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(54) **Title:** PHARMACEUTICAL COMPOSITIONS

(57) **Abstract:** The present Invention relates to long acting pharmaceutical compositions of hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-adenine), useful in the treatment or prevention of Human Immunodeficiency Virus (HIV) infections.



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PHARMACEUTICAL COMPOSITIONS

CROSS-REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

This is a Patent Cooperation Treaty application and claims the benefit of US

- 5 Provisional Application No. 61/693,851, filed August 28, 2012, which is hereby incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

WO 2007/130783 and WO2011/100698 disclose a class of compounds useful in the
10 treatment of HIV infection and AIDS. There is a continuing need for pharmaceutical compositions suitable for treatment over a long period of time. We have discovered pharmaceutical compositions of hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-adenine that are long-acting and therefore suitable for administration to patients in the treatment of HIV infections.

- 15 Patient non-compliance is a well known problem accompanying the complex HIV treatment regimens. Patient non-compliance is a critical problem in the treatment of HIV because such non-compliance may lead to the emergence of multiple-drug resistant strains of HIV.

The present invention addresses the issue of non-compliance by formulating
20 hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-adenine as a long-acting parenteral composition suitable for administration, for example, once per month, once every 2 months, once every 3 months, once every 6 months or once every 12 months.

The compositions of the present invention provide for once monthly dosing or longer, thereby addressing the problem of patient non-compliance and pill burden.

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SUMMARY OF THE INVENTION

The present Invention relates to pharmaceutical compositions and formulations of hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-adenine useful in the treatment or prevention of HIV infections.

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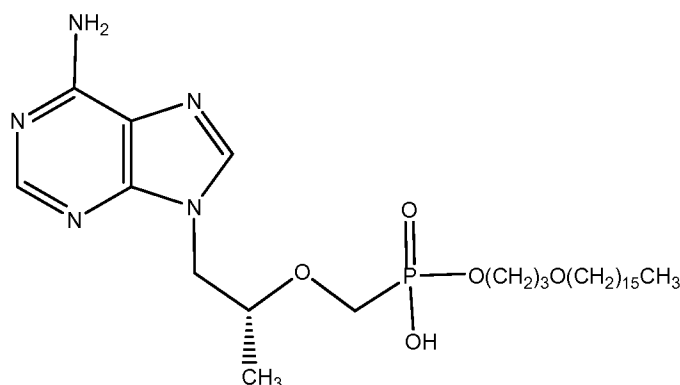
DETAILED DESCRIPTION OF THE INVENTION

Hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-

adenine ("hexadecyloxypropyl tenofovir" or "CMX-157"), a compound of formula (I), also referred to as compound (I) herein, has proven antiviral activity against HIV. See Lanier, E., *et al. Antiviral Therapy*, 13:4 (2008), and Painter G., *et al., Antimicrobial Agents and Chemotherapy*, 51:10 (3505-3509) (2007).

5

Formula (I) or Compound (I):



CMX157 is a lipid (1-O-hexadecyloxypropyl, HDP) conjugate of the acyclic nucleotide analogue tenofovir. Tenofovir is the molecule underlying the marketed tenofovir disoproxil fumarate prodrug called Viread[®], which is an antiviral agent approved for the treatment of human immunodeficiency virus (HIV) and chronic hepatitis B. Viread[®] is one of the most widely used nucleoside/tide reverse transcriptase inhibitors for treating HIV. Unfortunately, it loses activity against some specific HIV mutants, including those with K65R, multiple thymidine analog mutations or multi-NRTI resistant mutations and has also been associated with nephrotoxicity. See Lanier, E., *et al. Antiviral Therapy*, 13:4 (2008). In addition, Viread[®] is rapidly cleaved *in vivo*, leading to suboptimal uptake by target cells.

CMX157 was designed to improve bioavailability and increase target cell penetration of tenofovir while decreasing peripheral exposure and nephrotoxicity. CMX157 is up to 300 times more potent *in vitro* against wild type HIV and clinically relevant mutants than Viread[®]. See Lanier, B., *et al.*, 17th Intl HIV Drug Resistance Workshop, June 10-14, 2008, Sitges, Spain.

