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(54) Title: FIXED DOSE COMPOSITIONS OF CABOTEGRAVIR AND RILPIVIRINE

(57) Abstract: The invention relates to a pharmaceutical composition administered in a form of injection comprising fixed dose of two or more active ingredients namely Cabotegravir and Rilpivirine and optionally other active ingredients, a process for preparing such pharmaceutical composition. Use of such fixed dose pharmaceutical composition for the prevention, treatment and prophylaxis of AIDS are also described herein.

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FIXED DOSE COMPOSITIONS OF CABOTEGRAVIR AND RILPIVIRINE

CROSS-REFERENCE TO RELATED APPLICATIONS:

This application claims priority to Indian Application No. 202021044747, filed 14 October 2020 and entitled "Fixed Dose compositions" which is incorporated herein in its entirety.

FIELD OF INVENTION:

The present invention relates to a pharmaceutical composition administered in a form of injection comprising fixed dose of two or more active ingredients, a process for preparing such pharmaceutical composition, and use of the said pharmaceutical composition for the prevention, treatment and prophylaxis of AIDS.

BACKGROUND AND PRIOR ART:

Human immunodeficiency virus infection and related diseases are a major public health problem worldwide. Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, et al. N. Engl. J. Med. (1998) 338:853-860; Richman, D. D. Nature (2001) 410:995-1001).

A goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient. Treatment guidelines published by the United States Department of Health and Human Services provide that achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes. (Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Section accessed

Mar. 14, 2013.) In addition, decisions regarding the treatment of HIV infected patients are complicated when the patient requires treatment for other medical conditions (Id. at E-12). Because the standard of care requires the use of multiple different drugs to suppress HIV, as well as to treat other conditions the patient may be experiencing, the potential for drug interaction is a criterion for selection of a drug regimen. As such, there is a need for antiretroviral therapies having a decreased potential for drug interactions and with even more therapeutic potencies.

A standard course of care for a patient infected with HIV is to treat them with a combination of two or more antiviral agents. Frequently, this treatment uses at least one antiretroviral agents targeting HIV reverse transcriptase (a "backbone") and/or one or more agents active against one or more different HIV targets, such as an HIV protease inhibitor, an HIV non-nucleoside or non-nucleotide inhibitor of reverse transcriptase, an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV integrase inhibitor, an HIV non-catalytic site (or allosteric) integrase inhibitor, or a combination thereof. For certain patients infected with HIV or diagnosed with AIDS, there is an unmet medical need to treat them with fewer antiviral agents.

While ART has led to substantial increases in life expectancy and quality of life for HIV-infected persons, HIV infection requires lifelong treatment. This means that as HIV-infected individuals achieve life expectancies near those of persons without HIV, HIV-infected individuals are likewise starting to receive treatment for non-HIV, common conditions such as diabetes, cardiovascular disease, arthritis, osteoporosis, or other age-associated conditions and diseases. (Zhou et al., Total Daily Pill Burden in HIV-Infected Patients in the Southern United States, 2014 AIDS PATIENT CARE and STDs 28(6): 311-317.) This increased drug burden (of HIV patients also now taking medications for HIV-unrelated indications) raises risks of drug-drug interactions and overlapping toxicities, not to mention it increases the patient's healthcare costs and dosing hassle. (Zhou et al., AIDS PATIENT CARE and STDs 28(6): 311-317.) Further, increasing medication

complexity may affect treatment adherence and virologic suppression. (Zhou et al., AIDS PATIENT CARE and STDs 28(6): 311-317.)

Fewer drugs in HIV infected patients are also desired for those that are likely to tolerate two drugs rather than more such as aging patients, those with advanced HIV infections or other diseases, or to avoid drug-drug interactions, and to limit side effects among patients.

Additionally, an issue associated with administration of HIV medications, including both bictegravir and emtricitabine, is patient compliance. Because all HIV drugs must be taken as part of a combination regimen, there must be better ways to ensure patient compliance in taking medication as prescribed. If there are too many pills to swallow, at too many time intervals, then dosing becomes inconvenient and complicated, and patient compliance with the treatment regimen is less likely.

Long-acting injectable ART may provide some patients with a convenient and discreet approach to manage HIV infection. Margolis D A, Boffito M. Long-acting antiviral agents for HIV treatment. Curr Opin HIV AIDS 2015; 10(4): 246-52.

WO2006116764 discloses integrase strand transfer inhibitors (INSTI) useful in the treatment of HIV infection and AIDS. One of the compounds disclosed is cabotegravir ((3S,11aR)-N-[(2,4-difluorophenyl)methyl]-2,3,5,7,11,11a-hexahydro-6-hydr- oxy-3-methyl-5,7-dioxo-oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide) a compound of formula (I), also referred to as compound (I), has proven antiviral activity against human immunodeficiency virus (HIV).

WO2006106103 discloses parenteral formulations of TMC 278 (known as Rilpivirine) to be administered intermittently at a time interval of at least one week, and may also be administered at longer time intervals such as several weeks, e.g. 2, 3, 4, 5 or 6 weeks, or at time intervals of one month, or of several months, e.g. 2, 3, 4, 5 or 6 months or even longer, e.g. 7, 8, 9 or 12 months for prevention/ prophylaxis of HIV.

WO2007082922 discloses parenteral formulations of TMC278 (known as Rilpivirine) to be administered intermittently at a time interval of at least one week, or in particular at a time interval mentioned for the treatment of HIV wherein the intervals may be shorter where the blood plasma levels of TMC278 are deemed too low, e.g. when these approach the minimum blood plasma level specified hereinafter. The intervals may be longer where the blood plasma levels of TMC278 are deemed too high

WO2012140220 discloses freeze dried/ lyophilized nanosuspension composition of Rilpivirine and a steric stabilizer, a surfactant (e.g. a polymeric surfactant) or a polymer for administration either through intramuscular (IM) or subcutaneous (SC) injection.

US 20170027933 discloses parenteral pharmaceutical composition of compound of formula (I) (known as cabotegravir) and a surfactant system comprising polysorbate, polyethylene glycol, mannitol, and water, wherein the composition has mean particle size of 200 .mu.m or less.

