film coat. In a class of the invention, the film coating is an aqueous film coating. In a subclass of the invention, the film coating comprises hydroxypropylmethylcellulose, such as Opadry® II. Opadry® II, which is available from Colorcon, Inc., Harleysville, Pa., contains hydroxypropyl methyl cellulose (also known as "HPMC" or "hypromellose"), titanium dioxide, lactose monohydrate, triacetin and iron oxide yellow.

In an embodiment of the invention, the pharmaceutical composition has a polishing aid. In a class of the invention, the polishing aid is carnauba wax.

In an embodiment of the invention, the first layer comprises a glidant that is colloidal silica; a diluent that is microcrystalline cellulose; a disintegrant that is croscarmellose sodium; and a lubricant that is magnesium stearate.

In an embodiment of the invention, the second layer comprises a glidant that is colloidal silica; a diluent that is microcrystalline cellulose; a disintegrant that is croscarmellose sodium; and lubricants that are magnesium stearate and sodium stearyl fumarate.

The term "tablet" as used herein is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes, whether uncoated or coated. Substances which may be used for coating include hydroxypropylmethylcellulose, hydroxypropylcellulose, titanium dioxide, talc, sweeteners and colorants.

The novel pharmaceutical compositions of the instant invention address the need for incorporation of high doses of doravirine, lamivudine and tenofovir disoproxil fumarate into a compact, single-unit dosage form while still maintaining comparable bioperformance to formulations of individually co-dosed doravirine, lamivudine and tenofovir disoproxil fumarate.

Initial efforts to simply combine the three active ingredients into a homogeneous composition were unsuccessful. At

first, the amorphous dispersion formulation of doravirine, lamivudine and tenofovir disoproxil fumarate were roller-compacted as a single granulation and compressed into a monolithic tablet of ≤1.6 grams. However, the tablet disintegration time was very long (more than 30 min), and the in-vitro dissolution was poor. Subsequent attempts were made to prepare separate granulations for the amorphous dispersion of doravirine and for lamivudine and tenofovir disoproxil fumarate and compress the combined granulations into a monolithic tablet of ≤1.6 grams. These attempts also resulted in relatively slow tablet disintegration and slow dissolution of doravirine.

In an effort to improve the in vitro and in vivo performance of the doravirine formulation, a bilayer configuration wherein the dissolution of the doravirine moiety is not impeded by the tenofovir/lamivudine formulations was developed. Historically, a bilayer tablet configuration has been utilized to formulate active agents with physical or chemical incompatabilities resulting in degradation of interactions such as those which slow down dissolution and lower bioperformance. Doravirine is a low solubility compound classified as a class II compound based on the biopharmaceutics classification system. Hence, it is critical that the release of the active from the fixed dose combination mimics the release from the single entity formulation to ensure comparable efficacy. For the soluble actives, tenofovir disoproxil fumarate and lamivudine, co-granulating the two actives results in an eroding layer which is mechanistically different from the single entities which release the drug through layer disintegration. Separating the lamivudine and tenofovir by incorporating lamivudine in the doravirine (first) layer speeds up release of both lamivudine and tenofovir disoproxil fumarate, but considerably slows down doravirine release. Hence, achieving comparable exposure from the fixed dose combination for these actives is challenging, and the configuration in which these three moieties are presented to ensure similar performance to single entities was previously unknown

The tablets of the instant invention incorporate high loading of an amorphous dispersion formulation of doravirine in one layer and high loadings of crystalline formulations of lamivudine and tenofovir disoproxil fumarate in a separate layer. It was not until the discovery of the instant invention that a physically and chemically stable tablet could be obtained that contained all three active ingredients.

Increased complexity is imparted due to the hygroscopicity of the amorphous dispersion of doravirine in one layer owing to the polymer (for example, HPMCAS), and the susceptibility to hydrolytic degradation of the crystalline tenofovir disoproxil fumarate in the other layer. The novel pharmaceutical compositions of the instant invention address the need for adequate physical and chemical stability of the tablets. Stability of the tablet, namely, chemical stability of tenofovir disoproxil fumarate and physical stability of doravirine, was ensured by controlling water ingression into and water activity in the packaging configuration. One such way is through the use of desiccants in closed containers. Another approach to ensure chemical stability of tenofovir is through physical separation between tenofovir disoproxil fumarate and lamivudine, either within the layer or the dosage form. The separation of tenofovir and lamivudine can be done either as separate layers or as separate granulations in the second layer.

In addition, the novel pharmaceutical compositions of the instant invention address the need for process robustness upon scale up. The first layer containing doravirine is susceptible to capping and interfacial crack issues during bilayer compression as well as decapping and assay loss during processing. While interfacial cracking of bilayer tablets due to low interfacial strength or differential swelling at high temperature and relative humidity is well known, bilayer cracking due to deaeration issues of the amorphous dispersion in the first layer was not known. The low bulk density of the amorphous dispersion formulation, designed to address loss on recompaction and ensure acceptable interfacial strength between the two layers, is a key factor. Deaeration based cracking was also not seen for the single entity formulation and is exacerbated for the large bilayer image. In some cases, these cracks may not be initially present on the exterior of the tablet and hence may not be visible to the naked eye but under conditions of stress such as heat and shear in a coating pan, the cracks can propagate towards the exterior and present themselves to the naked eye. A complex interplay of roller compaction pressure, tamp force and tamp positioning optimization during bilayer compression was critical to resolving the bilayer cracking. The second layer of lamivudine and tenofovir disoproxil fumarate is prone to roll sticking during roller compaction due to the high drug loadings and the inherent sticking propensity of tenofovir. The second layer formulation is also prone to extrusion during roller compaction due to the low glass transition temperature of tenofovir. Mitigation of roll sticking and extrusion required optimal selection of lubricant systems and control of process temperature. The second layer formulation is also susceptible to layer edge chipping during film coating, due to the low tensile strength of the second layer. Edge chipping was circumvented through appropriate selection of film coating systems and optimization of coating process parameters.