In spite of major progress made in the past decade to inhibit the replication of HIV-1, thereby preventing the clinical presentation of AIDS, none of the currently available treatments for HIV infection can cure the infection. Also HAART, or highly active antiretroviral therapy consisting of at least three antiretroviral drugs, may fail following the development of viral resistance. Factors contributing to the incomplete suppression of HIV and to the development of resistance include insufficient drug potency, non-compliance, restricted tissue penetration, drug resistance and several host factors, such as host genetics. Thus,

compliance during a life-long treatment is crucial, as establishing minimal inhibitory drug concentrations in the blood inhibits viral growth and the development of resistant strains

The present invention addresses such problematic issues in the treatment of HIV by formulating CMX157 or hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-adenine as a
5 long-acting parenteral (LAP) composition or depot formulation suitable for administration, for example, once per month, once every 2 months, once every 3 months, once every 6 months or once every 12 months.

Long-acting parenteral formulations of hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-adenine could generate sustained effective inhibitory
10 concentrations with infrequent dosing and may improve adherence to therapy. Next to facilitating maintenance of viral suppression following traditional anti-HIV therapy, a long-acting formulation, may also serve as a practical opportunity for pre-exposure prophylaxis.

The present invention features pharmaceutical compositions comprising the active ingredient hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-adenine, or a
15 pharmaceutically acceptable salt thereof, suitable for administration once monthly or longer.

A further feature of the present invention is a method of using these pharmaceutical compositions.

The present invention features pharmaceutical compositions, comprising hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-adenine, or a pharmaceutically
20 acceptable salt thereof, and a surfactant system.

The present invention features a pharmaceutical composition, comprising a therapeutically effective amount of hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-adenine, or a pharmaceutically acceptable salt thereof, and a surfactant system.

Pharmaceutically acceptable salts include, but are not limited to calcium, magnesium,
25 sodium, or potassium salts and solvates such as hydrates or alcoholates.

The term "therapeutically effective amount," as used herein, means a sufficient amount of a drug, compound, composition, product or pharmaceutical agent to abate or reverse or treat a malady in a human or other mammal.

The present invention features parenteral pharmaceutical compositions for
30 administration to a subject, for example a human.

The present invention features long-acting parenteral pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a surfactant system for once monthly administration.

The present invention features long-acting parenteral pharmaceutical compositions
35 comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a surfactant system for bi-monthly (once every two months) administration.

The present invention features long-acting parenteral pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a surfactant system for tri-monthly (once every three months) administration.

5 The present invention features long-acting parenteral pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a surfactant system administration once every six or twelve months, or any time point within this range.

10 The compositions of the present invention provide for the slow release of a compound of formula (I). Therefore, in order to achieve therapeutic levels of drug, a compound of formula (I) advantageously is released from the composition within approximately one to three months, or any time point within this range.

15 An embodiment of the present invention is a pharmaceutical composition suitable for parenteral administration comprising a compound of formula (I) and a surfactant system comprising a combination of polymers providing for the release of a compound of formula (I) over a period of one to three months. A suitable combination of polymers is, for example, polysorbate 20 and polyethylene glycol (PEG) 3350.

20 A suitable combination of polymers, namely wetting agent and stabilizer, is required to manufacture a stable suspension. Wetting agents can be selected from a class of non-ionic and anionic surfactants. Representative examples of wetting agents include polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (Polysorbate), sorbitan esters of fatty acids (SPAN), Poloxamers, such as LUTROLTM F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide, sodium dodecylsulfate and sodium lauryl sulphate.

25 Representative stabilizers include, but are not limited to, polyethylene glycols, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polysaccharides, hyaluronic acid, polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP).

30 An example of combination of polymers includes a polysorbate, for example, polysorbate 20 or polysorbate 60 as wetting agent and a polyethylene glycol (PEG), for example, PEG 3350, PEG4000 or PEG8000 as stabilizer.

The present invention features a parenteral pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and polysorbate 20 and polyethylene glycol (PEG) 3350.

35 An embodiment of the present invention is a pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system that may be nanomilled to 200nm.

An embodiment of the present invention is a pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system that may be nanomilled to 200nm in less than 10 hours on a ball mill.

5 An embodiment of the present invention is a pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system that may be size reduced to a mean particle size of 0.1 – 1.0 μm .

An embodiment of the present invention is a pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system that may be size reduced to a mean particle size of 0.1 – 0.5 μm or 0.2 – 0.4 μm .

10 An embodiment of the present invention is a pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system that may be size reduced to a mean particle size of 0.1 – 1.0 μm using wet bead milling.

15 An embodiment of the present invention is a pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system that may be size reduced to a mean particle size of 0.1 – 1.0 μm using a high pressure milling technology such as microfluidizer or other rotor-stator type of mill or jet mill.