US 20200147079 discloses method of treating HIV comprising intramuscular administration once every 4 weeks or less frequently of a combination of cabotegravir or a pharmaceutically acceptable salt thereof and rilpivirine or a pharmaceutically acceptable salt thereof, however, as per the regimen, there are two separate injections (or vials) as kit which need to be administered separately and requires specific task to health care givers and patients to administer “initial” and “maintenance” doses. Apart from that, the said kit product has already been commercially approved at least in Canada in the name of “Cabenuva” which specifically requires maintenance of the product under low temperatures of 2 ºC to 8 ºC. It would be noted that while handling of such temperature sensitive products, extreme care needs to be taken within the complete supply chain from logistics

perspective, and any possible faltering may lead to degradation of the product leading to serious stability issue of the fixed dose product.

Thus, there is a need for new treatment regimens which suppress viral load in humans having HIV where the treatment regimen comprises a fixed dose composition of at least two anti-retroviral agents with therapeutically effective and long lasting dosing schedule which is easily administered. The fixed dose combination formulations containing potent antiretroviral drugs proven to be useful in the prophylaxis and/ or treatment of HIV infection. The said fixed dose composition of at least two anti-retroviral agents is desired to be convenient and easy to administer, as well as showing good physical stability and low degradant/ impurity levels.

OBJECT OF THE INVENTION:

An object of the present invention is to provide a fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer.

Another object of the present invention is to provide a process of manufacturing fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer.

Yet another object of the present invention is to provide a fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering

once every 4 weeks or once every 8 weeks or longer for the prophylaxis and/ or treatment of HIV infection.

Still another object is to provide a method of alleviating or treating or prophylaxis HIV infection by administering a fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer.

Still another object is to provide the use of fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer in the treatment and/ or prophylaxis of HIV infection.

SUMMARY OF THE INVENTION:

According to one aspect of the present invention there is provided a fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer.

According to another aspect of the present invention there is provided a process of manufacturing fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer.

According to yet another aspect of the present invention, there is provided a fixed dose composition administered by injection comprising at least two anti-retroviral

agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer for the prophylaxis and/ or treatment of HIV infection.

According to still another aspect of the present invention, there is provided a method of alleviating or treating or prophylaxis HIV infection by administering a fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer.

According to yet another aspect of the present invention there is provided a use of fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer in the treatment and/ or prophylaxis of HIV infection.

According to another aspect of the present invention there is provided a fixed dose composition administered by injection comprising cabotegravir or their salts, solvates, esters or other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients wherein the said composition is stable at room temperature.

According to another aspect of the present invention there is provided a drug product package comprising a fixed dose composition administered by injection comprising cabotegravir or their salts, solvates, esters or other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients filled in a unit-dose or multi-dose vial along with an injectable device comprising an auto-injector or a pre-filled syringe such as

a dual chamber pre-filled syringe and the instructions for using such injectable device.

According to yet another aspect of the present invention there is provided a drug product package comprising a fixed dose composition administered by injection comprising cabotegravir or their salts, solvates, esters or other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients filled in an injectable device comprising an auto-injector or a pre-filled syringe such as a dual chamber pre-filled syringe and the instructions for using the same.

DETAILED DESCRIPTION OF THE INVENTION:

Rilpivirine or 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]-amino]-benzonitrile is a known NNRTI, which can be prepared as described in WO03/016306. Rilpivirine can be used in base form or, which is preferred, as a suitable pharmaceutically acceptable salt form, in particular as an acid addition salt form. The pharmaceutically acceptable addition salts are meant to comprise the therapeutically active non-toxic salt forms. The acid addition salt forms can be obtained by treating the base form with appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxy-propanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzene-sulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Preferred for use in the present invention are the hydrohalic acid salts, in particular the hydrochloride salt.

Rilpivirine occurs in stereoisomeric forms, more in particular as E- and Z-isomeric forms. Both isomers may be used in the combinations of the present invention.

Whenever reference is made herein to Rilpivirine, the E- and the Z-form as well as any mixture of both forms are meant to be included.

A preferred form of Rilpivirine for use in the invention is the E-isomer, i.e. (E)-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]-amino]-benzonitrile (hereinafter called E-Rilpivirine). The Z-isomer of Rilpivirine, i.e. (Z)-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]-amino]-benzonitrile (hereinafter called compound Z-Rilpivirine) can also be used. It has relatively high potency against wild-type HIV-1 but is less active against single and double mutants in comparison to the E-isomer. Table 1 shows the IC50 value in nM of the E and Z-isomer of Rilpivirine.

Cabotegravir or (3S,11aR)--N-[(2,4-difluorophenyhmethyl]-2,3,5,7,11,11a-hexahydro-6-hydroxy-3-methyl-5,7-dioxo-oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide which is an HIV integrase strand transfer inhibitor and can be prepared as described in WO2006088173.

Based on the need for developing a potential fixed dose composition by administering long acting parenteral dose of combination of therapeutically effective amount of cabotegravir and rilpivirine along with one or more pharmaceutically acceptable excipients, the inventors of the present invention have developed a fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer which not only solves the difficulty in arriving at the fixed dose composition but also improves patient compliance, and comparatively simplifies the task of health care givers as well as provides a room-temperature stable product which prominently differentiates from any existing therapies known for the prophylaxis and/ or treatment of HIV infection.

According to an aspect of some embodiments of the present invention there is provided a fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer. The fixed dose composition according to this aspect of the present invention comprise an effective amount of cabotegravir and rilpivirine or their respective pharmaceutically acceptable salt, solvates, esters or other forms thereof, and one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer.

According to another embodiment, the fixed dose composition may be provided in multi-dose vials or with a suitable prefilled syringe (PFS) device or an auto-injector for e.g. dual chamber syringe device associated with the said fixed dose composition comprising a therapeutically effective amount of amount of cabotegravir and rilpivirine or their respective pharmaceutically acceptable salt, solvates, esters or other forms thereof, and one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer as a drug product package.