Co-granulating tenofovir disoproxil fumarate and lamivudine results in an eroding layer which is mechanistically different from the formulations of the single entities, which release each drug through layer disintegration. It was not known if the mechanistically different dissolution behaviors would have an impact on bioperformance. Furthermore, in the combined tablet, it was unknown whether there would be an interaction between lamivudine and tenofovir disoproxil fumarate, which could result in chemical instability of tenofovir disoproxil fumarate.

The instant invention also addresses the chemical instability of tenofovir disoproxil fumarate, which hydrolyses to form a metabolite, tenofovir mono-POC (also known as "tenofovir monoisoproxil"). The tenofovir disoproxil fumarate stability issue is exacerbated under higher temperature and humidity conditions. These higher temperature and humidity conditions can be found in Zone III (hot, dry climate, 30° C./35% RH)/Zone IV (hot, humid climate, 30° C./75% RH) countries, which include countries in South America (Brazil), sub-Saharan Africa, South Asia (India), and Southeast Asia. Some of these geographical regions coincidentally also happen to be areas where the HIV disease is most prevalent thereby making it imperative for the product to be stable in these hot and humid regions.

The pharmaceutical compositions of the instant invention are stable at temperatures up to 25° C. and up to 60% relative humidity for at least 36 months. The pharmaceutical compositions of the instant invention are stable at temperatures up to 30° C. and up to 65% relative humidity for at least 24 months. Optionally, the packaging storage can include the use of desiccants to further enhance the stability at high relative humidity.

The instant invention also addresses the need for fixed dose pharmaceutical compositions containing doravirine, lamivudine and tenofovir disoproxil fumarate. A compact

single-unit dosage form with an image size no larger than 1.6 grams was developed, comprising 100 mg of doravirine (equivalent to 500 mg of doravirine spray dried intermediate), 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate. Also, a compact dosage form for two-unit administration (taking two tablets at a time) with an image size no larger than 1.0 grams was developed, comprising 50 mg of doravirine (equivalent to 250 mg of doravirine spray dried intermediate), 150 mg of lamivudine and 150 mg of tenofovir disoproxil fumarate.

In another embodiment, the second layer can also contain lamivudine and tenofovir disoproxil fumarate which were separately granulated. As can be seen in Example 7, lamivudine and tenofovir disoproxil fumarate were granulated separately by roller compaction. In Example 8, lamivudine and tenofovir disoproxil fumarate were granulated separately by wet granulation. Probe stability data indicated that the separate granulation approaches can improve the stability profile by reducing the rate of tenofovir mono-POC (also called "mono-POC") formation, as shown in Example 9 (accelerated study at 60° C./ambient, 3 weeks).

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope of the invention.

EXAMPLE 1

50 MG DORAVIRINE/150 MG LAMIVUDINE/150 MG TENOFOVIR DISOPROXIL FUMARATE BILAYER TABLETS

Components	Function	Amount [mg]	Percentage in Each Layer
Layer 1			
		Intragranular	
Doravirine[1]	Active	50.00	10.0%
Hypromellose acetate succinate - LG (HPMC-ASLG)[1]	Polymer	200.0	40.0%
Acetone[2]	Solvent	—	
Water, Purified[2]	Solvent	—	
Microcrystalline Cellulose	Diluent	107.5	21.5%
Lactose Monohydrate	Diluent	107.5	21.5%
Croscarmellose Sodium	Disintegrant	15.00	3.0%
Colloidal Silica	Glidant	2.50	0.50%
Magnesium Stearate	Lubricant	1.25	0.25%
		Extragranular	
Croscarmellose Sodium	Disintegrant	15.00	3.0%
Magnesium Stearate	Lubricant	1.25	0.25%
Layer 1 Weight		500.0	100.0%
Layer 2			
		Intragranular	
Lamivudine	Active	150.0	30.0%
Tenofovir Disoproxil Fumarate	Active	150.0	30.0%
Microcrystalline Cellulose	Diluent	120.0	24.0%
Lactose Monohydrate	Diluent	55.0	11.0%
Croscarmellose Sodium	Disintegrant	10.00	2.0%
Magnesium Stearate	Lubricant	1.25	0.25%
		Extragranular	
Croscarmellose Sodium	Disintegrant	10.00	2.0%
Magnesium Stearate	Lubricant	3.75	0.75%

-continued

50 MG DORAVIRINE/150 MG LAMIVUDINE/150 MG TENOFOVIR DISOPROXIL FUMARATE BILAYER TABLETS

Components	Function	Amount [mg]	Percentage in Each Layer
Layer 2 Weight		500.0	100.0%
Core Tablet Weight		1000.0	
Opadry II 39K Film Coat	Film Coat	25.00	
Water, Purified[2]	Solvent	—	
Film-Coated Tablet Weight		1025.0	

[1]Prepared as spray dried intermediate

[2]Removed during processing

Doravirine layer granulation. Doravirine spray dried intermediate (see, PCT International Publication WO2015/077273), microcrystalline cellulose, lactose monohydrate, colloidal silica (sieved thru 30 Mesh with microcrystalline cellulose) and croscarmellose sodium were blended in V-blender at 25 rpm for 10 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 37 bars, 2.0 mm gap, 1.6 mm/0.8 mm CONIDUR screens. Then, croscarmellose sodium was added to V-blender and blended at 25 rpm for 5 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min.