20 An embodiment of the present invention is a pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system suitable for commonly known sterilization technologies such as gamma irradiation, electron beam irradiation and autoclave sterilization.

An embodiment of the present invention is a pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system that can be manufactured using aseptic technique.

25 An embodiment of the present invention is a pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system suitable for gamma radiation sterilization.

30 An embodiment of the present invention is a pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system suitable for sterilization technologies by electron beam irradiation or autoclave sterilization.

An embodiment of the present invention is a pharmaceutical composition for parenteral administration that can be presented as a “ready to use” sterile suspension or lyophile for reconstitution.

35 In general, the pharmaceutical compositions of the present invention comprise 0.1 - 50% by weight of a compound of formula (I). In general, the pharmaceutical compositions of the present invention comprise 0.1 – 5% polysorbate 20 as a surfactant and 0.1 – 5% polyethylene glycol. The pharmaceutical compositions of the present

invention may comprise 0.1 – 10% polysorbate 20 as a surfactant and 0.1 – 10% polyethylene glycol.

5 The compositions of the present invention may be administered by subcutaneous or intramuscular injection. The compositions of the present invention may be administered by intradermal or intravitreal injection or implant. The compositions of the present invention may be administered by other parenteral routes of administration.

The preparation of the compositions of the present invention may be performed by milling using a wet bead mill and sterilized by gamma irradiation.

10 Another feature of the present invention is to simplify treatment regimens for HIV with the goal of enhancing patient compliance by providing a simplified dosage form containing therapeutically effective amounts of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15 The present invention also features a method for treating HIV infections in a human, which method comprises administering to said human a composition according to the invention. The present invention features the use of a pharmaceutical composition according to the invention in the treatment of HIV infections. The present invention features the manufacture of a medicament according to the invention for use in medical therapy.

20 The present invention also features a method for treating HIV infections in a human which method comprises administering to said human a composition according to the invention before, during, or after therapy with a compound of formula (I) in tablet or solution form.

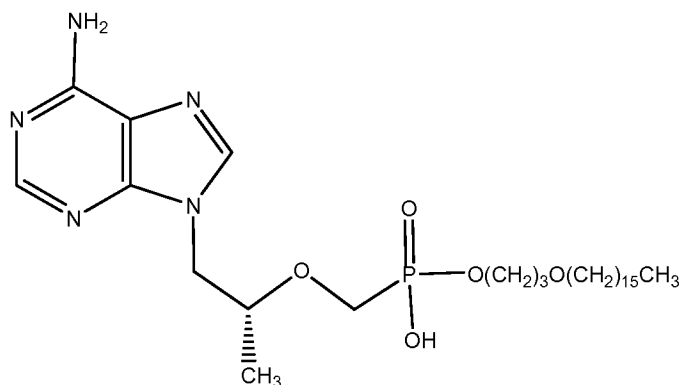
It will be appreciated by those skilled in the art that reference herein to “treatment” extends to treatment of an established malady, infection or symptoms thereof.

25 The present invention also features a method for preventing HIV infections in a human, which method comprises administering to said human a composition according to the invention. The present invention features the use of a pharmaceutical composition according to the invention in the prevention of HIV infections. The present invention features the manufacture of a medicament according to the invention for use in prophylactic medical therapy.

30 The present invention also features a method for treating or preventing HIV infections in a human which method comprises administering to said human a composition according to the invention before, during, or after therapy with a compound of formula (I) in tablet or solution form.

35 Therefore, in certain embodiments of the present invention, there is provided a single treatment pharmaceutical composition comprising a therapeutically effective amount of a long acting formulation comprising a compound of formula (I):

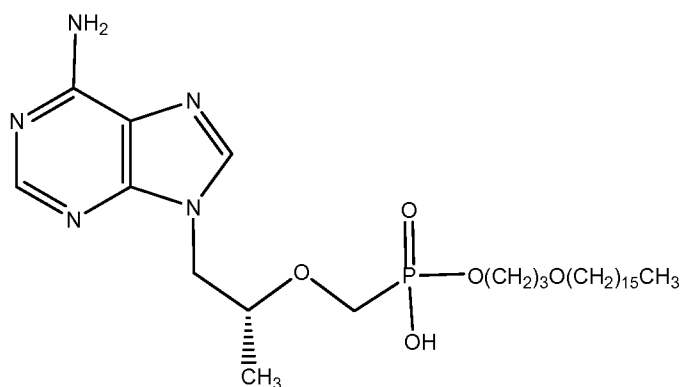
(I)



or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier for parenteral administration.