The room-temperature stability of the fixed dose composition substantially depends on the specific composition of the polymers used, and the mean particle size of the composition ranging from 0.1-1.0µm, more specifically about 0.1 µm to about 0.3 µm. The fixed dose composition allows administration of high doses of both cabotegravir and rilpivirine which significantly uptakes the existing therapy from an acceptance perspective thereby leading to success of therapeutic regimen.

As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a

process, the term “comprising” means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term “comprising” means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

As used in this specification, the singular forms “a,” “an” and “the” specifically also encompass the plural forms of the terms to which they refer, unless the content clearly dictates otherwise.

The term “about” is used herein to mean approximately, in the region of, roughly, or around. When the term “about” is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of 20%.

It will be well appreciated that the term “cabotegravir” and/ or “rilpivirine” as used herein is denoted in broad sense to include not only “cabotegravir” and/ or “rilpivirine” *per se* but also its pharmaceutically acceptable derivatives thereof. Suitable pharmaceutically acceptable derivatives include pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable anhydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable esters, pharmaceutically acceptable isomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable tautomers, pharmaceutically acceptable complexes etc.

The term "treating" or "treatment" as used herein refers to relieving, reducing or alleviating at least one symptom in a subject or effecting a delay of progression of a disease. For example, treatment can be the diminishment of one or several symptoms of a disorder or complete eradication of a disorder, such as cancer.

Within the meaning of the present invention, the term "treat" also denotes to arrest, delay the onset (i.e., the period prior to clinical manifestation of a disease) and/or reduce the risk of developing or worsening a disease.

The term “prophylaxis” as used herein refers to treatment for a subject who, while not being infected by HIV , is in a situation wherein they are susceptible to or subject to the possibility of acquiring the disease.

The term "pharmaceutically acceptable salt" refers to a charged species of the parent compound and its counter ion, which is typically used to modify the solubility characteristics of the parent compound and/or to reduce any significant irritation to an organism by the parent compound, while not abrogating the biological activity and properties of the administered compound. Examples, without limitation, of pharmaceutically acceptable salts include salts comprising an anion such as a carboxylate or sulfate anion, and/or a cation such as, but not limited to, ammonium, sodium, potassium, and the like. Suitable salts are described in, e.g., Birge et ai. [J Pharma Sci 1977, 66: 1-19],

The term "fixed dose composition" refers to a formulation of cabotegravir and rilpivirine described herein with other chemical components such as pharmaceutically acceptable carriers and excipients as a single composition, or alternatively, two separate formulations each of cabotegravir and rilpivirine with their respective chemical components such as pharmaceutically acceptable carriers and excipients configured in a suitable injectable device for simultaneous or concomitant administration.

The term "pharmaceutically acceptable carrier" refers to a carrier, adjuvant, or a diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

The term “excipient(s)" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of an active ingredient. Examples, without limitation, of excipients include surfactants, lyoprotectants, isotonicity agents, pH adjusters, buffers, preservatives, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

According to the present invention, there is provided a room temperature stable fixed dose composition administered by injection comprising cabotegravir and rilpivirine along with one or more pharmaceutically acceptable excipients. The fixed dose composition comprising cabotegravir and rilpivirine along with one or more pharmaceutically acceptable excipients is meant to be administered once every 4 weeks or once every 8 weeks or longer.

Suitably, the fixed dose composition, according to the present invention there may be provided a drug product package comprising a fixed dose composition administered by injection comprising cabotegravir or their salts, solvates, esters or other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients filled in a unit-dose or multi-dose vial along with an injectable device comprising an auto-injector or a pre-filled syringe such as a dual chamber pre-filled syringe and the instructions for using such injectable device. According to a preferred embodiment, there may be at least one unit-dose or multidose vial comprising the fixed dose composition as described above along with a suitable injectable device.

Alternatively, there may be provided a drug product package comprising a fixed dose composition administered by injection comprising cabotegravir or their salts, solvates, esters or other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients filled in an injectable device comprising an auto-injector or a pre-filled syringe such as a dual chamber pre-filled syringe and the instructions for using the same.

According to a preferred embodiment, the fixed dose composition may be presented in the form of liquid solution/ suspension or as powder for solution/ suspension or as liposomal formulation comprising a therapeutically effective amount of cabotegravir or their salts, solvates, esters or other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients for injectable administration through a suitable injectable device as a single composition. The liquid solution/ suspension or as powder for solution/ suspension or as liposomal formulation may be packed in a unit dose or multidose vial or in an injectable device as a single composition as referred within the specification.

According to another preferred embodiment, the fixed dose composition may be presented with individual formulations each comprising a therapeutically effective amount of cabotegravir or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients for injectable administration and a therapeutically effective amount of rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients for injectable administration. The scope of the present invention may envisage same presentation or different presentation of cabotegravir formulation and rilpivirine formulation respectively i.e. a fixed dose composition may either comprise a liquid solution of cabotegravir formulation and a liquid solution of rilpivirine formulation or, may comprise a liquid suspension of cabotegravir formulation and a liquid solution of rilpivirine formulation, or may comprise a liquid solution of cabotegravir formulation and a liquid suspension of rilpivirine formulation, or a powder for solution/ suspension of cabotegravir formulation and a powder for solution/ suspension of rilpivirine formulation, or liposomal presentation each of cabotegravir formulation and rilpivirine formulation, and other possible combinations may be envisaged under the scope of the present invention.

The fixed dose composition may comprise from about 400 mg/ vial to about 600 mg/ vial of Cabotegravir (with an equivalent concentration of 100 mg/ml to 300

mg/ml) and from about 600 mg/ vial to about 900 mg/ vial of Rilpivirine (with an equivalent concentration of 100 mg/ml to 450 mg/ml) of the total weight of the composition and the volume of the fixed dose composition is about 2 ml to about 10 ml, preferably about 3 ml to about 7 ml.