LAM/TDF blending and roller compaction. TDF, lamivudine, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium were sieved through 30 Mesh and blended in V-blender at 25 rpm for 10 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 55 bars, 2.0 mm gap, 1.6 mm/0.8 mm CONIDUR screens. Then, croscarmellose sodium was added to V-blender and blended at 25 rpm for 5 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min.

Bilayer Compression. Doravirine lubricated granules (layer 1) and LAM/TDF lubricated granules (layer 2) were compressed into bilayer tablets on the Piccola press using the following parameters (oval tooling, 0.708"×0.354", 500 mg layer 1 fill weight, 500 mg layer 2 fill weight, 20 kp hardness, 7.3 mm thickness, 1.7 kN tamping force, 18 kN main compression force, 10 rpm turret speed).

Film Coating. An aqueous suspension of Opadry 39K, 15% by weight, was prepared. The compressed tablets were film-coated in the O'Hara (19" pan) using the following parameters (2.5 kg tablet load, exhaust temp=45° C., air flow=400 ft^3/min, pan speed=10 rpm, spray rate=10 g/min).

EXAMPLE 2

100 MG DORAVIRINE/300 MG LAMIVUDINE/300 MG TENOFOVIR DISOPROXIL FUMARATE BILAYER TABLETS

Components	Function	Amount [mg]	Percentage in Each Layer
Layer 1			
		Intragranular	
Doravirine[1]	Active	100.0	12.8%
Hypromellose acetate succinate - LG (HPMC-ASLG)[1]	Polymer	400.0	51.3%
Acetone[2]	Solvent	—	
Water, Purified[2]	Solvent	—	
Microcrystalline Cellulose	Diluent	224.0	28.7%
Croscarmellose Sodium	Disintegrant	24.0	3.1%
Colloidal Silica	Glidant	4.00	0.51%
Magnesium Stearate	Lubricant	2.00	0.26%
		Extragranular	
Croscarmellose Sodium	Disintegrant	24.00	3.1%
Magnesium Stearate	Lubricant	2.00	0.26%
Layer 1 Weight		780.0	100%
Layer 2			
		Intragranular	
Lamivudine	Active	300.0	38.5%
Tenofovir Disoproxil Fumarate	Active	300.0	38.5%
Microcrystalline Cellulose	Diluent	103.8	13.3%
Croscarmellose Sodium	Disintegrant	23.4	3.0%
Colloidal Silica	Glidant	7.80	1.0%
Magnesium Stearate	Lubricant	7.80	1.0%
Sodium Stearyl Fumarate	Lubricant	7.80	1.0%
		Extragranular	
Croscarmellose Sodium	Disintegrant	23.40	3.0%
Magnesium Stearate	Lubricant	6.00	0.77%
Layer 2 Weight		780.0	100%
Core Tablet Weight		1560	
Opadry II 39K Film Coat	Film Coat	39.00	
Water, Purified[2]	Solvent	—	
Carnauba Wax	Polishing Aid	0.05	
Film-Coated Tablet Weight		1599	

[1]Prepared as spray dried intermediate
[2]Removed during processing

Doravirine layer granulation. Doravirine spray dried intermediate, microcrystalline cellulose, colloidal silica (sieved thru 30 Mesh with microcrystalline cellulose) and croscarmellose sodium were blended in 1800-L Bohle bin at 6 rpm for 30 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 6 rpm for 10 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-200 at the following settings: 75 mm knurled roll, 5.6 kN/cm, 2.0 mm gap, 2.0 mm/1.0 mm CONIDUR screens. Then, croscarmellose sodium was added to the Bohle bin and blended at 6 rpm for 30 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 6 rpm for additional 10 min.

LAM/TDF blending and roller compaction. TDF, lamivudine, microcrystalline cellulose, colloidal silica (sieved thru 30 mesh with microcrystalline cellulose), and croscarmellose sodium were blended in 1800-L Bohle bin at 6 rpm for 30 min. Sodium stearyl fumarate and magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 6 rpm for 10 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-200 at the following settings: 75 mm knurled roll, 7.1 kN/cm, 2.0 mm gap, 2.0 mm/1.0 mm wire screens. Then, croscarmellose sodium was added to the Bohle bin and blended at 6 rpm for 30 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 6 rpm for 10 min.

Bilayer Compression. Doravirine lubricated granules (layer 1) and LAM/TDF lubricated granules (layer 2) were compressed into bilayer tablets on the Fette 3090 press (49 stations) using the following parameters (oval tooling, 0.850"×0.445", 780 mg layer 1 fill weight, 780 mg layer 2 fill weight, 23 kp hardness, 7.3 mm thickness, 5 kN tamping force, 37 kN main compression force, 10 rpm turret speed).