- 5 In other embodiments, there is provided a parenteral pharmaceutical composition comprising a compound of formula (I):

(I)



or a pharmaceutically acceptable salt thereof.

- 10 In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I) that is formulated for subcutaneous administration.

In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I) that is formulated for intramuscular administration.

- 15 In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I) that is formulated for administration once weekly or longer.

In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I) that is formulated for administration once weekly.

In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I) that is formulated for administration once per month.

In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I) that is formulated for administration once every two months.

5 In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I) that is formulated for administration once every three months.

In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I) that is formulated for administration at any interval between 30 and 365 days.

10 In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I), wherein the compound of formula (I) is present in the composition in amount that is from about 10 mg to about 500 mg per ml of the composition.

15 In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I), wherein the compound of formula (I) is present in the composition in a particle size of less than or equal to 200 nm.

In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I), wherein the compound of formula (I) is present in the composition in a particle size within the range of about 0.1 μ m to about 0.5 μ m.

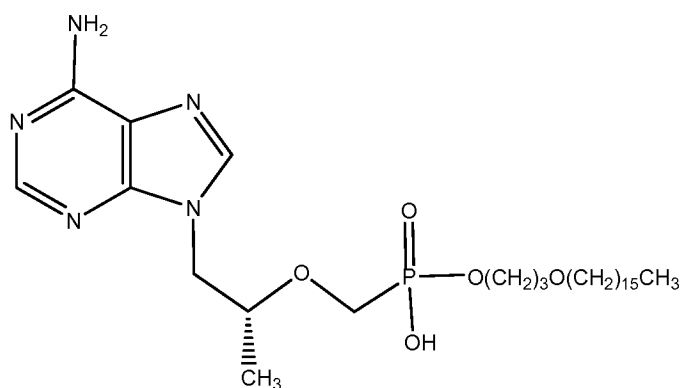
20 In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I), wherein the compound of formula (I) is present in the composition in the form of crystalline nanoparticles.

25 In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I), wherein the compound of formula (I) is present in the composition in the form of matrix release particles.

In other embodiments, there is provided a pharmaceutical composition comprising a compound of formula (I), wherein the composition can be terminally sterilized by gamma irradiation.

30 In other embodiments, there is provided a method for the treatment of an HIV infection in a human having an HIV infection comprising administering to the human a single treatment pharmaceutical composition comprising a therapeutically effective amount of a long acting formulation comprising a compound of formula (I):

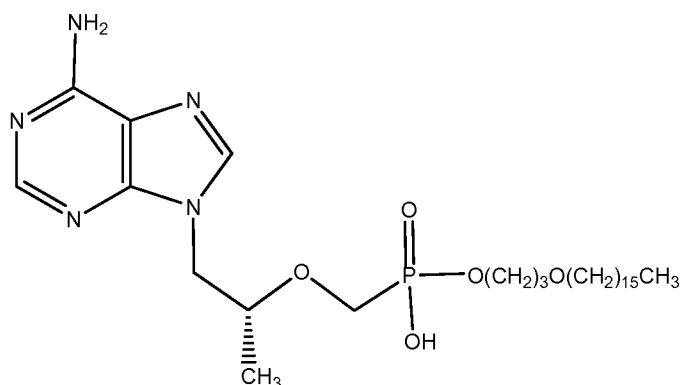
(I)



or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier for parenteral administration.

- 5 In other embodiments, there is provided a method for the prevention of an HIV infection in a human comprising administering to a human at risk of acquiring an HIV infection, a single treatment pharmaceutical composition comprising a therapeutically effective amount of a long acting formulation comprising a compound of formula (I):

(I)



- 10 or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier for parenteral administration.

- Methods for the preparation of a compound of formula (I) are described in WO2007/130783, WO2011/100698, WO2011053812, and Beadle, J., *et al.*, J. Med. Chem. 49:2010-2015 (2006), Painter, G., *et al.*, Antimicrob. Agents Chemother. 51:3505-3509 (2007), which are incorporated herein by reference.

- 15 The pharmaceutical compositions of the invention are presented as pharmaceutical compositions suitable for parenteral administration. The compositions may also include a safe and effective amount of other active ingredients, such as antimicrobial agents, antiviral agents, or preservatives.