The fixed dose composition of the present invention may comprise cabotegravir and rilpivirine in micronized form or as a slurry. Suitable micronization techniques like microfluidizer, high pressure homogenizer, ball mill, sonication and other such techniques commonly known in the art can be employed to effectively size reduce the average particle size of cabotegravir and rilpivirine thereof. The average particle size of both cabotegravir and rilpivirine desired for effective usage of the compositions of the present invention can range from about 0.1 μm to about 5.0 μm. According to a preferred embodiment, the average particle size of the fixed dose composition plays an important role, and the desired average particle size range of the fixed dose composition may range from 0.1 μm to 0.5 μm.

The fixed dose composition of the present invention may have a pH range of about 3 to about 8. The pH may be adjusted by the addition of one or more pharmaceutically acceptable acids. Examples of suitable pharmaceutically acceptable acids include inorganic acids, such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, and phosphoric acid, and combinations thereof. Examples of other suitable pharmacologically acceptable acids include organic acids, such as ascorbic acid, citric acid, malic acid, maleic acid, tartaric acid, succinic acid, fumaric acid, acetic acid, formic acid, and/or propionic acid or other than acid variants which comprises sodium hydroxide. In one embodiment, the pH is maintained using combination of buffering agents and/ or pH adjusting agent. In another embodiment, the pH is maintained using pharmaceutically acceptable buffers comprising organic or inorganic buffering agents such as citrate, acetate, ascorbate acid, succinate, maleate, borate and phosphate, fumaric acid and citric acid.

Suitable tonicity adjusting agents may include, but are not limited to, ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethyl sulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, glucose anhydrous/ monohydrate, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine, zinc sulfate, and mixtures thereof. The tonicity adjusting agent in the fixed dose composition of the present invention may range from 10.0 % to 20.0% w/w of the total composition e.g. glucose monohydrate. Suitable lyoprotectants that may be used under the present context for the fixed dose composition include, but are not limited to, natural lyoprotectants which includes sugars such as sucrose, glucose monohydrate/ anhydrous or trehalose, or other lyoprotectants like an amino acid, such as monosodium glutamate, non-crystalline glycine or histidine; a methylamine such, as betaine; a lyotropic salt, such as magnesium sulfate; a polyol, such as trihydric or higher sugar alcohols, e.g., glycerin, erythritol, glycerol, arabitol, xylitol, sorbitol, and mannitol; propylene glycol; polyvinylpyrrolidones (e.g. PVP K-12, PVP K-17 and other categories), polyethylene glycol; poloxamers; Pluronics and combinations thereof. The lyoprotectants in the fixed dose composition of the present invention may range from about 1% w/w to about 20% w/w of the total composition e.g. PVP.

Suitable surfactants that may be used under the present context for the fixed dose composition as suspending/ wetting agents include, but are not limited to, nonionic surfactants, such as polysorbates (e.g., polysorbate 80 or polysorbate 20); sorbitan fatty acid ester (Span 20 or 80); Poloxamers (e.g., Poloxamer 188, Poloxamer 338); Polyoxyl castor oil (e.g., Cremophor EL); Polyoxyl hydrogenated castor oil (e.g., Cremophor RH 40); Triton™ (e.#., Triton™X-100). Other surfactants include but are not limited to, Myristyl-gamma-picolinium chloride (MGP), sodium dodecyl sulfate (SDS); sodium octyl glycoside; lauryl-sulfobetaine; myristyl-sulfobetaine; linoleyl-sulfobetaine; stearyl-sulfobetaine; lauryl-sarcosine; myristyl-sarcosine; linoleyl-sarcosine; stearyl-sarcosine; linoleyl-betaine; myristyl-betaine; cetyl-betaine; lauroamidopropyl-betaine; cocamidopropyl-betaine; linoleamidopropyl-betaine; myristamidopropyl-betaine, palmidopropyl-betaine; isostearamidopropyl-betaine (e.g., lauroamidopropyl); myristarnidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl ofeyl-taurate; and the Monaquat™ series (Mona Industries, Inc., Paterson, N.J.); polyethyl glycol; polypropyl glycol; and copolymers of ethylene and propylene glycol (e.g., pluronics, PF68) and combinations thereof. The surfactants in the fixed dose composition of the present invention may range from about 0.1% w/w to about 30% w/w of the total composition e.g. Poloxamer.

Any solvent/ cosolvent that is suitable for injectables and capable of dissolving or dispersing cabotegravir and/ or rilpivirine in the mixture of cosolvent and water can be used, or merely, water may be used as the vehicle without any solvents/ co-solvents. Examples of suitable cosolvents include, for example, alcohols, ethers, hydrocarbons, and perfluorocarbons. Preferably, the cosolvent is a short chain polar alcohol. More preferably, the cosolvent is an aliphatic alcohol having from one to six carbon atoms, such as ethanol or isopropanol. The most preferred cosolvent is ethanol. Examples of suitable hydrocarbons include n-butane, isobutane, pentane, neopentane and isopentanes. Examples of suitable ethers include dimethyl ether and diethyl ether. Examples of suitable perfluorocarbons include perfluoropropane, perfluorobutane, perfluorocyclobutane, and perfluoropentane. The cosolvents in the

fixed dose composition of the present invention may range from about 5% w/w to about 50% w/w of the total composition.

Suitable antioxidants that may be used include, but are not limited to, ascorbic acid, monothioglycerol, L-Cysteine, L-Methionine, sodium meta bisuifite, sodium thiosulfate, Butylated hydroxyanisole, Butylated hydroxytoluene, Alpha Tocopherol etc.

Apart from the pharmaceutically acceptable excipients mentioned herein, other representative non-limiting examples of pharmaceutically acceptable excipients for use in the fixed dose composition presented as powder for solution/ suspension or liposomal formulation include, without limitation,; phospholipids such as egg yolk phosphatidylcholide, hydrogenated soybean phosphatidylcholide, dimyristoyphosphatidylcholide, diolyeolyl-dipalmitoyleolylphosphatidylcholide and dipalmitoyl phosphatidylcholide (DPPC) present in an amount ranging from about 0.05% w/v to about 5.0% w/v of the total composition.