Film Coating. An aqueous suspension of Opadry 39K, yellow, 18% by weight, was prepared. The compressed tablets were film-coated in the Vector FC 150 L, using the following parameters (88 kg tablet load, exhaust temp=45° C., air flow=1250 m^3/hr, pan speed=4-5 rpm, spray rate=175-200 g/min). Carnauba wax was added to the film-coated tablets at the end.

EXAMPLE 3

100 MG DORAVIRINE/300 MG LAMIVUDINE/300 MG TENOFOVIR DISOPROXIL FUMARATE MONOLITHIC TABLETS

Components	Function	Amount [mg]
Granulation 1 (695 mg)		
Doravirine[1]	Active	100.0
Hypromellose acetate succinate - LG (HPMC-ASLG)[1]	Polymer	400.0
Acetone[2]	Solvent	—
Water, Purified[2]	Solvent	—
Microcrystalline Cellulose	Diluent	100.0
Lactose Monohydrate	Diluent	50.00
Croscarmellose Sodium	Disintegrant	40.00
Colloidal Silica	Glidant	3.00
Magnesium Stearate	Lubricant	2.00
Granulation 2 (700 mg)		
Lamivudine	Active	300.0
Tenofovir Disoproxil Fumarate	Active	300.0
Microcrystalline Cellulose	Diluent	50.00
Lactose Monohydrate	Diluent	25.00
Croscarmellose Sodium	Disintegrant	20.00
Magnesium Stearate	Lubricant	5.00
Extragranular (165 mg)		
Microcrystalline Cellulose	Diluent	100.0
Croscarmellose Sodium	Disintegrant	60.00
Magnesium Stearate	Lubricant	5.00
Core Tablet Weight		1560
Opadry II 39K Film Coat	Film Coat	39.00
Water, Purified[2]	Solvent	—
Film-Coated Tablet Weight		1599

[1]Prepared as spray dried intermediate
[2]Removed during processing

Doravirine blending and roller compaction. Doravirine spray dried intermediate, microcrystalline cellulose, lactose monohydrate, colloidal silica and croscarmellose sodium were sieved through 30 Mesh and blended in V-blender at 25 rpm for 15 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 28 bars, 2.0 mm gap, 1.6 mm/0.8 mm CONIDUR screens.

LAM/TDF blending and roller compaction. TDF, lamivudine, microcrystalline cellulose, lactose monohydrate, and croscarmellose sodium were sieved through 30 Mesh and blended in V-blender at 25 rpm for 15 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 20 bars, 2.0 mm gap, 1.6 mm/0.8 mm CONIDUR screens.

Granulation blending and lubrication. Doravirine roller-compacted granules, LAM/TDF roller-compacted granules, microcrystalline cellulose (thru 30 Mesh), and croscarmellose sodium (thru 30 Mesh) were added to V-blender and blended at 25 rpm for 5 min. Then, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min.

Compression. The lubricated blends were compressed on the Piccola press using the following parameters (oval tooling, 0.745"×0.383", 1560 mg fill weight, 20 kp hardness, 9.7 mm thickness, 15 kN main compression force, 8 rpm turret speed).

Film Coating. An aqueous suspension of Opadry 39K, 15% by weight, was prepared. The compressed tablets were film-coated in the O'Hara (19" pan) using the following parameters (2.82 kg tablet load, exhaust temp=45° C., air flow=250 ft^3/min, pan speed=8 rpm, spray rate=30 g/min).

EXAMPLE 4

Biocomparabiliy of Bilayer Tablets (50 MG/150 MG/150 MG), Monolithic Tablets (100 MG/300 MG/300 MG) and Co-Dosings

A biocomparability study was conducted to evaluate the relative bioavailability of the triple combinations of doravirine, lamivudine, and tenofovir disoproxil fumarate (two 50-mg bilayer tablets and a 100-mg monolithic tablet) compared to the bioavailability of doravirine, lamivudine, and tenofovir disoproxil fumarate co-administered as individual tablets (reference). The 50-mg bilayer formulation contained 50 mg doravirine, 150 mg lamivudine, and 150 mg tenofovir disoproxil fumarate, while the 100-mg monolithic formulation contained 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate. The data are summarized in the table below.

PK	2 × 50/150/150 Bilayer[a]		1 × 100/300/300 Monolithic[b]	
Parameter	GMR[c]	90% CI	GMR	90% CI
		Doravirine		
AUC0-∞	1.00	0.931-1.08	0.858	0.800-0.919
Cmax	0.977	0.893-1.07	0.713	0.652-0.781
C24 hr	1.02	0.926-1.12	0.871	0.817-0.929
		Lamivudine		
AUC0-∞	1.02	0.975-1.07	1.09	1.05-1.12
Cmax	0.926	0.859-0.999	1.08	1.02-1.15
		TDF		
AUC0-∞	0.994	0.946-1.04	0.975	0.923-1.03
Cmax	0.912	0.808-1.03	0.868	0.786-0.959

References: individual tablets of doravirine (100 mg), lamivudine (300 mg), TDF (300 mg)
[a]Bilayer Formulation: 2 tablets of 50 mg doravirine/150 mg lamivudine/150 mg TDF
[b]Monolithic Formulation: 1 tablet of 100 mg doravirine/300 mg lamivudine/300 mg TDF
[c]Geometric Mean Ratio