It will be appreciated by those skilled in the art that the amount of active ingredients required for use in treatment will vary according to a variety of factors, including the nature of the condition being treated and the age and condition of the patient, and will ultimately be at the discretion of the attending physician, veterinarian or health care practitioner.

Compositions of the present invention enable patients greater freedom from multiple dosage regimens and ease the needed diligence required in remembering complex daily dosing times and schedules. The compositions of the present invention are particularly suitable for administration as a single dose monthly, bi-monthly or tri-monthly, or at any interval between 30 and 365 days, including every six or twelve months

Advantageously, the compositions of the present invention may be administered once per month.

The compositions of the present invention conveniently allow administration in unit dosage form containing, for example, from about 1 mg to about 800 mg, 100 mg to about 800 mg of a compound of formula (I), from about 100 mg to about 600 mg or from about 100 mg to about 400 mg per unit dosage form.

The compositions of the present invention may be used in combination with other pharmaceutical formulations as a component of a multiple drug treatment regimen.

Compositions of the present invention may also be packaged as articles of manufacture comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof; and therapeutically effective amount of one or more of the following: nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, protease inhibitor, integrase inhibitor.

The packaging material may also have labelling and information related to the pharmaceutical composition printed thereon. Additionally, an article of manufacture may contain a brochure, report, notice, pamphlet, or leaflet containing product information. This form of pharmaceutical information is referred to in the pharmaceutical industry as a "package insert." A package insert may be attached to or included with a pharmaceutical article of manufacture. The package insert and any article of manufacture labelling provides information relating to the pharmaceutical composition. The information and labelling provides various forms of information utilized by health-care professionals and patients, describing the composition, its dosage and various other parameters required by regulatory agencies such as the United States Food and Drug Agencies.

The present invention further provides the following embodiments:

(a) A parenteral pharmaceutical composition comprising an effective amount of compound of formula (I) or a pharmaceutically acceptable salt thereof, for the long term

treatment of HIV infection, or prevention of HIV infection in an individual at risk of being infected by HIV, wherein the composition is administered intermittently at a time interval of at least one week.

5 (b) The composition according to (a) wherein the composition is administered once every two weeks.

(c) The composition according to (a) wherein the composition is administered once every month.

10 (d) The composition according to any one of (a) to (c) wherein the effective amount of compound of formula (I) or a pharmaceutically acceptable salt thereof is selected such that the blood plasma concentration of compound of formula (I) in a subject is kept during a prolonged period of time at a level between a maximum blood plasma level which is the blood plasma level that causes significant side effects and the minimum blood plasma level that is the lowest blood plasma level that causes a compound of formula (I) to provide effective treatment or prevention of HIV infection.

15 (e) The composition according to (d) wherein the blood plasma level of a subject is kept at a level equal to or above about 150 ng/ml, in particular equal to or above about 600 ng/ml.

(f) The composition according to any one of (a) to (e), wherein the composition is administered subcutaneously or intramuscularly.

20 (g) The composition according to any one of (a) to (f), which comprises the aforementioned surfactant system comprising polysorbate and /or polyethylene glycol.

(h) A method for the treatment or prevention of an HIV infection in a human comprising a pharmaceutical composition according to any of the above (a) to (g).

25 The dose of a compound of formula (I) administered, which is the amount of compound (I) in the parenteral composition for use in the invention, may be selected such that the blood plasma concentration of compound (I) in a subject is kept during a prolonged period of time above a minimum blood plasma level. The term "minimum blood plasma level" (or $C_{min.}$) in this context refers to the lowest efficacious blood plasma level, that is, the blood plasma level of compound (I) that provides effective prevention or treatment HIV infection. In the case of transmission of HIV from an individual infected by HIV to an individual not infected by HIV, this is the lowest blood plasma level that is effective in inhibiting said transmission.

35 The blood plasma level of compound (I) in a subject may be kept at a level above a minimum blood plasma level of about 170 ng/ml, about 700 ng/ml, or about 1000 ng/ml. The blood plasma levels of compound (I) in a subject may be kept above these minimum blood plasma levels because at lower levels the drug may no longer be effective, thereby increasing the risk of transmission of HIV infection, and may be suboptimal for treatment

of HIV infected subjects. Plasma levels of compound (I) may be kept at higher levels to avoid the development of HIV mutations, while maintaining a safety margin.

5 An advantage of the mode of administration of compound (I) is that high C_{min} levels can be achieved without a commensurate high C_{max} , which could mitigate potential side effects associated with C_{max} .