According to the present invention, and as per a preferred embodiment, the fixed dose composition that is presented with individual formulations each comprising a therapeutically effective amount of cabotegravir or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients for injectable administration and a therapeutically effective amount of rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients for injectable administration may be administered for prevention and/ or treatment comprising administration every 4 weeks or one month, more particularly the treatment is every 4 weeks. In this embodiment, the dose is 400 mg cabotegravir and 600 mg rilpivirine, administered every four weeks. In a further embodiment the 400 mg cabotegravir and 600 mg rilpivirine, are administered separately in two 2-mL injections, every four weeks. Preferably, the dosing regimen may involve stabilizing the patient with oral therapy for one month with both the respective drugs, followed by loading dose of extended release

injections of 600mg cabotegravir (3mL) and 900mg rilpivirine (3mL) as two separate injections for the second month, and later, a maintenance dose of Extended release injections of 400mg cabotegravir (2mL) and 600mg rilpivirine (2mL) as two separate injections for the third month.

According to the present invention, and as per another preferred embodiment, the fixed dose composition that is presented with individual formulations each comprising a therapeutically effective amount of cabotegravir or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients for injectable administration and a therapeutically effective amount of rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients for injectable administration may be administered for prevention and/ or treatment comprising administration every 8 weeks or 2 months, more particularly the treatment is every 8 weeks. In this embodiment, the dose is 600 mg cabotegravir and 900 mg rilpivirine, administered every eight weeks. In a further embodiment, the 600 mg cabotegravir and 900 mg rilpivirine, are administered separately in two 3-mL injections, every 8 weeks.

According to the present invention, and as per another preferred embodiment, the fixed dose composition that is presented as a single composition comprising a therapeutically effective amount of cabotegravir or their salts, solvates, esters or other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients for injectable administration may be administered for prevention and/ or treatment comprising administration every 4 weeks or 8 weeks. In this embodiment, the dose is 600 mg cabotegravir and 900 mg rilpivirine, or 400 mg cabotegravir and 600 mg rilpivirine administered every four weeks as a single injection. In a further embodiment, dose is 600 mg cabotegravir and 900 mg rilpivirine, or 400 mg cabotegravir and 600 mg rilpivirine administered every four weeks are administered separately in two separate injections, every four weeks.

According to the present invention, there is provided a process of preparing a fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer. Preferably, the composition according to the present invention may be manufactured by conventional techniques known to person skilled in the art to arrive at either liquid solution/ suspension, powder for solution/ suspension or a liposomal formulation.
According to the present invention, there is provided a fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer for the prophylaxis and/ or treatment of HIV infection.

According to the present invention, there is provided a method of alleviating or treating or prophylaxis HIV infection by administering a fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer.

According to the present invention, there is provided a use of fixed dose composition administered by injection comprising at least two anti-retroviral agents, in particular, cabotegravir and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients by administering once every 4 weeks or once every 8 weeks or longer in the treatment and/ or prophylaxis of HIV infection.

According to the present invention, there is provided a fixed dose composition administered by injection comprising cabotegravir or their salts, solvates, esters or

other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients wherein the said composition is stable at room temperature.

According to the present invention, there is provided a drug product package comprising a fixed dose composition administered by injection comprising cabotegravir or their salts, solvates, esters or other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients filled in a unit-dose or multi-dose vial along with an injectable device comprising an auto-injector or a pre-filled syringe such as a dual chamber pre-filled syringe and the instructions for using such injectable device.

According to the present invention, there is provided a drug product package comprising a fixed dose composition administered by injection comprising cabotegravir or their salts, solvates, esters or other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients filled in an injectable device comprising an auto-injector or a pre-filled syringe such as a dual chamber pre-filled syringe and the instructions for using the same.

It may be well appreciated by a person skilled in the art that the fixed dose composition comprising Cabotegravir and Rilpivirine may require specific dosage amounts and specific frequency of administrations specifically considering their individual established doses, the dosing frequency, patient adherence and the regimen adopted. As described herein, considering that there are various parameters to govern the dosage and administration of the combination composition as per the present invention, it would be well acknowledged by a person skilled in the art to exercise caution with respect to the dosage, specifically, for special populations associated with other disorders.

In order that this invention be more fully understood, the following preparative and testing methods and examples are set forth. The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the present invention.

EXAMPLES

Following are representative label contents of the fixed dose composition, as envisaged per the invention:

Formulation I: Cabotegravir + Rilpivirine fixed dose combination (Single Injection) - Liquid suspension / Lyophilized product

Composition	**Quantity (mg/ vial)**	**Role**
Fixed dose liquid Injectable Suspension		
Cabotegravir	400 - 600	Active ingredient
Rilpivirine	600 - 900	Active ingredient
Poloxamer 338	50-200	Wetting/ Suspending agent
Citric acid monohydrate	2 - 50	Buffering agent
Glucose monohydrate	50- 300	Tonicity agent
Sodium hydroxide and/ or Hydrochloric acid	qs	pH adjusting agent
Water for Injection	qs to 4 - 6 mL	Vehicle
Fixed dose Lyophilized Injection for Injectable suspension		
PVP K-17/ Sucrose*	25- 150	Lyoprotectant
Water for Injection**	qs to 4 - 6 ml	Vehicle

*Lyo protectants such as PVP K-17, K-30 or Sucrose may be added to minimize particle aggregation during lyophilization process.

** In lyophilized product, Water for injection is removed during lyophilization process and present in the final product in trace quantity.

Manufacturing process

A) Preparation of excipient phase

1. Collect required amount (about 60% batch volume) of Water for Injection in suitable manufacturing vessel.

2. Add and dissolve Poloxamer 388, while mixing gently using a mixer/ overhead stirrer.
3. Add and dissolve the inactive ingredients such as citric acid , glucose monohydrate and PVP K-17/ Sucrose (where applicable) in sequential manner under stirring using a mixer/ overhead stirrer.
4. Adjust the pH, if required using diluted hydrochloric acid or sodium hydroxide solution to about pH 7 (Range 4 - 7).
5. Perform the filtration using 0.22 µm PVDF membrane to obtain a sterile filtrate.