The relative bioavailability of doravirine after administration of either the bilayer or monolithic formulation was comparable to the reference. The geometric mean ratios (GMR) of $AUC_{0-\infty}$, C_{max} and C_{24hr} of doravirine were 1.00, 0.977, and 1.02, respectively, for the bilayer tablet, indicating that bioavailability was the same as the reference. Slight decreases of 14%, 29%, and 13% were noted in $AUC_{0-\infty}$, C_{max} and C_{24hr} of doravirine, respectively, after administration of the monolithic tablet compared to the reference with GMRs of 0.858, 0.713, and 0.871, respectively. Doravirine was absorbed with a median t_{max} of 3 hr for the bilayer tablet and 4 hr for the monolithic tablet, comparable to the t_{max} of the reference (3 hr). The elimination tin of doravirine (~17-19 hr) was similar after all three treatments.

The relative bioavailability of lamivudine was similar to the reference with GMRs of $AUC_{0-\infty}$ and C_{max} of 1.02 and 0.926, respectively, for the bilayer tablet, and the corresponding values for the monolithic tablet were 1.09 and 1.08, respectively. Following administration as a monolithic or bilayer tablet, elimination tin of lamivudine was not altered compared to the reference (12.5 hr, and 12.6 hr respectively, compared to 11.6 hr). Lamivudine t_{max} was 2 hr for bilayer tablet and 1 hr for the monolithic tablet, similar to the t_{max} of the reference (1 hr).

The relative bioavailability of tenofovir disoproxil fumarate when administered in both the bilayer and monolithic formulations was comparable to the reference. The geometric mean ratios of $AUC_{0-\infty}$ and C_{max} of tenofovir disoproxil fumarate were 0.994 and 0.912, respectively, for the bilayer tablet, similar to the reference, while the values for the monolithic tablet were 0.975 and 0.868, respectively. A slight decrease (~13%) of the geometric mean C_{max} was observed for the monolithic tablet vs. the reference.

The median t_{max} for tenofovir disoproxil fumarate was 1 hr for both the bilayer and monolithic tablets, and was similar to the t_{max} of the reference (1 hr). The elimination $t_{1/2}$ of tenofovir disoproxil fumarate was similar after administration of the bilayer tablet (18.0 hr), or monolithic tablet (17.8 hr) or as a co-administered tablet with lamivudine and tenofovir disoproxil fumarate tablets (18.1 hr).

EXAMPLE 5

Biocomparabiliy of Bilayer Tablets (100 MG/300 MG/300 MG) and Co-Dosings

A biocomparability study was conducted to evaluate the comparative bioavailability of a bilayer fixed-dose combination ("FDC") tablet comprised of 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate (TDF) to the bioavailability of co-administration of:

Doravirine 100 mg oral tablet from Merck Sharp & Dohme Corp., USA

Epivir® (lamivudine) 300 mg tablets from ViiV Healthcare UK Limited, United Kingdom and

Viread® (tenofovir disoproxil fumarate) 245 mg tablets from Gilead Sciences International Limited, United Kingdom

The FDC is a film-coated, bilayer tablet with doravirine in one layer and lamivudine and TDF in the other layer, as described herein.

1 × 100/300/300 Bilayer[a] vs Co-Dosings[b]

PK Parameter	GMR[c]	90% CI
Doravirine		
$AUC_{0-\infty}$	1.01	0.94-1.08
AUC_{0-last}	1.02	0.95-1.09
C_{max}	0.99	0.91-1.09
$C_{24\ hr}$	1.02	0.94-1.12
Lamivudine		
AUC0-∞	1.04	1.00-1.09
AUC_{0-last}	1.04	1.00-1.08
C_{max}	1.00	0.91-1.09
TDF		
$AUC_{0-\infty}$	0.98	0.93-1.03
AUC_{0-last}	0.99	0.94-1.04
C_{max}	0.87	0.78-0.97

[a]Bilayer Formulation: 1 tablet of 100 mg doravirine/300 mg lamivudine/300 mg TDF
[b]Reference: individual tablets of DORAVIRINE (100 mg), Epivir ® (300 mg), Viread ® (245 mg)
[c]Geometric Mean Ratio

As shown above, the pharmacokinetics of doravirine, lamivudine, and tenofovir disoproxil fumarate were generally similar when administered as a bilayer fixed-dose combination or the individual components. While tenofovir disoproxil fumarate C_{max} was slightly decreased after administration of the bilayer fixed-dose combination tablet, compared to administration as Viread®, this decrease is not expected to be clinically meaningful.

EXAMPLE 6

Chemical Stability Data for Bilayer Tablets (100 MG/300 MG/300 MG)

The re-evaluation date ("RED") for the FDC (100 mg doravirine/300 mg tenofovir disoproxil fumarate/300 mg lamuvidine) film-coated bilayer tablet is 24 months (worldwide) stored at 2 to 25° C., based on 12-month probe stability data generated at 30° C./65% RH. The tablets were packaged in 120-mL high-density polyethylene ("HDPE") bottles with induction-sealed caps and 4 g or more of desiccant. Alternative packaging configurations, such as 90 mL or 100 mL HDPE bottles with at least 3 g or 4 g of desiccant, respectively, could be used. The alternative packaging configurations should provide similar, if not better humidity control compared to the primary package. The RED is the currently assigned shelf-life, based on the available data at the time, and can be extended with additional stability data from later timepoints. Hence, the eventual or achievable commercial shelf life can be and is expected to be longer than the mentioned RED. The tables below provide analysis of the assay and degradates for each of DORAVIRINE, lamivudine and TDF, after storage at various temperature/RH conditions at various time points. The mono-POC degradate in TDF is the key degradate which governs the shelf-life. The specification for mono-POC in the fixed-dose combination tablet is 3.5% wt.

