SUMMARY ~~OF THE INVENTION~~

[0003] Described is a hemifumarate form of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. The name for 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine is tenofovir alafenamide. The hemifumarate form of tenofovir alafenamide is also referred to herein as tenofovir alafenamide hemifumarate.

[0004] In one aspect, there~~embodiment of the invention~~ is provided tenofovir alafenamide hemifumarate.

[0005] In another embodiment is provided tenofovir alafenamide hemifumarate, wherein the ratio of fumaric acid to tenofovir alafenamide is 0.5 ± 0.1, or 0.5 ± 0.05, or 0.5 ± 0.01, or about 0.5.

[0005a] In one aspect, there is provided a composition comprising tenofovir alafenamide hemifumarate as defined above, wherein the ratio of fumaric acid to tenofovir alafenamide is 0.5 ± 0.1.

[0006] In one embodiment is provided tenofovir alafenamide hemifumarate in a solid form.

[0007] In one aspect, there~~embodiment~~ is provided tenofovir alafenamide hemifumarate wherein~~that has~~ an X-ray powder diffraction (XRPD) pattern comprises~~having~~ 2theta values of 6.9 ± 0.2° and 8.6 ± 0.2°. In another embodiment is provided tenofovir alafenamide hemifumarate wherein the XRPD pattern comprises 2theta values of 6.9 ± 0.2°, 8.6 ± 0.2°, 11.0 ± 0.2°, 15.9 ± 0.2°, and 20.2 ± 0.2°.

[0008] In one embodiment is provided tenofovir alafenamide hemifumarate that has a differential scanning calorimetry (DSC) onset endotherm of 131 ± 2 °C, or 131 ± 1 °C.

[0009] In one aspect, there~~embodiment~~ is provided a pharmaceutical composition comprising tenofovir alafenamide hemifumarate and a pharmaceutically acceptable excipient. In another embodiment is provided the pharmaceutical composition, further comprising an additional therapeutic agent. In a further embodiment, the additional therapeutic agent is selected from the group consisting of human immunodeficiency virus (HIV) protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

[0010] In one embodiment is provided a method for treating a human immunodeficiency virus (HIV) infection comprising administering to a subject in need thereof a therapeutically effective amount of tenofovir alafenamide hemifumarate. In another embodiment is provided a method for treating an HIV infection comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising tenofovir alafenamide hemifumarate. In a further embodiment, the method comprises administering to the subject one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

[0011] In one embodiment is provided a method for treating a hepatitis B virus (HBV) infection comprising administering to a subject in need thereof a therapeutically effective amount of tenofovir alafenamide hemifumarate. In another embodiment is provided a method for treating an HBV infection comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition comprising tenofovir alafenamide hemifumarate.

[0012] In one aspect, there~~embodiment~~ is provided a method for preparing a pharmaceutical composition comprising combining tenofovir alafenamide hemifumarate and a pharmaceutically acceptable excipient to provide the pharmaceutical composition.

[0012a] In one aspect, there is provided a method for preparing tenofovir alafenamide hemifumarate comprising combining a) an aprotic organic solvent, b) fumaric acid, c) tenofovir alafenamide, and d) one or more seeds of tenofovir alafenamide hemifumarate, and additional crystallizing of the tenofovir alafenamide.

[0012b] In one aspect, there is provided a method for preparing tenofovir alafenamide hemifumarate comprising combining a) a solvent comprising water, isopropyl alcohol, acetone, acetonitrile, toluene, ethyl acetate, isopropyl acetate, heptane, tetrahydrofuran, 2-methyl tetrahydrofuran, methyl ethyl ketone, or methyl isobutyl ketone, or a mixture thereof, b) fumaric acid, c) tenofovir alafenamide, and d) one or more seeds of tenofovir alafenamide hemifumarate, and additional crystallizing of the tenofovir alafenamide at a temperature in the range of from 0°C to 70°C.

[0013] In one embodiment is provided a method for preparing tenofovir alafenamide hemifumarate comprising subjecting a solution comprising a suitable solvent; fumaric acid; tenofovir alafenamide; and, optionally, one or more seeds of tenofovir alafenamide hemifumarate to conditions that provide for the crystallization of the fumaric acid and the tenofovir alafenamide. In one embodiment, the solvent comprises acetonitrile. In another embodiment, the solution is subjected to a temperature in the range of from about 0 °C to about 75 °C.

[0014] In one embodiment is provided tenofovir alafenamide hemifumarate for use in medical therapy.

[0015] In one embodiment is provided the use of tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of an HIV infection. In another embodiment is provided the use of tenofovir alafenamide hemifumarate to treat an HIV infection. In a further embodiment is provided the use of tenofovir alafenamide hemifumarate for the preparation or manufacture of a medicament for the treatment of an HIV infection. In another further embodiment is provided tenofovir alafenamide hemifumarate for use in treating an HIV infection.

[0015a] In one aspect, there is provided a composition for treating a human immunodeficiency virus (HIV) infection administered to a subject in need thereof, comprising a therapeutically effective amount of the hemifumarate as defined above.

[0015b] In one aspect, there is provided the composition for treating an HIV infection as defined above administered to a subject in need thereof at a therapeutically effective amount.

[0016] In one embodiment is provided the use of tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of an HBV infection. In another embodiment is provided the use of tenofovir alafenamide hemifumarate to treat an HBV infection. In a further embodiment is provided the use of tenofovir alafenamide hemifumarate for the preparation or manufacture of a medicament for the treatment of an HBV infection. In another further embodiment is provided tenofovir alafenamide hemifumarate for use in treating an HBV infection.

[0016a] In one aspect, there is provided the composition for treating a hepatitis B virus (HBV) infection administered to a subject in need thereof, comprising a therapeutically effective amount of the hemifumarate as defined above.

[0016b] In one aspect, there is provided the composition for treating an HBV infection as defined above administered to a subject in need thereof at a therapeutically effective amount.

[0017] In some embodiments of the ~~invention~~disclosure, the methods of treating and the like comprise administration of multiple daily doses. In other embodiments, the methods of treating and the like comprise administration of a single daily dose.

[0018] In one embodiment of the ~~invention~~disclosure is provided a composition consisting essentially of tenofovir alafenamide hemifumarate.

BRIEF DESCRIPTIONS OF THE DRAWINGS

[0019] **FIG. 1** shows the X-ray powder diffraction (XRPD) pattern of tenofovir alafenamide hemifumarate.

[0020] **FIG. 2** shows a graph of the DSC analysis of tenofovir alafenamide hemifumarate.

[0021] **FIG. 3** shows a graph of the thermogravimetric analysis (TGA) data for tenofovir alafenamide hemifumarate.