B) **Preparation of drug suspension**

1. Add and suspend required amount of Cabotegravir and Rilpivirine aseptically while mixing to form a vortex using a high shear or USM mixer or an overhead stirrer to obtain sterile drug slurry.

2. Subject the drug suspension for particle size reduction in nano-mill or ball milling instrument under sterile conditions.

3. Make up the volume with sterile water for injection to batch volume to get the sterile liquid drug suspension of 100-300 mg/ml Cabotegravir and 150-450mg/mL Rilpivirine concentration.

4. The product can be filled in a suitable ampule, vial or prefilled syringes and supplied as a Liquid suspension product.

Alternatively, the suspension can be lyophilized further.

C) Lyophilization of liquid drug suspension

- Fill the drug suspension in suitable vials with appropriate fill volume and load the vials on lyophilization chamber and lyophilized to remove the water with appropriate selection and control of freezing, sublimation and secondary drying parameters.

The lyophilized product appropriate reconstitution using 3 - 6 ml of Water for Injection before administration.

Further vials also may be terminally sterilized using gamma or e-beam radiation of finished product instead of aseptic processing.

Formulation II:Cabotegravir + Rilpivirine fixed dose combination (Single Injection - Liquid suspension/ Lyophilized product)

Ingredients	**Quantity in mg/ mL**	**Role**
Fixed dose liquid Injection		
Cabotegravir	400 - 600	Active ingredient
Rilpivirine	600 - 900	Active ingredient
Polysorbate 20 and/ or Span 20	20 – 120	Surfactant/ Wetting agent
PEG 3350/ Carboxy methyl cellulose sodium	20 – 160	Suspending agent
Sodium chloride	16 - 36	Tonicity agent
Hydrochloric acid and/or sodium hydroxide	Qs to adjust pH between 4 - 8	pH Adjusting agents
Water	qs to 4 - 6 ml	Vehicle
Fixed dose Lyophilized Injection		
PVP K-17/ Sucrose*	25- 150	Lyoprotectant
Water for Injection**	qs to 4 - 6 ml	Vehicle

*Lyo protectants such as PVP K-17, K-30 or Sucrose may be added to minimize particle aggregation during lyophilization process.

** In lyophilized product, Water for injection is removed during lyophilization process and present in the final product in trace quantity.

Manufacturing process

A) Preparation of excipient phase

1. Collect required amount (Approx. 60% batch volume) of WFI in suitable manufacturing vessel.

2. Add and dissolve the suspending agents such as PEG 3350 or carboxymethyl cellulose sodium, surfactants such as Polysorbate 20 and/ or Span 20 sequentially while mixing gently using a mixer/ overhead stirrer.

3. Add and dissolve tonicity adjusting agent such as sodium chloride under stirring using a mixer/ overhead stirrer.

4. Adjust the pH, if required using diluted hydrochloric acid or sodium hydroxide solution to about pH about 7 (Range 4 to 8).

5. Perform the filtration using 0.22 µm PVDF membrane to obtain a sterile filtrate.

B) **Preparation of drug suspension**

1. Add and suspend required amount of Cabotegravir and Rilpivirine aseptically while mixing to form a vortex using a high shear or USM mixer or an overhead stirrer to obtain sterile drug slurry.

2. Subject the drug slurry for particle size reduction in nano-mill or ball milling instrument under sterile conditions.

3. Make up the volume with sterile water for injection to batch volume to get the sterile liquid drug suspension of 100-300 mg/ml Cabotegravir and 150 - 450 mg/mL Rilpivirine concentration.

4. The product can be filled in a suitable ampule, vial or prefilled syringes and supplied as a Liquid suspension product.

Alternatively, the suspension can be lyophilized further.

C) Lyophilization of liquid drug suspension

- Fill the drug suspension in suitable vials with appropriate fill volume (3- 6 mL) and load the vials on lyophilization chamber and lyophilized to remove the water with appropriate selection and control of freezing, sublimation and secondary drying parameters.

The lyophilized product appropriate reconstitution using 3 - 6 ml of Water for Injection before administration.

Further vials also may be terminally sterilized using gamma or e-beam radiation of finished product instead of aseptic processing.

Formulation III:

Cabotegravir + Rilpivirine Extended release suspension -Fixed Dose Combination (FDC) packed in a Dual chamber pre-filled syringe

- The lyophilized formulations (mentioned in the Formulation I and II above) can be filled in a dual chamber prefilled syringe along with the diluents (lyophilized cake in first chamber and diluent filled in second chamber) to be administered directly to the patient.
- The dual chamber pre-filled syringe will have a room temperature storage conditions.

Formulation IV:

Kit presentation containing Cabotegravir Extended release Injection and Rilpivirine Extended release injections

A. Cabotegravir Extended Release Suspension

1. **Preparation and nano milling of drug slurry**

Composition of drug slurry	Quantity (mg/ml)

Cabotegravir	200 to 400
Poloxamer 338	75 to 150
Water for Injection	q. s. to 1 ml

Manufacturing process.

i. Collect required amount of Water for Injection (about 20 - 30% batch volume) in suitable manufacturing vessel.
ii. Add and dissolve Poloxamer 388, using mixer or overhead stirrer under gentle mixing.
iii. Add and suspend required amount of Cabotegravir using mixer or overhead stirrer.
iv. Make up the volume of drug slurry with Water for Injection to get the required strength of drug slurry (about 50% of batch volume).
v. Subject the drug slurry for particle size reduction in nano-mill instrument or ball milling instrument.