Assay/Degradates for Film-Coated Bilayer Tablet ("FCT") 100 mg/300 mg/300 mg: Doravirine

Storage Condition	Timepoints (months)	Assay (% claim)	1.28RRT (% claim)
5° C./amb RH closed	1	97.99	0.03
25° C./60% RH closed	1	96.39	0.04
30° C./65% RH closed	1	95.20	0.05
40° C./75% RH closed	1	97.36	0.07
25° C./60% RH closed	2	98.22	0.05
30° C./65% RH closed	2	98.82	0.06
40° C./75% RH closed	2	97.92	0.09
25° C./60% RH closed	5	96.73	0.07
30° C./65% RH closed	5	96.98	0.09
40° C./75% RH closed	5	97.79	0.10
25° C./60% RH closed	8	96.34	0.07
30° C./65% RH closed	8	96.33	0.09
30° C./65% RH closed	12	98.32	0.10

Assay/Degradates for Film-Coated Bilayer Tablet 100 mg/300 mg/300 mg FCT: Lamivudine

Storage Condition	Timepoints (months)	Assay (% claim)	0.39RRT (% claim)
5° C./amb RH closed	1	100.06	ND
25° C./60% RH closed	1	100.86	ND
30° C./65% RH closed	1	101.03	ND
40° C./75% RH closed	1	100.51	ND
25° C./60% RH closed	2	100.15	ND
30° C./65% RH closed	2	99.88	ND
40° C./75% RH closed	2	100.49	ND
25° C./60% RH closed	5	99.67	ND
30° C./65% RH closed	5	100.7	ND
40° C./75% RH closed	5	99.33	0.07
25° C./60% RH closed	8	100.94	ND
30° C./65% RH closed	8	98.87	ND
30° C./65% RH closed	12	99.67	ND

Assay/Degradates for Film-Coated Bilayer Tablet 100 mg/300 mg/300 mg FCT: TDF

Storage	Timepoints	Assay	Degradates (% claim)				
Condition	(months)	(% claim)	0.53RRT	0.59RRT	0.62RRT	0.66RRT	0.69RRT
5° C./amb RH	1	102.12	0.58	ND	ND	ND	ND
25° C./60% R	1	100.88	0.62	0.01	ND	ND	ND
30° C./65% R	1	101.40	0.66	0.02	ND	ND	ND
40° C./75% R	1	101.01	0.85	0.09	ND	ND	ND
25° C./60% R	2	103.28	0.68	0.01	ND	ND	ND
30° C./65% R	2	102.13	0.75	0.03	ND	ND	ND
40° C./75% R	2	101.69	1.06	0.13	0.04	ND	ND

-continued

Assay/Degradates for Film-Coated Bilayer Tablet 100 mg/300 mg/300 mg FCT: TDF

Storage Condition	Timepoints (months)	Assay (% claim)	Degradates (% claim) 0.53RRT	0.59RRT	0.62RRT	0.66RRT	0.69RRT
25° C./60% R	5	100.29	0.77	0.04	ND	ND	ND
30° C./65% R	5	101.13	0.92	0.07	ND	ND	ND
40° C./75% R	5	100.54	1.53	0.22	0.15	0.09	0.08
25° C./60% R	8	101.78	0.84	0.05	0.04	ND	ND
30° C./65% R	8	98.83	1.01	0.09	0.05	0.04	0.04
30° C./65% R	12	100.49	1.20	0.10	0.05	0.05	0.06

(*) mono-POC is expressed as % LC by weight relative to TDF
ND: Not detected
RH: Relative Humidity
RRT: Relative Retention Time (compared to the parent drug in a column)

EXAMPLE 7

100 MG DORAVIRINE/300 MG LAMIVUDINE/300 MG TENOFOVIR DISOPROXIL FUMARATE BILAYER TABLETS

Components	Function	Amount [mg]	Percentage in Each Layer
Layer 1			
		Intragranular	
Doravirine[1]	Active	100.0	12.8%
Hypromellose acetate succinate - LG (HPMC-ASLG)[1]	Polymer	400.0	51.3%
Acetone[2]	Solvent	—	
Water, Purified[2]	Solvent	—	
Microcrystalline Cellulose	Diluent	224.0	28.7%
Croscarmellose Sodium	Disintegrant	24.0	3.1%
Colloidal Silica	Glidant	4.00	0.51%
Magnesium Stearate	Lubricant	2.00	0.26%
		Extragranular	
Croscarmellose Sodium	Disintegrant	24.00	3.1%
Magnesium Stearate	Lubricant	2.00	0.26%
Layer 1 Weight		780	100%
Layer 2			
		Intragranular	
Tenofovir Disoproxil Fumarate	Active	300.0	38.5%
Microcrystalline Cellulose	Diluent	51.93	6.7%
Croscarmellose Sodium	Disintegrant	11.70	1.5%
Colloidal Silica	Glidant	3.12	0.40%
Sodium Stearyl Fumarate	Lubricant	4.50	0.58%
Magnesium Stearate	Lubricant	4.50	0.58%
Lamivudine	Active	300.0	38.5%
Microcrystalline Cellulose	Diluent	55.68	7.1%
Croscarmellose Sodium	Disintegrant	11.70	1.5%
Colloidal Silica	Glidant	3.12	0.40%
Sodium Stearyl Fumarate	Lubricant	2.25	0.29%
Magnesium Stearate	Lubricant	2.25	0.29%
		Extragranular	
Croscarmellose Sodium	Disintegrant	23.40	3.0%
Magnesium Stearate	Lubricant	6.00	0.77%
Layer 2 Weight		780	100%
Core Tablet Weight		1560	
Opadry II 39K Film Coat	Film Coat	39.00	