The effective amount of compound (I) to be administered may be selected such that the blood plasma concentrations in a subject are kept during a prolonged period of time at a level between a maximum plasma level (or C_{max}) and the minimum blood plasma level (or C_{min}).

10 In some embodiments the blood plasma level of compound (I) in a subject may be kept between the minimum blood plasma level (or C_{min} as specified above) and the lower maximum plasma level of compound (I) (or C_{max}) which is defined as the level that corresponds to the lowest blood plasma level where compound (I) acts therapeutically. The lowest level where compound (I) acts therapeutically is the lowest blood plasma
15 level that is effective in inhibiting replication of HIV in individuals infected by HIV so that the viral load of HIV is relatively low, for example where the viral load (represented as the number of copies of viral RNA in a specified volume of serum) is below about 200 copies/ml, in particular below about 100 copies/ml, more particularly below 50 copies/ml, specifically below the detection limit of the assay for HIV.

20 As mentioned above, the blood plasma levels of compound (I) depend on the amount of active ingredient in each parenteral dosage administered. However, it also depends on the frequency of the administrations (i.e. the time interval between each administration). Both parameters can be used to direct the blood plasma levels to the desired values. The dose may be higher where administrations are less frequent.

25 Although the plasma levels of compound (I) should remain below a maximum or above a minimum value, they may surpass the maximal value or drop below the minimal value during relatively short periods of time, which may be as short as possible. The maximum and minimum plasma levels therefore can be expressed as mean plasma levels during a certain period of time.

30 In some instances there may be a small initial plasma concentration peak shortly after administration, after which the plasma levels achieve a steady-state.

The dose to be administered may be calculated on a basis of about 1 mg/day to about 50 mg/day, preferably 3 mg/day to about 30 mg/day. This corresponds to a weekly dose of about 7 mg to about 350 mg, preferably about 20 mg to about 200 mg, or
35 to a monthly dose of about 30 mg to about 1500 mg, preferably about 90 mg to about 900 mg. Doses for other dosing regimens can readily be calculated by multiplying the daily dose with the number of days between each administration.

The dose to be administered may be calculated on a basis of about 0.001mg/kg/day to about 1 mg/kg/day, preferably 0.05mg/kg/ day to about 0.5 mg/kg/day. This corresponds to a weekly dose of about 0.5 mg to about 500 mg, preferably about 20 mg to about 200 mg, or to a monthly dose of about 30 mg to about 1500 mg, preferably about 90 mg to about 900 mg. Doses for other dosing regimens can readily be calculated by multiplying the daily dose with the number of days between each administration.

Once administered, the blood plasma levels of compound (I) in a subject may be more or less stable. After initial rise of the blood plasma levels, a steady state mode may be achieved during a prolonged period of time. By "steady state" is meant the condition in which the amount of drug present in the blood plasma of a subject stays at more or less the same level over a prolonged period of time. The plasma levels of compound (I) may then gradually decrease over time, and when the minimum plasma level is reached, then the next dose of compound (I) may be administered. The term "stays at more or less the same level" does not exclude that there can be small fluctuations of the plasma concentrations within an acceptable range, for example, within about 30%, about 20%, or about 10%.

The parenteral compositions of compound (I) may be administered by intravenous injection or, preferably by subcutaneous or intramuscular administration.

The present invention is based on the use of parenteral compositions of the active ingredient compound (I) and therefore the nature of the carrier is selected for suitability for parenteral administration. The carrier in most cases will comprise sterile water, in although other ingredients, for example, to aid solubility, may be included. Injectable solutions or suspensions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Further, the carrier may contain the surfactant system mentioned above such as polysorbate and polyethyleneglycol.

Effect of the Invention

The parenteral pharmaceutical composition comprising compound (I) of the present invention is long-acting. Accordingly, the composition is useful for the treatment or prevention of HIV infection with administration at long time intervals, compared with conventional compositions or with other compounds similar to compound (I) in chemical structure. The compositions of the present invention can be intermittently administered to a patient, e.g., once per week, once per month, once per every 2 months, or one per every 3 months. Therefore, the compositions of the present invention and an administration by subcutaneous (SC) or intramuscular (IM) injection using the same can

lead to a remarkable reduction in medication (pill) burden or difficulty in patient compliance. Further, such intermittent administration of a composition of the present invention can contribute to maintaining therapy at appropriate compliance which leads to prevention of emergence of drug resistant HIV and maintaining the efficacy of therapy for an extended period of time.