2. Preparation of excipient phase

Composition of excipient phase	**Quantity mg/ml**
Citric acid anhydrous	10 to 20
Glucose monohydrate	50
PVP K-17	50
Water for Injection	q.s. to 1 ml

Manufacturing process

i. Collect required amount of WFI (about 30% batch volume) in suitable manufacturing vessel and warm it upto 40°C.
ii. Add and dissolve citric acid anhydrous, glucose monohydrate and PVP K-17 in sequential manner under gentle mixing to obtain a clear solution.

iii. Adjust the pH, if required using diluted hydrochloric acid or sodium hydroxide solution to about pH 6 to 7.

iv. Make up the volume (to about 50% of batch volume) using water for Injection under mixing.

v. Check clarity and perform the filtration using 0.22 µm PVDF membrane

3. Preparation of final liquid drug suspension

Composition of liquid drug suspension	**Quantity (mg/ml)**
Cabotegravir	100 to 200 mg
Poloxamer 338	37.5 to 75
Citric acid anhydrous	5.0 to 10
Glucose monohydrate	25
PVP K-17	25
WFI	q.s. to 1 ml

Manufacturing process

i. Mix the excipient phase into the drug slurry in 1:1 ratio to obtain the final liquid drug suspension having 100 mg to 200 mg of Cabotegravir concentration.

ii. The product can be filled dual chamber prefilled syringes (2 mL to 4 mL filled in in either chamber 1 or 2) and supplied as a Liquid suspension product.

4. Preparation of lyophilized product

i. Fill the drug suspension (2 mL to 4 mL) in suitable vials (preferably 6R vials) or in a dual chamber syringe and lyophilized to remove the water with appropriate selection and control of freezing, sublimation and secondary drying parameters.

The lyophilized product appropriate reconstitution using 3 - 6 ml of Water for Injection before administration.

Further vials also may be terminally sterilized using gamma or e-beam radiation of finished product instead of aseptic processing.

B. Rilpivirine Extended release injections

1. Preparation and nano milling of drug slurry

Composition of drug slurry	**Quantity (mg/ml)**
Rilpivirine	200 to 400
Poloxamer 338	75 to 150
Water for Injection	q. s. to 1 ml

Manufacturing process.

i. Collect required amount of Water for Injection (about 45% batch volume) in suitable manufacturing vessel.
ii. Add and dissolve Poloxamer 388, using mixer or overhead stirrer under gentle mixing.
iii. Add and suspend required amount of Rilpivirine using mixer or overhead stirrer.
iv. Make up the volume of drug slurry with Water for Injection to get the required strength of drug slurry (about 75% of batch volume).
v. Subject the drug slurry for particle size reduction in nano-mill instrument or ball milling instrument.

2. Preparation of excipient phase

Composition of excipient phase	**Quantity mg/ml**
Citric acid anhydrous	10 to 20
Glucose monohydrate	100
PVP K-17	100
Water for Injection	q.s. to 1 ml

Manufacturing process

i. Collect required amount of WFI (about 20% batch volume) in suitable manufacturing vessel and warm it upto 40°C.
ii. Add and dissolve citric acid anhydrous, glucose monohydrate and PVP K-17 in sequential manner under gentle mixing to obtain a clear solution.
iii. Adjust the pH, if required using diluted hydrochloric acid or sodium hydroxide solution to about pH 6 to 7.
iv. Make up the volume (to about 25% of batch volume) using water for Injection under mixing.
v. Check clarity and perform the filtration using 0.22 µm PVDF membrane

3. Preparation of final liquid drug suspension

Composition of liquid drug suspension	**Quantity (mg/ml)**
Rilpivirine	150 to 300 mg
Poloxamer 338	56 to 112
Citric acid anhydrous	2.5 to 5
Glucose monohydrate	25
PVP K-17	25
WFI	q.s. to 1 ml

Manufacturing process

i. Mix the excipient phase into the drug slurry in 1:3 ratio to obtain the final liquid drug suspension having 150 mg to 300 mg of Rilpivirine concentration.

ii. The product can be filled dual chamber prefilled syringes (3 mL to 6 mL filled in in either chamber 1 or 2) and supplied as a Liquid suspension product.

5. **Preparation of lyophilized product**

i. Fill the drug suspension (4 mL to 6 mL) in suitable vials (preferably 10R vials) or in a dual chamber syringe and lyophilized to remove the water with appropriate selection and control of freezing, sublimation and secondary drying parameters.

The lyophilized product appropriate reconstitution using 3 - 6 ml of Water for Injection before administration.

Formulation V:

Cabotegravir Extended Release Suspension – Lyophilized Formulation – Different Lyoprotectants (Formulation Y)

Composition	**Quantity**
Ingredients	**mg/ml**
Cabotegravir	200
Polysorbate 20	20
PEG 3350	20
Lyoprotectants*	45-50
Hydrochloric acid and/or sodium hydroxide	Qs to adjust pH between 4 - 8
Water for injection	q.s. to ml

***Screened lyoprotectant at 5% w/v concentration**

PVPK-12, PVP K-17, Trehalose, Sorbitol, Sucrose, Glucose Monohydrate, Mannitol

Manufacturing process:

1. Collect required amount of Water for injection (about 60%) in suitable manufacturing vessel.

2. Add and dissolve PEG-3350 and polysobate 20, lyoprotectant in sequential manner using overhead stirring.
3. Adjust the pH, if required using diluted hydrochloric acid or sodium hydroxide solution to about pH 6 to 7.
4. Add and suspend required amount of Cabotegravir to drug suspension under vigorous mixing to obtain a uniform suspension.
5. Subject the drug suspension for nano-milling or ball milling to obtain nano-suspenion .
6. Make up the volume of drug suspension with Water for injection.
7. Fill the drug suspension in suitable vials with appropriate fill volume (1 – 4 mL) in ampule, vial or prefilled syringe.

Lyophilization: Lyophilized product suitable for room temperature storage can be prepared by freeze drying the vials on lyophilization chamber to remove the water with appropriate selection and control of freezing, sublimation and secondary drying parameters.

We claim,

1. A long acting parenteral fixed dose pharmaceutical composition comprising cabotegravir or its pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipient thereof,

in combination with a Rilpivirine or its pharmaceutically acceptable salt and a pharmaceutically acceptable excipient thereof.

2. The fixed dose pharmaceutical composition of claim 1 comprising cabotegravir or its pharmaceutically acceptable salt thereof in an amount from about 400 mg/ vial to about 600 mg/ vial and rilpivirine or its pharmaceutically acceptable salt thereof in an amount from about 600 mg/ vial to about 900 mg/ vial of the total weight of the composition.