-continued

100 MG DORAVIRINE/300 MG LAMIVUDINE/300 MG TENOFOVIR DISOPROXIL FUMARATE BILAYER TABLETS

Components	Function	Amount [mg]	Percentage in Each Layer
Water, Purified[2]	Solvent	—	
Film-Coated Tablet Weight		1599	

[1]Prepared as spray dried intermediate
[2]Removed during processing

Doravirine layer granulation. Doravirine spray dried intermediate, microcrystalline cellulose, colloidal silica (sieved thru 34 T Mesh with microcrystalline cellulose) and croscarmellose sodium were blended in 40 L Bohle bin at 25 rpm for 10 min. Magnesium stearate was sieved through 74 T Mesh and added to the blender, which was blended at 25 rpm for 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 33 bars, 2.0 mm gap, 2.0 mm/1.0 mm wire mesh screens. Then, croscarmellose sodium was added to Bohle bin and blended at 25 rpm for 10 min. Finally, magnesium stearate was sieved through 74 T Mesh and added to the blender, which was blended at 25 rpm for additional 5 min.

LAM/TDF layer blend. (i) LAM blending and roller compaction. Lamivudine (sieved thru 22 T Mesh), microcrystalline cellulose, colloidal silica (sieved thru 34 T Mesh with microcrystalline cellulose) and croscarmellose sodium were blended in 40 L Bohle bin at 25 rpm for 10 min. Sodium stearyl fumarate and magnesium stearate was sieved through 74 T Mesh and added to the blender, which was blended at 25 rpm for 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 36 bars, 2.0 mm gap, 2.0 mm/1.0 mm wire screens. (ii) TDF blending and roller compaction. TDF, microcrystalline cellulose, colloidal silica (sieved thru 34 T mesh with microcrystalline cellulose), croscarmellose sodium were blended in 40 L Bohle bin at 25 rpm for 10 min. Sodium stearyl fumarate and magnesium stearate was sieved through 74 T Mesh and added to the blender, which was blended at 25 rpm for 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 22 bars, 2.0 mm gap, 2.0 mm/1.0 mm wire screens. (iii) LAM and TDF granulations blending and lubrication. LAM granulation, TDF granulation and croscarmellose sodium were added to a Bohle bin and blended at 25 rpm for 10 min.

Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for 5 min.

Bilayer Compression. Doravirine lubricated granules (layer 1) and LAM/TDF lubricated granules (layer 2) were compressed into bilayer tablets on the Fette 3090 press (14 stations) using the following parameters (oval tooling, 0.850"×0.445", 780 mg layer 1 fill weight, 780 mg layer 2 fill weight, 24 kp hardness, 5 kN tamping force, 35 kN main compression force, 10 rpm turret speed).

Film Coating. An aqueous suspension of Opadry 39K, yellow, 18% by weight, was prepared. The compressed tablets were film-coated in the Vector LCDS 2.5 L, using the following parameters (1.5 kg tablet load, exhaust temp=40° C., air flow=40 cfm, pan speed=12 rpm, spray rate=7.0 g/min).

EXAMPLE 8

100 MG DORAVIRINE/300 MG LAMIVUDINE/300 MG TENOFOVIR DISOPROXIL FUMARATE BILAYER TABLETS

Components	Function	Amount [mg]	Percentage in Each Layer
Layer 1			
		Intragranular	
Doravirine[1]	Active	100.0	12.8%
Hypromellose acetate succinate - LG (HPMC-ASLG)[1]	Polymer	400.0	51.3%
Acetone[2]	Solvent	—	
Water, Purified[2]	Solvent	—	
Microcrystalline Cellulose	Diluent	224.0	28.7%
Croscarmellose Sodium	Disintegrant	24.0	3.1%
Colloidal Silica	Glidant	4.00	0.51%
Magnesium Stearate	Lubricant	2.00	0.26%
		Extragranular	
Croscarmellose Sodium	Disintegrant	24.00	3.1%
Magnesium Stearate	Lubricant	2.00	0.26%
Layer 1 Weight		780	100%
Layer 2			
		Intragranular	
Tenofovir Disoproxil Fumarate	Active	300.0	43.80
Croscarmellose Sodium	Disintegrant	13.19	1.93%
Hydroxypropyl-cellulose - EXF	Binder	16.49	2.41%
Lamivudine	Active	300.0	43.80%
Croscarmellose Sodium	Disintegrant	13.19	1.93%
Hydroxypropyl-cellulose - EXF	Binder	16.49	2.41%
		Extragranular	
Croscarmellose Sodium	Disintegrant	20.80	3.0%
Magnesium Stearate	Lubricant	4.80	0.70%
Layer 2 Weight		685	100%
Core Tablet Weight		1465	
Opadry II 39K Film Coat	Film Coat	36.6	
Water, Purified[2]	Solvent	—	
Film-Coated Tablet Weight		1501.6	