EXAMPLES

The following examples further describe and exemplify particular embodiments within the scope of the present Invention. The examples are given solely for illustration and are not to be construed as limitations as many variations are possible without departing from spirit and scope of the Invention.

The compound of Formula I (hexadecyloxypropyl-9-*R*-[2-(phosphonomethoxy)propyl]-adenine), may be synthesized by one of skill in the art by following the teachings of PCT Published Application Nos. WO 2007/130783 and WO2011/100698, which disclose a class of compounds useful in the treatment of HIV infection and AIDS.

Example 1: Pharmaceutical Composition

Table 1 Composition of a compound of formula (I) Injectable Suspension

Component	Quantity (mg /mL)	Function
Compound of Formula (I)	200.0	Active
Mannitol	45.0	Tonicity agent
Polysorbate 20	20.0	Wetting agent
Polyethylene Glycol (PEG) 3350	20.0	Stabilizer
Water for Injection	QS to 1.0 mL	Solvent

Manufacturing Process

A compound of formula (I), mannitol, polysorbate 20, PEG 3350, and water for injection could be compounded and milled using a wet bead mill. The resulting suspension could be filled into 3 mL, USP Type I glass vials at a fill volume of 1.5mL, the vials would be stoppered and sealed, and then terminally sterilized by gamma irradiation.

Example 2: Particle Size

A sample of a compound of formula (I) injectable suspension could be prepared by the process as described in Example 1 and then irradiated by gamma irradiation at 29.9-31.5 kGy dose. The milling time should be 5 hours. The particle size would then be determined by laser diffraction technique and potentially show the following:

- 5 X10 = 75 nm
 X50 = 157 nm
 X90 = 646 nm
 X 50 of less than 200nm might be achieved.

10 Example 3: Gamma Irradiation

- A sample of a compound of formula (I) injectable suspension could be prepared by the process as described in Example 1 and could be irradiated by gamma irradiation at 29.9-31.5 kGy dose. Samples pre gamma irradiation and post gamma irradiation could be tested for drug related impurities by HPLC. For example, the following measure of drug
 15 related impurities could be seen before and after Gamma Irradiation.

	Total Drug Related Impurities, %area/area
Pre Gamma Irradiation	0.19
Post Gamma Irradiation	0.16

20 The formulation should be stable upon gamma irradiation.

Example 4: Manufacturing process using high pressure Microfluidizer

- 25 Table 2 Composition of a compound of formula (I) Injectable Suspension

Component	Quantity (mg /mL)	Function
Compound of Formula (I)	200.0	Active
Mannitol	45.0	Tonicity agent
Polysorbate 20	20.0	Wetting agent
Polyethylene Glycol (PEG) 3350	20.0	Stabilizer
Water for Injection	QS to 1.0 mL	Solvent

Manufacturing Process

A compound of formula (I), mannitol, polysorbate 20, PEG 3350, and water for injection could be compounded and microfluidized using a Microfluidizer M-110P. The

suspension could then be passed through an interaction chamber (G10Z) with a minimum internal dimension of 87 μ m and after 50 pass could achieve particle sizes approximating those listed below:

X10 = 82 nm

5 X50 = 221 nm

X90 = 726 nm

10

15

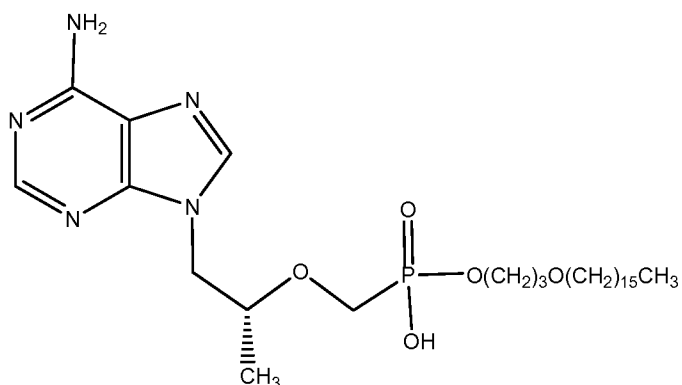
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Claims:

1. A single treatment pharmaceutical composition comprising a therapeutically effective amount of a long acting formulation comprising a compound of formula (I):

(I)