3. The fixed dose composition of claim 1 wherein the volume of the fixed dose composition is about 2 ml to about 10 ml.

4. The fixed dose composition of claim 1 wherein the particle size of cabotegravir or its pharmaceutically acceptable salt thereof and rilpivirine or its pharmaceutically acceptable salt thereof range from about 0.1 µm to about 5.0 µm.

5. The fixed dose composition of claim 1 wherein the composition has a pH from about 3 to about 8.

6. The fixed dose composition of claim 1 wherein the composition further comprises of pH adjusting agent selected from inorganic acids, such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, and phosphoric acid, organic acids, such as ascorbic acid, citric acid, malic acid, maleic acid, tartaric acid, succinic acid, fumaric acid, acetic acid, formic acid, propionic

acid or other than acid variants which comprises sodium hydroxide and combinations thereof.

7. The fixed dose composition of claim 1 wherein the composition further comprises of pharmaceutically acceptable buffers comprising organic or inorganic buffering agents such as citrate, acetate, ascorbate acid, succinate, maleate, borate and phosphate, fumaric acid and citric acid and combinations thereof.

8. The fixed dose composition of claim 1 wherein the composition further comprises of tonicity adjusting agents selected from ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethyl sulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, glucose anhydrous/ monohydrate, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine, zinc sulfate, and mixtures thereof present in an amount from 10.0 % to 20.0% w/w of the total composition.

9. The fixed dose composition of claim 1 wherein the composition further comprises of lyoprotectants selected from sucrose, glucose monohydrate/

anhydrous , trehalose, an amino acid such as monosodium glutamate, non-crystalline glycine or histidine; a methylamine such, as betaine; a lyotropic salt, such as magnesium sulfate; a polyol, such as trihydric or higher sugar alcohols, such as glycerin, erythritol, glycerol, arabitol, xylitol, sorbitol, and mannitol; propylene glycol; polyvinylpyrrolidones, polyethylene glycol; poloxamers; Pluronics and combinations thereof in an amount from about 1% w/w to about 20% w/w of the total composition.

10. The fixed dose composition of claim 1 wherein the composition further comprises of surfactants selected from nonionic surfactants, such as polysorbates , sorbitan fatty acid ester , Poloxamers, Polyoxyl castor oil, Polyoxyl hydrogenated castor oil , Triton™ , Myristyl-gamma-picolinium chloride (MGP), sodium dodecyl sulfate (SDS); sodium octyl glycoside; lauryl-sulfobetaine; myristyl-sulfobetaine; linoleyl-sulfobetaine; stearyl-sulfobetaine; lauryl-sarcosine; myristyl-sarcosine; linoleyl-sarcosine; stearyl-sarcosine; linoleyl-betaine; myristyl-betaine; cetyl-betaine; lauroamidopropyl-betaine; cocamidopropyl-betaine; linoleamidopropyl-betaine; myristamidopropyl-betaine, palmidopropyl-betaine; isostearamidopropyl-betaine , myristarnidopropyl-, palmidopropyl-,isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, disodium methyl ofeyl-taurate; polyethyl glycol; polypropyl glycol; and copolymers of ethylene and propylene glycol (e.g., pluronics, PF68) and combinations thereof at an amount from about 0.1% w/w to about 30% w/w of the total composition.

11. The fixed dose composition of claim 1 wherein the composition further comprises of solvent and cosolvent selected from alcohols, ethers, hydrocarbons, and perfluorocarbons, short chain polar alcohol, ethanol, isopropanol, n-butane, isobutane, pentane, neopentane and isopentanes, dimethyl ether and diethyl ether, perfluoropropane, perfluorobutane, perfluorocyclobutane, perfluoropentane and combinations thereof in an amount from about 5% w/w to about 50% w/w of the total composition.

12. The fixed dose composition of claim 1 wherein the composition further comprises of antioxidants selected from ascorbic acid, monothioglycerol, L-Cysteine, L-Methionine, sodium meta bisuifite, sodium thiosulfate, Butylated hydroxyanisole, Butylated hydroxytoluene, Alpha Tocopherol and combinations thereof.

13. The fixed dose composition of claim 1 wherein the composition further comprises of egg yolk phosphatidylcholide, hydrogenated soybean phosphatidylcholide, dimyristoyphosphatidylcholide, diolyeolyl-dipalmitoyleolylphosphatidylcholide and dipalmitoyl phosphatidylcholide (DPPC) in an amount ranging from about 0.05% w/v to about 5.0% w/v of the total composition.

14. The fixed dose composition of claim 1 wherein the composition is in the form of powder for solution, powder for suspension, liposomal formulation suitable for parenteral administration.

15. The fixed dose composition of claim 1 wherein the composition is administered once every 4 weeks, once every 8 weeks.

16. The fixed dose composition of claim 1 wherein the composition is used for treatment of HIV infection.

17. The fixed dose composition of claim 1 wherein the composition is stable at room temperature.

18. A drug product package comprising :
    i) a vial filled with fixed dose composition comprising cabotegravir or their salts, solvates, esters or other forms and rilpivirine or their salts, solvates, esters or other forms along with one or more pharmaceutically acceptable excipients

ii) an injectable device comprising an auto-injector or a pre-filled syringe such as a dual chamber pre-filled syringe and the instructions for using such injectable device.

19. The drug product package as claimed in claim 18, wherein the vial is a unit dose vial, multi -dose vial.

20. The drug product package as claimed in claim 18 is stable at room temperature.

21. The drug product package as claimed in claim 18, wherein the composition is administered once every 4 weeks, once every 8 weeks.

22. The drug product package as claimed in claim 18,wherein the composition is used for treatment of HIV infection.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2021/050986

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/19 A61K31/4985 A61K31/505 A61K47/26 A61P31/18
ADD.

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)
A61K A61P

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)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	claims 1-5 paragraph [0011] paragraph [0071]	1-22
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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2022	11/02/2022

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 2012/140220 A1 (JANSSEN PHARMACEUTICA NV [BE]; UNIV FRIEDRICH ALEXANDER ER [DE] ET AL.) 18 October 2012 (2012-10-18) cited in the application claims 1-21 -----	1-22

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