[1]Prepared as spray dried intermediate
[2]Removed during processing

Doravirine layer granulation. Doravirine spray dried intermediate, microcrystalline cellulose, colloidal silica (sieved thru 30 Mesh with microcrystalline cellulose), croscarmellose sodium were blended in 40 L Bohle bin at 25 rpm for 10 min. Magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for 5 min. The lubricated blend was roller-compacted using the Alexanderwerk WP-120 at the following settings: 40 mm knurled roll, 34 bars, 2.0 mm gap, 2.0 mm/1.0 mm wire mesh screens. Then, croscarmellose sodium was added to the Bohle bin and blended at 25 rpm for 10 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for additional 5 min.

LAM/TDF layer blend. (i) LAM wet granulation. Lamivudine, croscarmellose sodium and hydropropyl cellulose were charged into a 10 L FIELDER blender (1.8 kg total) and blended for 1 min at impeller speed of 300 rpm. Then, the blend was wet-granulated with water as a granulation solution at the following settings: 300 rpm impeller speed, 1800 rpm chopper speed, 66 g/min solution delivery for 10 min. The wet granules were tray-dried at 35° C. The dried granules were milled using a Co-Mil with 40 G screen at 1500 rpm. (ii) TDF wet granulation. TDF, croscarmellose sodium and hydropropyl cellulose were charged into 10 L Fielder (2 kg total) and blended for 1 min at impeller speed of 300 rpm. Then, the blend was wet-granulated with water as a granulation solution at the following settings: 300 rpm impeller speed, 1800 rpm chopper speed, 100 g/min solution delivery for 10 min. The wet granules were tray-dried at 35° C. The dried granules were milled using a Co-Mil with 40 G screen at 1500 rpm. (iii) LAM and TDF granulations blending and lubrication. LAM granulation, TDF granulation, and croscarmellose sodium were added to a Bohle bin and blended at 25 rpm for 10 min. Finally, magnesium stearate was sieved through 60 Mesh and added to the blender, which was blended at 25 rpm for 5 min.

Bilayer Compression. Doravirine lubricated granules (layer 1) and LAM/TDF lubricated granules (layer 2) were compressed into bilayer tablets on the Fette 3090 press (7 stations) using the following parameters (oval tooling, 0.850"×0.445", 780 mg layer 1 fill weight, 685 mg layer 2 fill weight, 26 kp hardness, 5 kN tamping force, 25 kN main compression force, 10 rpm turret speed).

Film Coating. An aqueous suspension of Opadry 39K, yellow, 18% by weight, was prepared. The compressed tablets were film-coated in the Vector LCDS 2.5 L, using the following parameters (1.5 kg tablet load, exhaust temp=40° C., air flow=40 cfm, pan speed=12 rpm, spray rate=6.5 g/min).

EXAMPLE 9

CHEMICAL STABILITY DATA FOR BILAYER TABLETS (100 MG/300 MG/300 MG)

	0.53RRT mono-POC (% area)		
Formulation Example	5° C.	60° C.	mono-POC Growth (% area) over 3 weeks
EXAMPLE 2	0.71	3.47	2.76
EXAMPLE 7	0.69	2.31	1.62
EXAMPLE 8	0.65	1.67	1.02

The stability of different configurations of bilayer tablets in relation to tenofovir mono-POC formation is shown above. The different configurations are described in Examples 2, 7 and 8 wherein the doravirine layer is similar but the TDF/lamivudine consisting second layer is either co-granulated or separately granulated via dry or wet granulation techniques. The stability when TDF and lamivudine are spatially separated is improved relative to that when TDF and lamivudine are co-granulated.

What is claimed is:

1. A tablet comprising a first layer comprising an amorphous dispersion formulation of doravirine, and a second layer comprising lamivudine and tenofovir disoproxil fumarate.

2. The tablet of claim **1** wherein the first layer further comprises a polymer.

3. The tablet of claim **2** wherein the polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, polyvinylpyrrolidinone and polyvinylpyrrolidinone-polyvinylacetate copolymers.

4. The tablet of claim **3** wherein the polymer is hydroxypropyl methyl cellulose acetate succinate.

5. The tablet of claim **1** wherein the first layer further comprises microcrystalline cellulose.

6. The tablet of claim **1** wherein the first layer further comprises croscarmellose sodium.

7. The tablet of claim **1** wherein the second layer further comprises microcrystalline cellulose.

8. The tablet of claim **1** further comprising a film coat.

9. The tablet of claim **1** comprising 50 mg of doravirine, 150 mg of lamivudine and 150 mg of tenofovir disoproxil fumarate.

10. The tablet of claim **1** comprising 100 mg of doravirine, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate.

11. A tablet comprising (i) a first layer comprising an amorphous dispersion formulation of doravirine, hydroxypropyl methyl cellulose acetate succinate, microcrystalline cellulose, and croscarmellose sodium, and (ii) a second layer comprising lamivudine, tenofovir disoproxil fumarate and microcrystalline cellulose.

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