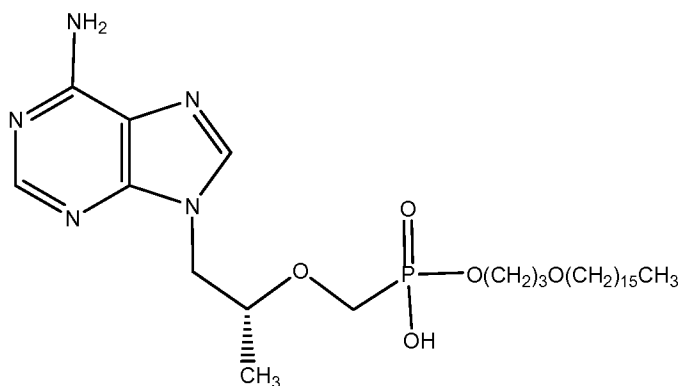


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or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier for parenteral administration.

2. A parenteral pharmaceutical composition comprising a compound of formula (I):

(I)



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or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition according to any of claims 1-2 for subcutaneous administration.

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4. A pharmaceutical composition according to any of claims 1-2 for intramuscular administration.

5. A pharmaceutical composition according to any of claims 1-4, wherein the parenteral composition is formulated for administration once weekly or longer.
- 5 6. A pharmaceutical composition according to claims 1-4, wherein the parenteral composition is formulated for administration once weekly.
7. A pharmaceutical composition according to any of claims 1-4, wherein the parenteral composition is formulated for administration once per month.
- 10 8. A pharmaceutical composition according to any of claims 1-4, wherein the parenteral composition is formulated for administration once every two months.
9. A pharmaceutical composition according to any of claims 1-4, wherein the parenteral composition is formulated for administration once every three months.
- 15 10. A pharmaceutical composition according to any of claims 1-4, wherein the parenteral composition is formulated for administration at any interval between 30 and 365 days.
- 20 11. A pharmaceutical composition according any of claims 1-10, wherein the amount of the compound of formula (I) present in the composition is from about 10 mg to about 500 mg per ml of the composition.
- 25 12. A pharmaceutical composition according any of claims 1-11, wherein the compound of formula I is present in the composition in a particle size of less than or equal to 200nm.
13. A pharmaceutical composition according to claim 12, wherein the the particle size is in the range of 0.1 – 0.5 μm .
- 30 14. A pharmaceutical composition according any of claims 1-13, wherein the compound of formula I is present in the composition in the form of crystalline nanoparticles.
- 35 15. A pharmaceutical composition according any of claims 1-13, wherein the compound of formula I is present in the composition in the form of matrix release particles.

16. A pharmaceutical composition according to any of claims 1 – 15, wherein the composition can be terminally sterilized by gamma irradiation.
- 5 17. A method for the treatment of an HIV infection in a human having an HIV infection comprising administering to the human a pharmaceutical composition according to any of claims 1 – 16.
- 10 18. A method for the prevention of an HIV infection in a human comprising administering to a human at risk of acquiring an HIV infection, a pharmaceutical composition according to any of claims 1 – 16.
19. Use of a pharmaceutical composition according to any of claims 1 – 14 in medical therapy.
- 15 20. Use of a pharmaceutical composition according to any of claims 1 – 14 in the treatment or prevention of an HIV infection.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 13/56766

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 57/00 or A61K 31/675 (2013.01)

USPC - 514/086; 514/081; 544/244

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/086; 514/081; 544/244

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Thomson innovation (US Grant, AU Innov, CA App, US App, AU Grant, FR App, EP Grant, AU App, DE Util, EP App, GB App, DE Grant, WO App, CA Grant, DE App, JP App, KR Grant, KR App, Other, JP Util, KR Util), surechem, google scholar, sciencedirect. Phosphonomethoxy, adenine, infection, parenteral, adenine, single treatment, dose, dosage

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0263536 A1 (Lanier et al.) 27 October 2011 (27.10.2011) entire document especially para [0008]; [0023]; [0025]; [0008]; [0077]; [0085]; [0012]; [0105]; [0110]	1-4
Y	US 2012/0058975 A1 (Hostetler et al.) 08 March 2012 (08.03.2012) entire document	1-4
Y	US 7,452,898 B2 (Hostetler et al.) 18 November 2008 (18.11.2008) entire document	1-4
Y	US 6,716,825 B2 (Hostetler et al.) 06 April 2004 (06.04.2004) entire document	1-4

☐ Further documents are listed in the continuation of Box C.



* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 December 2013 (15.12.2013)

Date of mailing of the international search report

23 DEC 2013

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

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PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 13/56766

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 5-20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.